Congenital and Pediatric Problems

Hsc
Home Study Course

Home Study Course

Section 1

September 2017

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

THE
HOME STUDY COURSE
IN
OTOLARYNGOLOGY — HEAD AND NECK SURGERY

SECTION 1

Congenital and Pediatric Problems

September 2017

SECTION FACULTY:

Jeffrey C. Rastatter, MD**
Carlton J. Zdanski, MD**
Matthew T. Brigger, MD
Eunice Y. Chen, MD, PhD
Joseph E. Dohar, MD, MS
Nira Goldstein, MD, MPH
Steven Goudy, MD
Erika King, MD

American Academy of Otolaryngology—Head and Neck Surgery Foundation

Section 1 suggested exam deadline: October 9, 2017
Expiration Date: August 7, 2018; CME credit not available after that date

SECTION 1 CONGENITAL AND PEDIATRIC PROBLEMS

Introduction (Purpose)

The Home Study Course is designed to provide relevant and timely clinical information for physicians in training and current practitioners in otolaryngology - head and neck surgery. The course, spanning four sections, allows participants the opportunity to explore current and cutting edge perspectives within each of the core specialty areas of otolaryngology.

The **Selected Recent Material** represents primary fundamentals, evidence-based research, and state of the art technologies in congenital and pediatric problems. The scientific literature included in this activity forms the basis of the assessment examination.

The number and length of articles selected are limited by editorial production schedules and copyright permission issues, and should not be considered an exhaustive compilation of knowledge on congenital and pediatric problems.

The **Additional Reference Material** is provided as an educational supplement to guide individual learning. This material is not included in the course examination and reprints are not provided.

Needs Assessment

AAO-HNSF's education activities are designed to improve healthcare provider competence through lifelong learning. The Foundation focuses its education activities on the needs of providers within the specialized scope of practice of otolaryngologists. Emphasis is placed on practice gaps and education needs identified within eight subspecialties. The *Home Study Course* selects content that addresses these gaps and needs within all subspecialties.

Target Audience

The primary audience for this activity is physicians and physicians-in-training who specialize in otolaryngology-head and neck surgery.

Outcomes Objectives

The participant who has successfully completed this section should be able to:

1. Describe the presentation and management of pediatric parotid and other salivary gland masses
2. Discuss the presentation and management of pediatric thyroid masses
3. Explore the presentation and management of pediatric vascular anomalies and hemangiomas
4. Identify the indications for propranolol administration to treat pediatric hemangiomas
5. Review the indications and methodology for airway evaluation by drug-induced sleep endoscopy (DISE)
6. Describe the presentation and management of pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS)
7. Discuss the presentation and management of pediatric deep neck and peritonsillar abscesses
8. Review the current recommended guidelines for managing pediatric obstructive sleep apnea (OSA) including adenotonsillar disease
9. Explore some aspects of workup and management of pediatric sensorineural hearing loss including genetic testing and cochlear implantation
10. Consider the current recommended guidelines for tympanostomy tube insertion
11. Discuss the management of velopharyngeal insufficiency and the relationship of this condition to cleft palate
12. Explain the diagnosis and management of common traumatic pediatric facial fractures
13. Review the management of Pierre Robin Sequence including indications for mandibular distraction osteogenesis (MDO)
14. Describe the presentation and management of orbital and central nervous system complications of acute sinusitis

Medium Used

The Home Study Course is available in electronic or print format. The activity includes a review of outcomes objectives, selected scientific literature, and a self-assessment examination.

Method of Physician Participation in the Learning Process

The physician learner will read the selected scientific literature, reflect on what they have read, and complete the self-assessment exam. After completing this section, participants should have a greater understanding of congenital and pediatric problems as they affect the head and neck area, as well as useful information for clinical application.

Estimated time to complete this activity: 40.0 hours

Accreditation Statement

The American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation

The AAO-HNSF designates this enduring material for 40.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim credit commensurate with the extent of their participation in the activity.

ALL PARTICIPANTS must achieve a **post-test score of 70% or higher** for a passing completion to be recorded and a transcript to be produced. Residents: results will be provided to the Training Program Director.

PHYSICIANS ONLY: In order to receive *Credi*t for this activity **a post-test score of 70% or higher is required.** Two retest opportunities will automatically be available if a minimum of 70% is not achieved with the first attempt.

Disclosure

The American Academy of Otolaryngology Head and Neck Surgery/Foundation (AAO-HNS/F) supports fair and unbiased participation of our volunteers in Academy/Foundation activities. All individuals who may be in a position to control an activity's content must disclose all relevant financial relationships or disclose that no relevant financial relationships exist. All relevant financial relationships with commercial interests[1] that directly impact and/or might conflict with Academy/Foundation activities must be disclosed. Any real or potential conflicts of interest[2] must be identified, managed, and disclosed to the learners. In addition, disclosure must be made of presentations on drugs or devices, or uses of drugs or devices that have not been approved by the Food and Drug Administration. This policy is intended to openly identify any potential conflict so that participants in an activity are able to form their own judgments about the presentation.

[1] A "Commercial interest" is any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

[2] "Conflict of interest" is defined as any real or potential situation that has competing professional or personal interests that would make it difficult to be unbiased. Conflicts of interest occur when an individual has an opportunity to affect education content about products or services of a commercial interest with which they have a financial relationship. **A conflict of interest depends on the situation and not on the character of the individual.**

Section 1 Congenital and Pediatric Problems September 2017 Faculty

Faculty

****Co-Chairs**

Jeffrey C. Rastatter, MD, Pediatric Otolaryngology - Head and Neck Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago; Associate Professor, Otolaryngology - Head and Neck Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois.
Disclosure: No relationships to disclose.

Carlton J. Zdanski, MD, Associate Professor of Otolaryngology/Head and Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
Disclosures: Salary: Research Triangle Institute
Royalty: Covidien
Intellectual Property: National Institutes of Health

Faculty

Matthew T. Brigger, MD, Associate Professor, Department of Surgery, Division of Otolaryngology, University of California San Diego, Rady Children's Hospital San Diego, San Diego, California.
Disclosure: No relationships to disclose.

Eunice Y. Chen, MD, PhD, Associate Professor, Department of Surgery and Pediatrics, Section of Otolaryngology-Head and Neck Surgery, Geisel School of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.
Disclosure: No relationships to disclose.

Joseph E. Dohar, MD, MS, Professor of Otolaryngology at the University of Pittsburgh School of Medicine, Professor of Communication Science and Disorders at the University of Pittsburgh School of Health and Rehabilitation. Clinical Director of the Pediatric Voice, Resonance and Swallowing Center at Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania.
Disclosure: Consultant: Otonomy.

Nira Goldstein, MD, MPH, Professor of Clinical Otolaryngology, Department of Otolaryngology, Division of Pediatric Otolaryngology, State University of New York Downstate Medical Center, Brooklyn, New York.
Disclosure: No relationships to disclose.

Steven Goudy, MD, Associate Professor, Director of Pediatric Otolaryngology, Emory University School of Medicine, Atlanta, Georgia.
Disclosure: No relationships to disclose.

Erika King, MD, Assistant Professor of Otolaryngology-Head and Neck Surgery, Oregon Health and Science University, Portland, Oregon.
Disclosure: No relationships to disclose.

Planner(s):

Linda Lee, AAO–HNSF Education Program Manager	No relationships to disclose
Stephanie Wilson, Stephanie Wilson Consulting, LLC; Production Manager	No relationships to disclose
Richard V. Smith, MD, chair, Education Steering Committee	Disclosure: Expert Witness: Various legal firms
Jeffrey P. Simons, MD, chair, AAO-HNSF Pediatric Otolaryngology Education Committee	No relationships to disclose

This 2017-18 Home Study Course Section 1 Course includes discussion of off-label uses of the following drugs and devices which have not been approved by the United States Food and Drug Administration:

Name of Drug(s) or Device(s)	**Nature of Off-label Discussion**
Cochlear Implant	Use in single-sided deafness

Disclaimer

The information contained in this activity represents the views of those who created it and does not necessarily represent the official view or recommendations of the American Academy of Otolaryngology – Head and Neck Surgery Foundation.

October 9, 2017: Suggested section 1 Exam submission deadline**; course closes August 7, 2018.**

EVIDENCE BASED MEDICINE

The AAO-HNSF Education Advisory Committee approved the assignment of the appropriate level of evidence to support each clinical and/or scientific journal reference used to authenticate a continuing medical education activity. Noted at the end of each reference, the level of evidence is displayed in this format: **[EBM Level 3]**.

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)	
Level 1	Randomized[1] controlled trials[2] or a systematic review[3] (meta-analysis[4]) of randomized controlled trials[5].
Level 2	Prospective (cohort[6] or outcomes) study[7] with an internal control group or a systematic review of prospective, controlled trials.
Level 3	Retrospective (case-control[8]) study[9] with an internal control group or a systematic review of retrospective, controlled trials.
Level 4	Case series[10] without an internal control group (retrospective reviews; uncontrolled cohort or outcome studies).
Level 5	Expert opinion without explicit critical appraisal, or recommendation based on physiology/bench research.

Two *additional ratings* to be used for articles that do not fall into the above scale. Articles that are informational only can be rated N/A , and articles that are a review of an article can be rated as Review. All definitions adapted from Glossary of Terms, Evidence Based Emergency Medicine at New York Academy of Medicine at www.ebem.org.

[1] A technique which gives every patient an equal chance of being assigned to any particular arm of a controlled clinical trial.
[2] Any study which compares two groups by virtue of different therapies or exposures fulfills this definition.
[3] A formal review of a focused clinical question based on a comprehensive search strategy and structure critical appraisal.
[4] A review of a focused clinical question following rigorous methodological criteria and employing statistical techniques to combine data from independently performed studies on that question.
[5] A controlled clinical trial in which the study groups are created through randomizations.
[6] This design follows a group of patients, called a "cohort", over time to determine general outcomes as well as outcomes of different subgroups.
[7] Any study done forward in time. This is particularly important in studies on therapy, prognosis or harm, where retrospective studies make hidden biases very likely.
[8] This might be considered a randomized controlled trial played backwards. People who get sick or have a bad outcome are identified and "matched" with people who did better. Then, the effects of the therapy or harmful exposure which might have been administered at the start of the trial are evaluated.
[9] Any study in which the outcomes have already occurred before the study has begun.
[10] This includes single case reports and published case series.

OUTLINE
Section 1 Congenital and Pediatric Problems
September 2017

I. **Airway, Bronchoesophagology, and Laryngology**

II. **Craniofacial Abnormalities and Trauma**

III. **Adenotonsillar Disease and Sleep Disorders**

IV. **Rhinology**

V. **Otology**

VI. **Head and Neck**

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Selected Recent Materials - Reproduced in this Study Guide

SECTION 1: CONGENITAL AND PEDIATRIC PROBLEMS
SEPTEMBER 2017

Summary: This is a retrospective review of 64 patients who had pharyngeal flap takedown due to hyponasality and obstructive sleep apnea. The authors primarily took down the pharyngeal flap, but occasionally also performed a Furlow palatoplasty at the time of flap take down. The speech results after flap take down were compared using objective speech analysis, which demonstrated that 90% of patients who have their pharyngeal flap taken down will not suffer from poorer speech.

Summary: This is a comprehensive review of the development, anatomy, and surgical considerations for surgery for the prominent ear. The authors review the specific physical findings and their relevance to the surgical approach, and then provide a reconstructive paradigm for addressing the specific ear deformity. The article includes wonderful diagrams illustrating the most common surgical approaches, which give very specific details about the surgery.

III. Adenotonsillar Disease and Sleep Disorders

Summary: This article correlates drug-induced sleep endoscopy (DICE) scores using the Chan-Parikh (C-P) scoring system with the preprocedural polysomnogram apnea-hypopnea index (AHI) and oxygen nadir in 127 children with obstructive sleep apnea. Fifty-six patients were syndromic and 21 had previous adenotonsillectomy. The mean C-P score positively correlated with the mean AHI and negatively correlated with mean oxygen nadir. The study provides further evidence that DICE is a useful tool to identify the location and severity of obstruction in pediatric obstructive sleep apnea.

Summary: This is a systematic review of the treatment for Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) focusing on tonsillectomy, antibiotic treatment/prophylaxis, intravenous immunoglobulin, and cognitive-behavioral therapy with or without selective serotonin reuptake inhibitors. A paucity of high-level studies was identified. Overall, tonsillectomy was not found to be an effective treatment modality. Antibiotics remain an option, although their efficacy is uncertain. Cognitive behavior therapy is a low-risk option for management of symptoms. Two studies support the use of intravenous immunoglobulin, but additional trials are needed given its potential risks.

Summary: This study is a prospective evaluation of the predictive utility of transcervical ultrasonography in identifying peritonsillar abscesses in children. The sensitivity and specificity of transcervical ultrasound when compared to clinical outcomes were 100% and 76.5%, respectively. There was a significant association between negative ultrasonography and successful medical management. Potential advantages of ultrasonography compared to CT are cost reduction, avoidance of unnecessary radiation exposure, avoidance of undue sedation, and real-time imaging.

Summary: Data from the Childhood Adenotonsillectomy Trial (CHAT), a randomized controlled trial of adenotonsillectomy versus watchful waiting for mild obstructive sleep apnea, were evaluated to compare improvements in disease-specific and global quality of life between groups. Greater improvements in most quality-of-life and symptom severity measurements were found in the adenotonsillectomy group using the Pediatric Quality of Life Inventory, the Obstructive Sleep Apnea-18 (OSA-18), the Sleep-Related Breathing Subscale of the Pediatric Sleep Questionnaire (PSQ-22), and the modified Epworth Sleepiness Scale. Results were not influenced by obesity or baseline sleep study indices, but some of the symptom measures were influenced by race.

Summary: This is a retrospective review of polysomnography outcomes after lingual tonsillectomy in children with Down syndrome with residual obstructive sleep apnea following adenotonsillectomy. There were significant improvements in change scores for apnea-hypopnea index (AHI), obstructive AHI, apnea index, hypopnea index, and oxygen saturation nadir, but not in time with CO_2 >50 mm Hg. The AHI was <5 events/hour in 61.9% of patients and ≤1 in 19% of patients. The study suggests that children with Down syndrome and persistent obstructive sleep apnea after adenotonsillectomy should be evaluated for lingual tonsil hypertrophy.

IV. Rhinology

Summary: Controversy exists as to whether minimally invasive endoscopic approaches are sufficient to treat serious suppurative intracranial complications of pediatric sinusitis. This study supports an important role for endoscopic sinus surgery in these cases and a role as sole surgical intervention for small epidural empyema.

Summary: Possible interference with facial growth has long been considered a possible complication of pediatric endoscopic sinus surgery (ESS) since animal studies in piglets done in the 1990s demonstrated fairly dramatic effects. Subsequent human studies have failed to confirm that hypothetical concern, and this study adds to the body of evidence supporting the safety of ESS by adding the unique study design of patients undergoing unilateral surgery for subperiosteal orbital abscess, enabling them to serve as their own control.

Summary: Continuing the theme of credible best-practice guidelines, this updated guideline is critical for providers who treat children with acute bacterial sinusitis. Changes in this revision include the addition of a clinical presentation designated as "worsening course," an option to either treat immediately or observe children with persistent symptoms for 3 days before treating, and a review of evidence indicating that imaging is not necessary in children with uncomplicated acute bacterial sinusitis.

V. Otology

Summary: The authors present a cost-benefit analysis of early cytomegalovirus (CMV) detection in Utah. They calculate the estimated costs of the early CMV detection program in place in Utah, and compare that to the costs incurred by society in untreated hearing loss due to CMV. They conclude that if antiviral therapies are used to mitigate hearing loss for one infant per year, then the public savings offset the costs of the screening program and antiviral therapy.

Summary: This retrospective case series looks at the rate of residual perforation following tympanoplasty in children in three different age groups (ages 2 to 4, 5 to 7, and 8 to 13 years). They found that on multivariate analysis, preschool-aged children had a 5× increased incidence of perforation when compared to the oldest children. This was mostly attributed to reperforation from eustachian tube dysfunction or acute otitis media after initial successful healing.

Friedmann DR, Ahmed OH, McMenomey SO, et al. Single-sided deafness cochlear implantation: candidacy, evaluation, and outcomes in children and adults. *Otol Neurotol*. 2016; 37(2):e154-e160. EBM level 4.....125-131

Summary: This is a retrospective case series of 16 patients (four children) with unilateral severe-to-profound sensorineural hearing loss who underwent ipsilateral cochlear implantation. The consonant-nucleus-consonant (CNC) and hearing-in-noise test scores were significantly improved from the preoperative condition.

Greinwald J, DeAlarcon A, Cohen A, et al. Significance of unilateral enlarged vestibular aqueduct. *Laryngoscope.* 2013; 123(6):1537-1546. EBM level 2.....132-141

Summary: The authors identified 144 children with unilateral and bilateral enlarged vestibular aqueducts (EVA) as well as a comparison group of children with hearing loss but no EVA. They looked at the incidence of ipsilateral and contralateral hearing loss as well as the rate of hearing loss progression. They found that children with unilateral EVA have a significant risk of progression of hearing loss in the ipsilateral and/or contralateral ear, and that they are more likely to progress than children with hearing loss without an EVA on imaging. This is a slightly older paper, but a revolutionary one.

Sloan-Heggen CM, Bierer AO, Shearer AE, et al. Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. *Hum Genet*. 2016; 135(4):441-450. EBM level 4.....142-151

Summary: This study details the results of samples from 1119 sequential patients referred to the University of Iowa for comprehensive genetic testing for hearing loss. Researchers identified the underlying genetic cause in 39% of samples. The diagnostic rate was highest for patients with autosomal dominant hearing loss, congenital onset, and bilateral symmetric hearing loss. The authors offer an algorithm for workup of patients based on phenotype.

Wang MC, Wang YP, Chu CH, et al. The protective effect of adenoidectomy on pediatric tympanostomy tube re-insertions: a population-based birth cohort study. *PLOS One*. 2014; 9(7):e101175. EBM level 2.....152-158

Summary: This article analyzed the rate of second set of tympanostomy tube insertion in cohorts of children in that underwent tube insertion alone vs. tube insertion with adenoidectomy. They found that adenoidectomy with the first set of tubes decreased the rate of tube reinsertion, especially for children over the age of 4 years at the time of their first tube surgery.

VI. Head and Neck

Summary: This article reviews the presentation, treatments, and outcomes of pediatric patients with salivary gland malignancies. A total of 56 patients were identified. The majority of patients presented with a painless mass without facial nerve weakness at a mean age of 14.1 years. Most of the tumors originated in the parotid gland (88%), with 5% in the submandibular gland and 7% in the minor salivary glands. The most common histologies in the major salivary glands were mucoepidermoid carcinoma and acinic cell carcinoma. Most were of low tumor grade, presenting at an early stage, and a majority were treated with total parotidectomy without adjuvant therapy. The rate of local recurrence was low (27%). Most patients with major salivary gland malignancies (85%) were alive with no evidence of disease. In patients with minor salivary gland malignancies, the recurrence rate was 75%, and the rate of distant metastasis and death was 50%.

Summary: This article describes a query of the SEER database to provide an update on the incidence, disease-specific survival, and treatment modalities of pediatric patients with thyroid cancer. A total of 1723 pediatric patients were identified with thyroid cancer between 2007-2012, giving an average age-adjusted rate of malignancy of 0.59 per 100,000 patients. Fifteen-year disease-specific survival is greater than 95% for the most common thyroid carcinoma subtypes, excluding medullary carcinoma, with appropriate treatment modalities (surgery with and without adjuvant radiation).

Summary: This article reviews the imaging characteristics of the most common congenital and acquired neck masses in the pediatric population. The article covers congenital masses such as thyroglossal duct anomalies, branchial apparatus anomalies, laryngeal anomalies, and vascular anomalies, as well as acquired masses such as ranula, fibromatosis colli, sialadenitis, and lymphadenitis. Ultrasound, MRI, and CT scan can be used along with the patient's age, clinical history, and examination results to provide an accurate diagnosis of pediatric neck masses.

Huyett P, Monaco SE, Choi SS, Simons JP. Utility of fine-needle aspiration biopsy in the evaluation of pediatric head and neck masses. *Otolaryngol Head Neck Surg*. 2016; 154(5):928-935. EBM level 4.....190-197

Summary: This article evaluates the use of fine-needle aspiration biopsy (FNAB) to assess head and neck masses in the pediatric population. A total of 257 consecutive patients underwent FNAB in the interventional radiology suite, operating room, clinic, or ward from 2007-2014. Most common diagnoses were reactive lymphadenopathy (38.5%), benign thyroid colloid nodule (12.1%), malignancy (8.2%), and atypical mycobacterial infection (5.8%). FNAB yielded an overall sensitivity of 94.6% and specificity of 97.7%. Complication rate was 2.1%. Most patients required sedation or anesthesia for the FNAB procedure. Negative FNAB can be utilized to provide reassurance to avoid unnecessary surgery with its associated morbidity and cost.

Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. *N Engl J Med*. 2015; 372(8):735-746. EBM level 1.....198-209

Summary: This article summarizes the results of a randomized controlled trial on the use of propranolol to treat complicated infantile hemangioma. A total of 460 patients were randomized to receive placebo or one of four propranolol dosing regimens (1 or 3 mg/kg/day for 3 or 6 months). The regimen of 3 mg/kg/day for 6 months was found to be the most effective dosing regimen, with 60% of patients having complete or near-complete resolution of hemangioma vs. 4% in the placebo group. Adverse events were more common in the propranolol-treated groups (90%) compared to the placebo group (76%).

2017-18 SECTION 1 ADDITIONAL REFERENCES

Adil E, Tarshish Y, Roberson D, et al. The public health impact of pediatric deep neck space infections. *Otolaryngol Head Neck Surg*. 2015; 153(6):1036-1041.

Amirazodi E, Propst EJ, Chung CT, et al. Pediatric thyroid FNA biopsy: outcomes and impact on management over 24 years at a tertiary care center. *Cancer Cytopathol*. 2016; doi:10.1002/cncy.21750. [Epub ahead of print].

Bedwell JR, Pierce M, Levy M, Shah RK. Ibuprofen with acetaminophen for postoperative pain control following tonsillectomy does not increase emergency department utilization. *Otolaryngol Head Neck Surg*. 2014; 151(6):963-966.

Bhattacharyya N. The prevalence of pediatric voice and swallowing problems in the United States. *Laryngoscope*. 2015; 125(3):746-750.

Boghani Z, Husain Q, Kanumuri VV, et al. Juvenile nasopharyngeal angiofibroma: a systematic review and comparison of endoscopic, endoscopic-assisted, and open resection in 1047 cases. *Laryngoscope*. 2013; 123(4):859-869.

Boyette JR. Facial fractures in children. *Otolaryngol Clin North Am*. 2014; 47(5):747-761.

Brietzke, SE, Shin JJ, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2014; 151(4):542-553.

Chong LY, Head K, Hopkins C, et al. Different types of intranasal steroids for chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2016 Apr 26; 4:CD011993.

Chong LY, Head K, Hopkins C, et al. Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2016 Apr 26; 4:CD011996.

Cofer SA, Baas B, Strand E, Cockerill CC. Augmentation pharyngoplasty for treatment of velopharyngeal insufficiency in children: results with injectable dextranomer and hyaluronic acid copolymer. *Laryngoscope*. 2016; 126 Suppl 8:S5-S13.

Colletti L, Colletti G, Mandalà M, Colletti V. The therapeutic dilemma of cochlear nerve deficiency: cochlear or brainstem implantation? *Otolaryngol Head Neck Surg*. 2014; 151(2):308-314.

Collins B, Stoner JA, Digoy GP. Benefits of ultrasound vs. computed tomography in the diagnosis of pediatric lateral neck abscesses. *Int J Pediatr Otorhinolaryngol*. 2014; 78(3):423-426.

Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics*. 2013; 131(1):128-140.

Gallagher TQ, Hill C, Ojha S, et al. Perioperative dexamethasone administration and risk of bleeding following tonsillectomy in children: a randomized controlled trial. *JAMA*. 2012; 308(12):1221-1226.

Givens DJ, Buchmann LO, Agarwal AM, et al. BRAF V600E does not predict aggressive features of pediatric papillary thyroid carcinoma. *Laryngoscope*. 2014; 124(9):E389-E393.

Hang AX, Roush PA, Teagle HF, et al. Is "no response" on diagnostic auditory brainstem response testing an indication for cochlear implantation in children? *Ear Hear*. 2015; 36(1):8-13.

Hilland M, Røksund OD, Sandvik L, et al. Congenital laryngomalacia is related to exercise-induced laryngeal obstruction in adolescence. *Arch Dis Child*. 2016; 101(5):443-448.

Katz ES, Moore RH, Rosen CL, et al. Growth after adenotonsillectomy for obstructive sleep apnea: an RCT. *Pediatrics*. 2014; 134(2):282-289.

Kheirandish-Gozal L, Bhattacharjee R, Bandla HP, Gozal D. Antiinflammatory therapy outcomes for mild OSA in children. *Chest*. 2014; 146(1):88-95.

Kim IA, Shapiro N, Bhattacharyya N. The national cost burden of bronchial foreign body aspiration in children. *Laryngoscope*. 2015; 125(5): 1221-1224.

Kozin ED, Cummings BM, Rogers DJ, et al. Systemwide change of sedation wean protocol following pediatric laryngotracheal reconstruction. *JAMA Otolaryngol Head Neck Surg*. 2015; 141(1):27-33.

Lam DJ, Tabangin ME, Shikary TA, et al. Outcomes of mandibular distraction osteogenesis in the treatment of severe micrognathia. *JAMA Otolaryngol Head Neck Surg*. 2014; 140(4):338-345.

Lee VS, Evans KN, Perez FA, et al. Upper airway computed tomography measures and receipt of tracheotomy in infants with Robin sequence. *JAMA Otolaryngol Head Neck Surg*. 2016; 142(8):750-757.

Lindstrand A, Bennet R, Galanis I, et al. Sinusitis and pneumonia hospitalization after introduction of pneumococcal conjugate vaccine. *Pediatrics*. 2014; 134(6):e1528-e1536.

Jones CM, Mackay AF, Mackay DR, Long RE. Do pharyngeal flaps restrict early midface growth in patients with clefts? *Cleft Palate Craniofac J*. 2016; 53(6):629-633.

Meier JD, Grimmer JF. Evaluation and management of neck masses in children. *Am Fam Physician*. 2014; 89(5):353-358.

Muntz HR. Management of sleep apnea in the cleft population. *Curr Opin Otolaryngol Head Neck Surg*. 2012; 20(6):518-521.

Nardone HC, Recko T, Huang L, Nuss RC. A retrospective review of the progression of pediatric vocal fold nodules. *JAMA Otolaryngol Head Neck Surg*. 2014; 140(3):233-236.

Okada H, Gosain AK. Current approaches to management of nonsyndromic craniosynostosis. *Curr Opin Otolaryngol Head Neck Surg*. 2012; 20(4):310-317.

Olarte L, Hulten KG, Lamberth L, et al. Impact of the 13-valent pneumococcal conjugate vaccine on chronic sinusitis associated *Streptococcus pneumoniae* in children. *Pediatr Infect Dis J*. 2014; 33(10):1033-1036.

Osborn AJ, de Alarcon A, Tabangin ME, et al. Swallowing function after laryngeal cleft repair: more than just fixing the cleft. *Laryngoscope*. 2014; 124(8):1965-1969.

Osborn AJ, Papsin BC, James AL. Clinical indications for canal wall-down mastoidectomy in a pediatric population. *Otolaryngol Head Neck Surg*. 2012; 147(2):316-322.

Oyewumi M, Inarejos E, Greer ML, et al. Ultrasound to differentiate thyroglossal duct cysts and dermoid cysts in children. *Laryngoscope*. 2015; 125(4):998-1003.

Patel RG, Daramola OO, Linn D, et al. Do you need to operate following recovery from complications of pediatric acute sinusitis? *Int J Pediatr Otorhinolaryngol*. 2014; 78(6):923-925.

Rogers DJ, Setlur J, Raol N, et al. Evaluation of true vocal fold growth as a function of age. *Otolaryngol Head Neck Surg*. 2014; 151(4):681-686.

Roland PS, Rosenfeld RM, Brooks LJ, et al. Clinical practice guideline: polysomnography for sleep-disordered breathing prior to tonsillectomy in children. *Otolaryngol Head Neck Surg*. 2011; 145(1S):S1-S15.

Rosbe KW, Milev D, Chang JL. Effectiveness and costs of sialendoscopy in pediatric patients with salivary gland disorders. *Laryngoscope*. 2015; 125(12):2805-2809.

Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children. *Otolaryngol Head Neck Surg*. 2013; 149(1S):S1-S35.

Runyan CM, Uribe-Rivera A, Karlea A, et al. Cost analysis of mandibular distraction versus tracheostomy in neonates with Pierre Robin sequence. *Otolaryngol Head Neck Surg*. 2014; 151(5):811-818.

Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg*. 2015; 152(1 Suppl):S1-S43.

Semenov YR, Yeh ST, Seshamani M, et al. Age-dependent cost-utility of pediatric cochlear implantation. *Ear Hear*. 2013; 34(4):402-412.

Sethi G, Chakravarti A. Quality of life after endoscopic sinus surgery in refractory pediatric chronic rhinosinusitis. *Int J Pediatr Otorhinolaryngol*. 2016; 90:160-164.

Sharma A, Glick H, Campbell J, et al. Cortical plasticity and reorganization in pediatric single-sided deafness pre- and postcochlear implantation: a case study. *Otol Neurotol*. 2016; 37(2):e26-e34.

Sladen DP, Carlson ML, Dowling BP, et al. Early outcomes after cochlear implantation for adults and children with unilateral hearing loss. *Laryngoscope*. 2016; doi:10.1002/lary.26337. [Epub ahead of print].

Sink JR, Kitsko DJ, Mehta DK, et al. Diagnosis of pediatric foreign body ingestion: clinical presentation, physical examination, and radiologic findings. *Ann Otol Rhinol Laryngol*. 2016; 125(4):342-350.

Tekes A, Koshy J, Kalayci TO, et al. S.E. Mitchell Vascular Anomalies Flow Chart (SEMVAFC): a visual pathway combining clinical and imaging findings for classification of soft-tissue vascular anomalies. *Clin Radiol*. 2014; 69(5):443-457.

Thottam PJ, Haupert M, Saraiya S, et al. Functional endoscopic sinus surgery (FESS) alone versus balloon catheter sinuplasty (BCS) and ethmoidectomy: a comparative outcome analysis in pediatric chronic rhinosinusitis. *Int J Pediatr Otorhinolaryngol*. 2012; 76(9):1355-1360.

Trosman SJ, Eleff DJ, Krishna J, Anne S. Polysomnography results in pediatric patients with mild obstructive sleep apnea: adenotonsillectomy vs. watchful waiting. *Int J Pediatr Otorhinolaryngol*. 2016; 83:25-30.

Venekamp RP, Thompson MJ, Hayward G, et al. Systemic corticosteroids for acute sinusitis. *Cochrane Database Syst Rev*. 2011 Dec 7; (12):CD008115.

Vercillo NC, Xie L, Agrawal N, Nardone HC. Pediatric tympanostomy tube removal technique and effect on rate of persistent tympanic membrane perforation. *JAMA Otolaryngol Head Neck Surg*. 2015; 141(7):614-619.

Ulualp SO. Modified expansion sphincter pharyngoplasty for treatment of children with obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg*. 2014; 140(9):817-822.

Villa MP, Rizzoli A, Rabasco J, et al. Rapid maxillary expansion outcomes in treatment of obstructive sleep apnea in children. *Sleep Med*. 2015; 16(6):709-716.

Zalewski CK, Chien WW, King KA, et al. Vestibular dysfunction in patients with enlarged vestibular aqueduct. *Otolaryngol Head Neck Surg*. 2015; 153(2):257-262.

Zalmanovici Trestioreanu A, Yaphe J. Intranasal steroids for acute sinusitis. *Cochrane Database Syst Rev*. 2013 Dec 2; (12):CD005149.

Review

Surgical Interventions for Pediatric Unilateral Vocal Cord Paralysis
A Systematic Review

Oleksandr Butskiy, BSc(Hons), MD; Bhavik Mistry, BHSc(Hons); Neil K. Chadha, MBChB(Hons), MPH, BSc(Hons), FRCS

IMPORTANCE The most widely used surgical interventions for pediatric unilateral vocal cord paralysis include injection laryngoplasty, thyroplasty, and laryngeal reinnervation. Despite increasing interest in surgical interventions for unilateral vocal cord paralysis in children, the surgical outcomes data in children are scarce.

OBJECTIVE To appraise and summarize the available evidence for pediatric unilateral vocal cord paralysis surgical strategies.

EVIDENCE REVIEW MEDLINE (1946-2014) and EMBASE (1980-2014) were searched for publications that described the results of laryngoplasty, thyroplasty, or laryngeal reinnervation for pediatric unilateral vocal cord paralysis. Further studies were identified from bibliographies of relevant studies, gray literature, and annual scientific assemblies. Two reviewers independently appraised the selected studies for quality, level of evidence, and risk of bias as well as extracted data, including unilateral vocal cord paralysis origin, voice outcomes, swallowing outcomes, and adverse events.

FINDINGS Of 366 identified studies, the inclusion criteria were met by 15 studies: 6 observational studies, 6 case series, and 3 case reports. All 36 children undergoing laryngeal reinnervation (8 studies) had improvement or resolution of dysphonia. Of 31 children receiving injection laryngoplasty (6 studies), most experienced improvement in voice quality, speech, swallowing, aspiration, and glottic closure. Of 12 children treated by thyroplasty (5 studies), 2 experienced resolution of dysphonia, 4 had some improvement, and 4 had no improvement (2 patients had undocumented outcomes). Thyroplasty resolved or improved aspiration in 7 of 8 patients.

CONCLUSIONS AND RELEVANCE Published studies suggest that reinnervation may be the most effective surgical intervention for children with dysphonia; however, long-term follow-up data are lacking. With the exception of polytetrafluoroethylene injections, injection laryngoplasty was reported to be a relatively safe, nonpermanent, and effective option for most children with dysphonia. Thyroplasty appears to have fallen out favor in recent years because of difficulty in performing this procedure in children under local anesthesia, but it continues to be a viable option for children with aspiration.

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Author Affiliations: Division of Pediatric Otolaryngology–Head and Neck Surgery, British Columbia Children's Hospital, Vancouver, British Columbia, Canada (Butskiy, Chadha); Division of Pediatric Otolaryngology, Department of Surgery, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada (Butskiy, Mistry, Chadha).

Corresponding Author: Neil K. Chadha, MBChB(Hons), MPH, BSc (Hons), FRCS, Division of Pediatric Otolaryngology–Head and Neck Surgery, British Columbia Children's Hospital, 4480 Oak St, Vancouver, BC V6H 3V4, Canada (nchadha@cw.bc.ca).

Unilateral vocal cord paralysis (UVCP) is defined as immobility of a vocal cord due to disruption of its motor innervation.[1] In the pediatric population, UVCP most commonly arises from iatrogenic recurrent laryngeal nerve injury during cardiac surgery. Other origins include iatrogenic injury from neck or mediastinal surgery as well as neurologic and idiopathic causes.[2] A pediatric otolaryngologist in a tertiary care center may expect to see approximately 4 to 10 patients with UVCP each year.[1,3,4]

Neonates and infants with UVCP typically present within the first 2 years of life with an abnormal cry or voice, stridor, or feeding difficulty.[1] Over time, many children achieve spontaneous symptomatic resolution due to compensation in glottic closure from the contralateral vocal cord or recovery of the injured nerve.[2,5] Unfortunately, 20% to 40% of children remain symptomatic after the recommended 8 to 12 months of observation and are considered candidates for surgical intervention.[2,6] The main indication for intervention in young children is airway protection. In older children, dysphonia becomes the primary reason for an intervention.[7] With an increased understanding of the negative effect of dysphonia on the lives of children,[8] some authors[9] have advocated earlier interventions for children with UVCP and dysphonia.

The interest in surgical interventions for pediatric UVCP has increased in the past 15 years. The 3 accepted surgical interventions for glottic closure improvement in children with UVCP are injection laryngoplasty, thyroplasty, and laryngeal reinnervation.[10] In injection laryngoplasty, glottic closure is improved by injecting the thyroarytenoid muscle in the paralyzed cord; however, these results may be temporary because some injection materials are reabsorbed over time. In thyroplasty, the paralyzed vocal cord is medialized permanently with an implant positioned by an external neck incision. Thyroplasty is generally reserved for adolescents who are able to tolerate the procedure while awake so that phonation can be tested for optimal vocal cord positioning.[7] Ansa cervicalis nerve to recurrent laryngeal nerve (ansa-RLN) reinnervation can restore the tone of paralyzed laryngeal muscles. Reinnervation may overcome the concerns about laryngeal growth, ongoing muscle atrophy, or the use of foreign material associated with the other 2 procedures, but there is a significant time lag between surgery and improvement.[11]

Despite increasing interest in surgical interventions for pediatric UVCP, the data on outcomes of these procedures in children are scarce. The goal of this systematic review is to synthesize and summarize available evidence on injection laryngoplasty, thyroplasty, and laryngeal reinnervation for pediatric UVCP. This information will help guide otolaryngologists in choosing an appropriate surgical technique for their patients.

Methods

Literature Search Strategy

We searched MEDLINE (1946 to 2014) and EMBASE (1980 to 2014) for relevant studies. The date of the last search was June 30, 2014. In addition, 2 authors (O.B., B.M.) screened the bibliographies of all relevant studies and searched available abstracts by hand from relevant scientific assemblies from 2003 through 2013: American Academy of Otolaryngology–Head and Neck Surgery, Canadian Society of Otolaryngology, American Society of Pediatric Otolaryngology, and European Society of Pediatric Otorhinolaryngology.

Study Selection Criteria

Two reviewers (O.B., B.M.) screened titles or abstracts from the initial search for the following inclusion criteria: (1) a primary research study (controlled trial or observational study, including case series and case reports); (2) study included data on the pediatric population (0-18 years old); (3) study investigated UVCP and 1 or more of the 3 surgical techniques: injection laryngoplasty, thyroplasty, and/or laryngeal reinnervation; (4) study documented outcomes of the surgical interventions for UVCP; (5) English-language study; and (6) not a duplicate study or a study on the same data set.

The same reviewers then screened the full texts of all chosen citations; studies that did not meet the selection criteria were excluded. All discrepancies were resolved by consensus.

Assessment of Quality, Level of Evidence, and Risk of Bias

The level of evidence from individual studies was assessed using the Oxford Centre for Evidence-Based Medicine Levels of Evidence from March 2009.[12] The risk of selection, performance, detection, attrition, and reporting bias in case series were assessed by determining a score from 0 (low risk) to 5 (high risk) using the following scoring system: (1) sample selection (consecutive or not: 1 indicates no or not stated and 0 indicates consecutive); (2) diagnostic criteria stated (1 indicates not stated and 0 indicates stated); (3) outcomes measured consistently for all patients (1 indicates not consistent and 0 indicates consistent); (4) outcomes reported consistently for all patients (1 indicates not consistent and 0 indicates consistent); and (5) follow-up period of 1 year or more (1 indicates <1 year and 0 indicates ≥1 year).

Data Extraction and Analysis

Data were extracted in duplicate using data forms and outcome measures developed a priori. Descriptive statistics were extracted, and qualitative syntheses of the results were reported. The primary outcome measure was the effect of the surgical intervention on voice as judged by clinical assessment and change in voice-related quality-of-life surveys. The secondary outcome measures were the effect of surgical intervention on swallowing, glottic closure as assessed by endoscopy, and adverse events.

Results

Study Selection

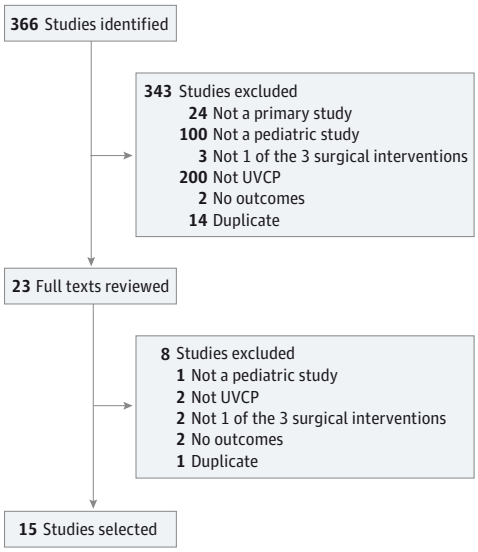
Using our search strategy, we identified 366 studies; 343 were excluded after review of title or abstracts, and 8 studies were excluded after full-text review. This yielded 15 studies for data extraction (**Figure**).

Injection Laryngoplasty

Six studies[1,13-17] reported on injection laryngoplasty for treatment of pediatric UVCP (**Table 1**). Thirty-one patients with a variety of UVCP origins were included in the studies (5 male patients, 3 female patients, and 23 patients with unknown sex). The mean age of the patients was 7.2 years (range, 1 month to 18 years). Dysphonia was the most common indication for injection laryngoplasty (at least 14 patients). In at least 5 patients, injection was performed for aspiration.

A few authors described the methods for injection laryngoplasty in detail. During the procedure, the airway was managed using

Figure. Study Selection



UVCP indicates unilateral vocal cord paralysis.

a variety of techniques: endotracheal intubation, total intravenous anesthesia with spontaneous respiration, jet ventilation, and tracheostomy. Local anesthesia was not used for any of the injections. A number of different injection materials were used (Table 1), but only 2 authors reported the injected volumes. Levine et al[14] used an absorbable gelatin sponge (Gelfoam; Pfizer Inc) and polytetrafluoroethylene and recommended injecting 0.3 to 0.4 mL twice with the Arnold-Bruennings syringe (once into the middle or posterior one-third of the true vocal process and once into the junction of the middle one-third and anterior one-third). Cohen et al[17] reported injecting 0.26 mL of calcium hydroxylapatite (Radiesse Voice; Merz Aesthetics Inc), 0.27 mL of sodium carboxymethylcellulose gel (Radiesse Voice Gel; Merz Aesthetics Inc), and 0.5 mL of an absorbable gelatin sponge (Gelfoam). Overall, the injected volumes varied from 0.2 to 0.6 mL depending on the injected material.

Injection laryngoplasty consistently improved swallowing and voice in children with UVCP in the 6 selected studies. Of 5 patients in whom injection was performed for recurrent aspiration, 3 patients with tracheotomies were decanulated,[13,14] one was weaned from the ventilator, and one stopped having choking episodes.[15] Dysphonia was the indication for 26 vocal cord injections (excluding the study by Cohen et al[17]). All 26 injections were deemed successful in improving voice by subjective measures. Objective measures of voice, including videostroboscopy and computerized voice analysis, were only documented in one patient.[15] Cohen et al[17] were the only authors to report success rates of less than 100% after injection laryngoplasty. Among patients injected for dysphonia, 94% experienced subjective or objective improvement in voice, and among patients injected for dysphagia or aspiration, improvement was seen in 85%. However, in addition to 8 patients with UVCP, this analysis included the outcomes of 5 patients with vocal cord scarring or atrophy.[17] Time to the additional injection was underreported and varied depending on the injected material (Table 1). Tucker[13] and Sipp et al[16] noted the effects of some injectables to last longer than they would expect in the adult population.[13,16] In the 6 studies, one patient with UVCP experienced a complication after vocal cord injection: granuloma formation after polytetrafluoroethylene injection.[1]

Thyroplasty

Five case reports (level 4 evidence) reported using thyroplasty in 12 pediatric patients (**Table 2**).[1,16,18-20] The mean age of the patients was 11.5 years (range, 2-18 years). Dysphonia and aspiration were indications for surgery in 8 patients, whereas 4 patients had dysphonia alone. Local anesthesia was used in 4 patients (aged 14-18 years). General anesthesia was used in 7 patients (aged 2-14 years). Several authors[16,20] advocated the use of laryngeal airway mask for intraoperative airway management.

Voice outcomes were not evaluated objectively in any of the studies. The authors relied on subjective reports by physician, parent, or patient to evaluate voice outcomes. Overall, thyroplasty was moderately effective in alleviating dysphonia. Five (42%) of 12 patients had resolution or improvement of dysphonia after thyroplasty. There were no apparent differences in rates of recovery from dysphonia in patients who underwent thyroplasty under general or local anesthesia. Dysphonia resolved or improved in 3 (43%) of 7 patients and 2 (50%) of 4 patients who underwent thyroplasty under general and local anesthesia, respectively. The laryngeal airway mask was used for 2 of 3 cases in which dysphonia was resolved while the patient was under general anesthesia. Link et al[19] attributed the lack of voice improvement in 3 patients to the use of an adult thyroplasty technique in which the prosthesis was placed above the vocal cords. The authors adjusted the adult technique in their last case by lowering the implant placement and reported a successful voice outcome.

Compared with voice improvement, thyroplasty was more effective in alleviating aspiration. Seven (88%) of 8 patients had resolution or improvement in aspiration after thyroplasty. The remaining 1 patient had effects of the thyroplasty deteriorate at approximately 6 months. However, this patient had a complicated preoperative history, including 3 failed polytetrafluoroethylene injections and an arterectomy that led to intractable aspiration.[18] There were no apparent differences in rates of recovery from aspiration in surgical patients under general or local anesthesia.

During the period of follow-up (range, 4-19 months), 4 of 12 patients had no complications, while complications were not mentioned in 7 patients. One patient had a major complication, aspiration pneumonia, that resulted in a 7-day period of intubation. In this 18-year-old patient, thyroplasty was performed, in addition to adduction arytenoidopexy and cricothyroid joint subluxation, with the patient under local anesthesia.[16]

Reinnervation

We identified 8 studies that reported outcomes of laryngeal reinnervation for UVCP in a pediatric population (**Table 3**).[7,9,13,16,21-24] These studies consisted of case reports and case series (level 4 evidence). Risk of bias was 5 in all except 2 studies.[22,24]

The population of patients in these 8 studies included children aged 2 to 16 years. The cause of UVCP in most of these patients (26 of 38) was patent ductus arteriosus ligation. Dysphonia was the indication for surgery in 37 of 38 patients.

Laryngeal electromyography (EMG) was not used in deciding the timing of surgical intervention in the included studies. How-

Table 1. Studies Reporting on Injection Laryngoplasty for Pediatric UVCP

Source (No. of Patients)	Level of Evidence/ Risk of Bias	Age, Mean (Range), y	UVCP Origin (No. of Patients)	Indication	Injected Material (No. of Injections)	Time to Additional Injection, mo	Results			Adverse Events (No. of Events)
							Voice	Swallow	Glottic Closure	
Tucker,[13] 1986 (2)	4/5	NA	NA	Aspiration	Gelatin sponge (2)	NA	NA	Improvement	NA	None
Levine et al,[14] 1995 (3)	4/5	11	Neurologic	Dysphonia and aspiration	Gelatin sponge (1)	NA	Improvement	Improvement	Improvement	None
		4	Idiopathic	Aspiration	Polytetrafluoroethylene (1)	NA	NA			
		7	Cardiac surgery		Polytetrafluoroethylene (1)	NA			NA	
Daya et al,[1] 2000 (2)	4/5	NA	Cardiac surgery	Dysphonia	Polytetrafluoroethylene (2)	NA	Improvement in 1 patient	NA	NA	Granuloma (1)
Patel et al,[15] 2003 (4)	4/4	5	Neurologic	Aspiration	Cadaveric dermis (6)	3-6	Improvement	Improvement	NA	None
		5	PDA ligation	Dysphonia			Improvement	NA		
		1 mo	Idiopathic	Aspiration			NA	Improvement	Improvement	
		18	Idiopathic	Dysphonia			Improvement	NA		
Sipp et al,[16] 2007 (12)	4/5	10.5 (2.5-18)	Thoracic surgery (5), prolonged intubation (4), and neurologic origin (3)	Dysphonia	Cadaveric dermis (11)	3-9	Improvement	NA	NA	None
					Sodium carboxymethylcellulose gel (1)	NA				
					Bovine collagen (1)	NA				
					Calcium hydroxylapatite (1)	NA				
					Hydrated gelatin powder (3)	1				
					Autologous fat (3)	1-6				
Cohen et al,[17] 2011 (8)	4/5	NA	Neck cannula (1), idiopathic (1), and NE (6)	Dysphonia and aspiration (1), aspiration (1), and NE (6)	Gelatin sponge (NE)	2.2 (range, 1.1-3.5)	NE: see text	NE: see text	NA	None
					Sodium carboxymethylcellulose gel (NE)	NA				
					Calcium hydroxylapatite (NE)	7.3 (range, 1.5-9.7)				

Abbreviations: NA, not applicable or stated; NE, not extractable; PDA, patent ductus arteriosus; UVCP, unilateral vocal cord paralysis.

ever, Zur[23] described using intraoperative EMG to establish the asymmetry between the right and left thyroarytenoid muscles. The authors did not provide information on whether any of the planned reinnervation procedures were aborted as a result of unexpected intraoperative EMG findings.

Ansa-RLN anastomosis was the reinnervation approach used in all identified studies. Smith et al[22] used ansa-RLN anastomosis in combination with arytenoid adduction in older children. Only 2 studies described the surgical technique in detail: one using a minimally invasive approach with the da Vinci System (Intuitive Surgical Inc)[21] and another using the operating microscope.[9] In both studies, ansa cervicalis was identified low in the neck around the omohyoid muscle, and end-to-end anastomosis was created with 8-0 monofilament in the first case and 10-0 nylon sutures in the other. An entire ansa was used in both studies and was believed to provide the best size match for the RLN.[9,21] At the time of surgery, most authors also performed a temporary injection laryngoplasty of the paralyzed vocal cord.

The results of laryngeal innervation were documented during a follow-up period that ranged from 3 months to 6 years. Many authors used validated subjective measures to assess the quality of voice and its effect on the child's life, including the Pediatric Voice-Related Quality of Life, Voice Handicap Index, and Consensus Auditory-Perceptual Evaluation of Voice, along with objective measures of voice, such as maximum phonation time and pitch range. Most studies did not collect preoperative voice data and instead relied solely on postoperative results to demonstrate the effect of the reinnervation on voice. Nevertheless, all the authors commented that reinnervation improved or resolved the dysphonia in children with UVCP. In the largest cohort of pediatric patients, Smith et al[24] found that ansa-RLN reinnervation led to a statistically significant improvement in mean parental global voice rating and GRBAS (grade, roughness, breathiness, asthenia, and strain) rating scale compared with preoperative data. In the same study,[24] the authors found that the mean parental assessment of dysphasia improved from 3.7 to 1.4 (P = .05). The other studies did not investigate the effect of reinnervation on dysphagia. Of 36 patients, one had a complication that was related to surgery: development of a hypertrophic neck scar.[24]

A few authors commented on the length of time from surgery to improvement in symptoms. Tucker[13] reported improvement or resolution of symptoms at 3 months postoperatively in all 3 of his patients. Sipp et al[16] reported that one patient improved at 3 months

Table 2. Studies Reporting on Thyroplasty for Pediatric UVCP

Source (No. of Patients)	Level of Evidence/ Risk of Bias	Age, y	UVCP Origin	Time to Surgery, y	Indication	Anesthesia or Airway Management	Results			Adverse Events
							Dysphonia	Swallow	Glottic Closure	
Isaacson,[18] 1990 (1)	4/5	14	Neurologic	10	Aphonia and aspiration	GA tracheostomy	Deteriorated at 6 mo	Deteriorated at 6 mo	Increase in glottic gap at 6 mo	None
Link et al,[19] 1999 (6)	4/5	17	Idiopathic	NA	Dysphonia	Local	Resolved	NA	NA	NA
		14	Congenital		Dysphonia	Local	Improvement	NA		
		12	Cardiac surgery		Dysphonia and aspiration	GA	No improvement	Improvement		
		14	Skull base tumor			Local	No improvement	Improvement		
		14	Skull base tumor			GA	No improvement	Improvement		
		2	Cardiac surgery			GA	Resolved	Resolved		
Gardner et al,[20] 2000 (2)	4/5	8	Thoracic surgery	6.5	Dysphonia and aspiration	LMA	Improvement	Resolved	NA	None
		4	PDA ligation	4	Dysphonia	LMA	Improvement	NA	Full closure	None
Daya et al,[1] 2000 (1)	4/5	3	Tracheo-esophageal fistula repair	NA	Dysphonia	NA	No improvement	NA	NA	NA
Sipp et al,[16] 2007 (2)	4/5	5.5	Thoracic surgery	NA	Dysphonia and aspiration	LMA	NA	Resolved	NA	None
		18	Neurologic	NA	Dysphonia and aspiration	Local	NA	Resolved	NA	Aspiration pneumonia and 7 days of intubation

Abbreviations: GA, general anesthesia; LMA, laryngeal mask airway; NA, not applicable or stated; PDA, patent ductus arteriosus; UVCP, unilateral vocal cord paralysis.

and another patient improved at 5 months postoperatively. Zur[23] reported resolution of glottic closure in 7 of 7 patients examined 6 months postoperatively. Finally, Marcum et al[9] reported improvement at 7 months postoperatively. Overall, it seems that most patients will experience symptomatic improvement between 3 and 7 months.

Discussion

Our report indicates the scarcity of objective data on surgical interventions for pediatric UVCP. We found 15 English-language studies reporting information on surgical interventions in 84 patients with UVCP. This report highlights the conclusion that surgical intervention for children with UVCP is guided by level 4 evidence. In our report, 13 of 16 studies received the highest risk of bias score (Tables 1, 2, and 3). The scarcity of data is somewhat expected given that symptomatic UVCP is relatively infrequent in a pediatric population.[25]

A key issue that remains controversial in the management of UVCP is the timing of surgical intervention. In adult patients, laryngeal EMG can be used as an adjunct for prognostication and deciding on the timing of permanent intervention. Currently, there are no EMG-validated studies in pediatric patients[24]; hence, the timing of intervention should be guided by symptom severity, knowledge of UVCP natural history, and the effect of dysphonia on the child. A study of 404 children by Jabbour et al[2] provides insights into the natural history of pediatric vocal cord paralysis. The authors note that, for unilateral and bilateral vocal cord paralysis, approximately half (45.8%) of the children achieve symptomatic recovery. Significantly, both the time to symptom resolution and the rate of symptom resolution had statistically significant variations based on the vocal cord paralysis. Children with vocal cord paralysis attributable to cardiac surgery or of neurologic origin achieved lower rates of vocal cord movement recovery (24% and 27%, respectively) than children with idiopathic vocal cord paralysis (40%). In addition, children with vocal cord immobility attributable to cardiac surgery or of neurologic origin had a shorter mean time to resolution of symptoms (6.3 and 9.9 months, respectively) than the idiopathic group (11.1 months). The longest time from diagnosis to spontaneous recovery of vocal cord movement in any category of patients was 38 months.[2]

Children who experience aspiration due to UVCP should be offered at least a temporary surgical intervention, such as tracheostomy or injection medialization. However, most children with UVCP experience dysphonia as their main symptom,[2] and it is currently unclear when to offer surgery for these patients. Literature on the effect of dysphonia on children is limited. One study[8] suggests that children as young as 6 years experience concern over dysphonia. Dysphonia was found to have a negative effect on the lives of children across the domains of physical, social or functional, and emotional performance. This negative effect became more pronounced with age. Given that UVCP was mostly diagnosed close to birth in children,[2] a logical algorithm for treatment of dysphonia would consist of conservative and/or temporary measures for the first few years after diagnosis until the possibility of spontaneous recovery is minimized. After observation and ideally before 6 years of age, a more

Table 3. Studies Reporting on Reinnervation for Pediatric UVCP

Source (No. of Patients)	Level of Evidence/ Risk of Bias	Age, y	UVCP Origin (No. of Patients)	Time to Surgery, y	Indication	Procedures	Results			Adverse Events (No. of Events)
							Dysphonia	Aspiration	Glottic Closure	
Tucker,[13] 1986 (3)	4/5	Infants	NA	NA	Dysphonia	NA	Improvement	NA	Full closure	NA
Sipp et al,[16] 2007 (2)	4/5	NA	NA	NA	Dysphonia	Ansa-RLN	Resolved	NA	Full closure	NA
		NA	NA	NA	Dysphonia	Ansa-RLN	Resolved	NA	Full closure	NA
Wright and Lobe,[21] 2008 (1)	4/5	>10	Cardiac surgery	>10	Dysphonia	Ansa-RLN[a]	Improvement	NA	NA	None
Smith et al,[22] 2009 (4)	4/2	16	PDA ligation	>1	Dysphonia	AA and ansa-RLN	Improvement	NA	NA	NA
		15	Skull base tumor			AA and ansa-RLN				
		16	Skull base tumor			AA and ansa-RLN				
		12	Intubation or tonsillectomy			Ansa-RLN				
Marcum et al,[9] 2010 (1)	4/5	6	PDA ligation	6	Dysphonia	Ansa-RLN	Improvement	NA	NA	NA
Zur,[23] 2012 (10)	4/5	2-15 (median, 5.4)	PDA ligation (9) and thoracic surgery (1)	2 to 12 (median, 5.4)	Dysphonia	Ansa-RLN	Improvement in at least 7/10 patients	NA	Full closure in 7/7 tested patients	None
Smith et al,[24] 2012 (13)	4/4	2.2-8.8 (mean, 5.3)	PDA ligation (12) and coarctation of aorta repair (1)	NA	Dysphonia and aspiration	Ansa-RLN	Improvement in 9/9 patients with follow-up data	Improvement in 7/9 patients with follow-up data	NA	Hypertrophic surgical scar (1)
Seltur et al,[7] 2012 (4)	4/5	12	PDA ligation	NA	Dysphonia	Ansa-RLN	Improvement	NA	NA	NA
		10	PDA ligation							
		2	PDA ligation							
		4	Ependymoma resection							

Abbreviations: AA, arytenoid adduction; NA, not applicable or stated; PDA, patent ductus arteriosus; RLN, recurrent laryngeal nerve; UVCP, unilateral vocal cord paralysis.

[a] Transaxillary totally endoscopic robot-assisted surgery.

permanent solution to dysphonia caused by UVCP should be offered as an option to the parents.

The only surgical option for a temporary relief of UVCP symptoms is injection medialization. The duration of effect depends on the type of injectable material used. Of interest, several authors[13,16] noted that the effect of vocal cord injection appears to last longer in a pediatric population compared with the expected duration using the same materials in adults. The reasons for this phenomenon are not understood. Tucker[13] suggested that the slow relateralization of a paralyzed vocal fold as the injected material disappears may encourage gradual hyperadduction of the contralateral vocal cord. A potential concern with using injection medialization in a pediatric population is the long-term effects of repeated injections on the vocal cords as tissues grow and develop. Long-term follow-up data on vocal cord medialization are required to address this concern.

Medialization thyroplasty is the least studied surgical solution for pediatric UVCP. Only 12 cases met our inclusion criteria. The benefit of thyroplasty in children is inconsistent. In a study by Link et al,[19] 3 of 6 children with UVCP had symptomatic improvement after medialization thyroplasty. The authors attributed this result to using an adult technique on a pediatric larynx and advocated for lower placement of prosthesis to improve glottic closure. A limitation of performing thyroplasty in children compared with adults is the necessity for a general anesthetic in children. General anesthesia takes away the ability to adjust the position of prosthesis based on real-time vocal feedback. Given this limitation, several authors[16,17] have argued for the use of flexible endoscopy through a laryngeal mask airway tube during surgery to improve the positioning of the prosthesis during surgery. Another limitation of pediatric thyroplasty is the lack of long-term follow-up data. Even though the growth of pediatric larynx has been well studied,[18] it is unclear if and how often revision thyroplasties are required for a child operated on at a young age. One interesting finding that has emerged from our study is the high rate of aspiration recovery or improvement after thyroplasty (88%). Overall, it seems that thyroplasty has fallen out of favor in a pediatric population but remains a surgical option for children with aspiration, older children who might be able to tolerate procedures without anesthesia, and patients with no alternatives.

Compared with thyroplasty, reinnervation of RLN for children with UVCP should prevent the loss of muscle bulk and lead to vocal improvement irrespective of laryngeal growth. With the exception of any injectable material used for injection laryngoplasty, which is often performed concurrently with reinnervation, no foreign material is added to the larynx in reinnervation of RLN, which mini-

mizes the chance of future inflammatory reactions. Reinnervation also preserves the possibility of laryngeal framework surgery later in life. Knowledge of origin-specific rates and timing of RLN recovery has allowed surgeons to be less fearful of sacrificing any potential for recovery of RLN function with the reinnervation procedures. Several studies[7,23,24] found that reinnervation can be safe for children as young as 2 years. One study[7] reported high rates of satisfaction after reinnervation as evidenced by Pediatric Voice-Related Quality of Life scores but only a modest improvement in objective measures of voice, such as maximum phonation time. These findings highlight the need for further investigation into reinnervation outcomes in children.

Conclusions

Our report highlights the lack of quality evidence on surgical interventions for pediatric UVCP. Recent data have clarified the natural history of pediatric UVCP and helped surgeons decide when to offer interventions for UVCP. For the first few years after diagnosis of UVCP, conservative measures and/or temporary measures should be offered. The data summarized in this report suggest that injection laryngoplasty, with the exception of polytetrafluoroethylene injections, is safe, nonpermanent, and effective in children. However, long-term follow-up for children who receive the injection intervention is lacking. Thyroplasty and reinnervation are 2 long-term surgical solutions. Although thyroplasty seems to have fallen out of favor in recent years because of the difficulty of positioning the prosthesis in anesthetized pediatric patients, it is still a viable option, especially for children with aspiration. Compared with thyroplasty, reinnervation has seen a resurgence of interest. Recent studies on reinnervation techniques offer encouraging results; however, long-term follow-up data are lacking. Surgeons who offer surgical solutions for pediatric UVCP are encouraged to systematically document and present their results to further collective knowledge on management of this condition.

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REFERENCES

1. Daya H, Hosni A, Bejar-Solar I, Evans JN, Bailey CM. Pediatric vocal fold paralysis: a long-term retrospective study. *Arch Otolaryngol Head Neck Surg*. 2000;126(1):21-25.

2. Jabbour J, Martin T, Beste D, Robey T. Pediatric vocal fold immobility: natural history and the need for long-term follow-up. *JAMA Otolaryngol Head Neck Surg*. 2014;140(5):428-433.

3. Shah RK, Harvey-Woodnorth G, Glynn A, Nuss RC. Perceptual voice characteristics in pediatric unilateral vocal fold paralysis. *Otolaryngol Head Neck Surg*. 2006;134(4):618-621.

4. de Gaudemar I, Roudaire M, François M, Narcy P. Outcome of laryngeal paralysis in neonates: a long term retrospective study of 113 cases. *Int J Pediatr Otorhinolaryngol*. 1996;34(1-2):101-110.

5. Woodson G. Evolving concepts of laryngeal paralysis. *J Laryngol Otol*. 2008;122(5):437-441.

6. Misono S, Merati AL. Evidence-based practice: evaluation and management of unilateral vocal fold paralysis. *Otolaryngol Clin North Am*. 2012;45(5):1083-1108.

7. Seltur J, Bunting GW, Ballif C, Hartnick CJ. Reinnervation for vocal fold paralysis: results in children. *Otolaryngol Head Neck Surg*. 2012;147(2)(suppl):235.

8. Connor NP, Cohen SB, Theis SM, Thibeault SL, Heatley DG, Bless DM. Attitudes of children with dysphonia. *J Voice*. 2008;22(2):197-209.

9. Marcum KK, Wright SC Jr, Kemp ES, Kitse DJ. A novel modification of the ansa to recurrent laryngeal nerve reinnervation procedure for young children. *Int J Pediatr Otorhinolaryngol*. 2010;74(11):1335-1337. doi:10.1016/j.ijporl.2010.08.002.

10. King EF, Blumin JH. Vocal cord paralysis in children. *Curr Opin Otolaryngol Head Neck Surg*. 2009;17(6):483-487.

11. Grover N, Bhattacharyya A. Unilateral pediatric vocal cord paralysis: evolving trends. *J Laryngol Voice*. 2012;2(1):5.

12. Oxford Centre for Evidence-Based Medicine Levels of Evidence. March 2009. CEBM. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed October 10, 2014.

13. Tucker HM. Vocal cord paralysis in small children: principles in management. *Ann Otol Rhinol Laryngol*. 1986;95(6, pt 1):618-621.

14. Levine BA, Jacobs IN, Wetmore RF, Handler SD. Vocal cord injection in children with unilateral vocal cord paralysis. *Arch Otolaryngol Head Neck Surg*. 1995;121(1):116-119.

15. Patel NJ, Kerschner JE, Merati AL. The use of injectable collagen in the management of pediatric vocal unilateral fold paralysis. *Int J Pediatr Otorhinolaryngol*. 2003;67(12):1355-1360.

16. Sipp JA, Kerschner JE, Braune N, Hartnick CJ. Vocal fold medialization in children: injection laryngoplasty, thyroplasty, or nerve reinnervation? *Arch Otolaryngol Head Neck Surg*. 2007;133(8):767-771. doi:10.1001/archotol.133.8.767.

17. Cohen MS, Mehta DK, Maguire RC, Simons JP. Injection medialization laryngoplasty in children. *Arch Otolaryngol Head Neck Surg*. 2011;137(3):264-268. doi:10.1001/archoto.2011.24.

18. Isaacson G. Extraluminal arytenoid reconstruction: laryngeal framework surgery applied to a pediatric problem. *Ann Otol Rhinol Laryngol*. 1990;99(8):616-620.

19. Link DT, Rutter MJ, Liu JH, Willging JP, Myer CM, Cotton RT. Pediatric type I thyroplasty: an evolving procedure. *Ann Otol Rhinol Laryngol*. 1999;108(12):1105-1110.

20. Gardner GM, Altman JS, Balakrishnan G. Pediatric vocal fold medialization with silastic implant: intraoperative airway management. *Int J Pediatr Otorhinolaryngol*. 2000;52(1):37-44.

21. Wright SK, Lobe T. Transaxillary totally endoscopic robot-assisted ansa cervicalis to recurrent laryngeal nerve reinnervation for repair of unilateral vocal fold paralysis. *J Laparoendosc Adv Surg Tech A*. 2009;19(suppl 1):S203-S206.

22. Smith ME, Roy N, Stoddard K. Ansa-RLN reinnervation for unilateral vocal fold paralysis in adolescents and young adults. *Int J Pediatr Otorhinolaryngol*. 2008;72(9):1311-1316.

23. Zur KB. Recurrent laryngeal nerve reinnervation for unilateral vocal fold immobility in children. *Laryngoscope*. 2012;122(suppl 4):S82-S83.

24. Smith ME, Roy N, Houtz D. Laryngeal reinnervation for paralytic dysphonia in children younger than 10 years. *Arch Otolaryngol Head Neck Surg*. 2012;138(12):1161-1166.

25. Martins RHG, Hidalgo Ribeiro CB, Fernandes de Mello BMZ, Branco A, Tavares ELM. Dysphonia in children. *J Voice*. 2012;26(5):674.e17-674.e20.

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Review Article

International Pediatric ORL Group (IPOG) laryngomalacia consensus recommendations

John Carter [a,*], Reza Rahbar [b], Matthew Brigger [c], Kenny Chan [d], Alan Cheng [e], Sam J. Daniel [f], Alessandro De Alarcon [g], Noel Garabedian [h], Catherine Hart [g], Christopher Hartnick [i], Ian Jacobs [j], Bryan Liming [k], Richard Nicollas [l], Seth Pransky [c], Gresham Richter [m], John Russell [n], Michael J. Rutter [g], Anne Schilder [o], Richard J.H. Smith [k], Julie Strychowsky [p], Robert Ward [q], Karen Watters [b], Michelle Wyatt [r], George Zalzal [s], Karen Zur [j], Dana Thompson [a]

[a] *Division of Otolaryngology-Head and Neck Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA*
[b] *Department of Otolaryngology and Communication Enhancement, Boston Children's Hospital, Boston, MA, USA*
[c] *Rady Children's Hospital, San Diego, CA, USA*
[d] *Children's Hospital Colorado, Aurora, CO, USA*
[e] *Department of Pediatric Otolaryngology, The Sydney Children's Hospital Network-Westmead Campus, The University of Sydney, Sydney, NSW, Australia*
[f] *Department of Otolaryngology – Head and Neck Surgery, Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada*
[g] *Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH, USA*
[h] *Pediatric ENT Department, Hôpital Necker-Enfants Malades, AP-HP, Université Paris Descartes, Paris, France*
[i] *Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA*
[j] *Division of Otolaryngology, Children's Hospital of Philadelphia, Philadelphia, PA, USA*
[k] *Department of Otolaryngology, University of Iowa Hospitals & Clinics, Iowa City, IA, USA*
[l] *Department of Pediatric Otolaryngology, La Timone Children's Hospital, Aix-Marseille Université, Marseille, France*
[m] *University of Arkansas for Medical Sciences, Little Rock, AR, USA*
[n] *Our Lady's Children's Hospital, Crumlin, Dublin, Ireland*
[o] *evidENT, UCL Ear Institute, Royal National Throat, Nose and Ear Hospital, London, UK*
[p] *Department of Otolaryngology-Head and Neck Surgery, Children's Hospital at London Health Sciences Centre, University of Western Ontario, London, Ontario, Canada*
[q] *Department of Otolaryngology-Head and Neck Surgery, NYU Langone Medical Center, New York, NY, USA*
[r] *Great Ormond Street Hospital for Children, London, UK*
[s] *Department of Otolaryngology, Children's National Hospital, Washington, DC, USA*

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ABSTRACT

Objective: To provide recommendations for the comprehensive management of young infants who present with signs or symptoms concerning for laryngomalacia.
Methods: Expert opinion by the members of the International Pediatric Otolaryngology Group (IPOG).
Results: Consensus recommendations include initial care and triage recommendations for health care providers who commonly evaluate young infants with noisy breathing. The consensus statement also provides comprehensive care recommendations for otolaryngologists who manage young infants with laryngomalacia including: evaluation and treatment considerations for commonly debated issues in laryngomalacia, initial work-up of infants presenting with inspiratory stridor, treatment recommendations based on disease severity, management of the infant with feeding difficulties, post-surgical treatment management recommendations, and suggestions for acid suppression therapy.
Conclusion: Laryngomalacia care consensus recommendations are aimed at improving patient-centered care in infants with laryngomalacia.

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* Corresponding author at: Division of Otolaryngology-Head and Neck Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 Chicago Ave. Chicago, IL 60611, USA. Tel.: +312 227 6814; fax: +312 227 9414.
E-mail address: jmcarter@luriechildrens.org (J. Carter).

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Contents

1. Consensus objectives

To provide recommendations for the comprehensive management of young infants who present with signs or symptoms concerning for laryngomalacia.

2. Target population

Pediatric patients with signs concerning for laryngomalacia.

3. Intended users

These consensus recommendations are intended to:

1. Provide initial care and triage recommendations for primary care practitioners and other health care providers who commonly evaluate young infants with noisy breathing.
2. Provide comprehensive care recommendations for otolaryngologists who manage young infants with laryngomalacia.

4. Methods

Expert opinion by the members of the International Pediatric Otolaryngology Group (IPOG). The mission of the IPOG is to develop expertise-based consensus recommendations for the management of pediatric otolaryngologic disorders with the goal of improving patient care. The consensus recommendations herein represent the second publication by the group.

4.1. Abbreviations

AP, anterior and posterior; CXR, chest x-ray; FEES, fiberoptic endoscopic evaluation of swallowing; FFL, flexible fiberoptic laryngoscopy; H2RA, histamine-2 blocker; IPOG, International Pediatric Otolaryngology Group; MRI, magnetic resonance imaging; PPI, proton pump inhibitor; VFSS, video fluoroscopic swallow study.

5. Recommendations and justification

The recommendations are outlined in the following appendices

- ***Section 1:*** evaluation and treatment considerations
- ***Section 2:*** initial presentation algorithm
- ***Section 3:*** comprehensive care algorithm
- ***Section 4:*** management of the difficult to feed infant with laryngomalacia
- ***Section 5:*** post-surgical treatment algorithm
- ***Section 6:*** recommendations for acid suppression therapy

6. Disclaimer

Members of the International Pediatric ORL Group (IPOG) prepared this report. Consensus recommendations are based on the collective opinion of the members of this group. Any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual patient and institutional circumstances.

6.1. **Section 1:** *evaluation and treatment considerations*

The members of the IPOG identified five frequently debated evaluation and treatment considerations in the management of laryngomalacia. Variation in practice among the current group members remains, and the purpose of this section is to provide a list of reasonable options based on expert opinion (Table 1).

6.2. **Section 2:** *initial presentation algorithm*

The initial presentation algorithm is designed to guide the initial evaluation of the infant presenting with inspiratory stridor. This may vary depending on what type of medical care setting the infant presents in. Urgency of referral to an otolaryngologist is guided by severity of disease. Those with more severe disease may warrant expedited referral and those who have significant apnea/desaturations and/or inability to feed may warrant inpatient admission. Those infants who may be aspirating and/or have pulmonary disease may benefit from chest x-ray to further evaluate this. Flexible fiberoptic laryngoscopy (FFL) by an otolaryngologist is important to confirm the diagnosis. Those infants whose laryngoscopy findings are not commensurate with the severity of their symptoms may benefit from airway films to screen for a secondary airway lesion. Further recommendations are detailed in Fig. 1.

6.3. **Section 3:** *comprehensive care algorithm*

The algorithm in Fig. 2 was designed to guide treatment for the infant that has been diagnosed with laryngomalacia, confirmed by FFL. This algorithm stratifies management decisions based on disease severity. The group suggests that the provider should recognize the presence of co-morbidities (see Fig. 2) that may lead to suboptimal outcomes. Additionally, supraglottoplasty should be carefully considered in those with neurologic disease whose aspiration could

Table 1
Frequently debated evaluation and treatment considerations.

Question	
1. What findings on initial presentation should prompt a more urgent evaluation by an otolaryngologist?	• Apnea • Tachypnea • Cyanosis • Failure to thrive • Difficult to feed despite acid suppression/texture modification • Aspiration/pneumonia • Cor pulmonale
2. Should I treat laryngomalacia empirically with acid suppression?	• Yes, if child having feeding and/or respiratory difficulties • Consider observation in those infants with mild respiratory symptoms and are gaining weight appropriately • Can use either step-up or step-down methodology (see Section 6) • Recommend weaning acid suppression based on symptoms vs. stopping abruptly • Consider GI referral for concurrent management
3. Should I formally assess the infant's swallow?	• Consider feeding/swallow evaluation and diet modification in cases where there is cough, choking, regurgitation, feeding difficulty, no weight gain, or failure to thrive • Strongly consider evaluation in children with evidence of aspiration or those with neurologic disease • Consider evaluation by either/both video fluoroscopic swallow study (VFSS) and/or fiberoptic endoscopic evaluation of swallowing (FEES). Assessment in conjunction with feeding therapy may aid diagnostic accuracy and feeding recommendations • Consider acid suppression in patients with laryngeal penetration and/or aspiration on swallow evaluation
4. What other consultations should I consider for the infant with severe disease?	• Pulmonary evaluation if disease on imaging or symptoms of asthma/reactive airway disease/chronic lung disease • Consider polysomnography or home oximetry monitoring if significant apnea • Cardiac consultation if heart disease suspected • GI evaluation if refractory to acid suppression therapy • Neurology and/or brain MRI if neurologic disease suspected (i.e. physical findings of hypotonia, aspiration, pooled/frothy secretions on endoscopy) to rule out CNS lesion, brainstem compression, and Chiari malformation • Genetics evaluation for those with craniofacial dysmorphism or severe disease • Craniofacial team evaluation for those with craniofacial anomalies
5. What assessment should be done for persistent symptoms after supraglottoplasty?	• Consider aerodigestive evaluation including pH/impedance probe to rule out persistent reflux, esophageal biopsies to rule out eosinophilic esophagitis, pulmonary evaluation to optimize respiratory function and assess chronic lung disease if present. • Consider polysomnography in patients with oxygen desaturations or signs of apnea • Consider gastrostomy tube and/or fundoplication for patients with esophageal reflux not managed on maximal medical therapy • Consider neurology and/or MRI brain if neurologic disease suspected • Consider tracheostomy in patients with multiple co-morbidities or synchronous airway lesions

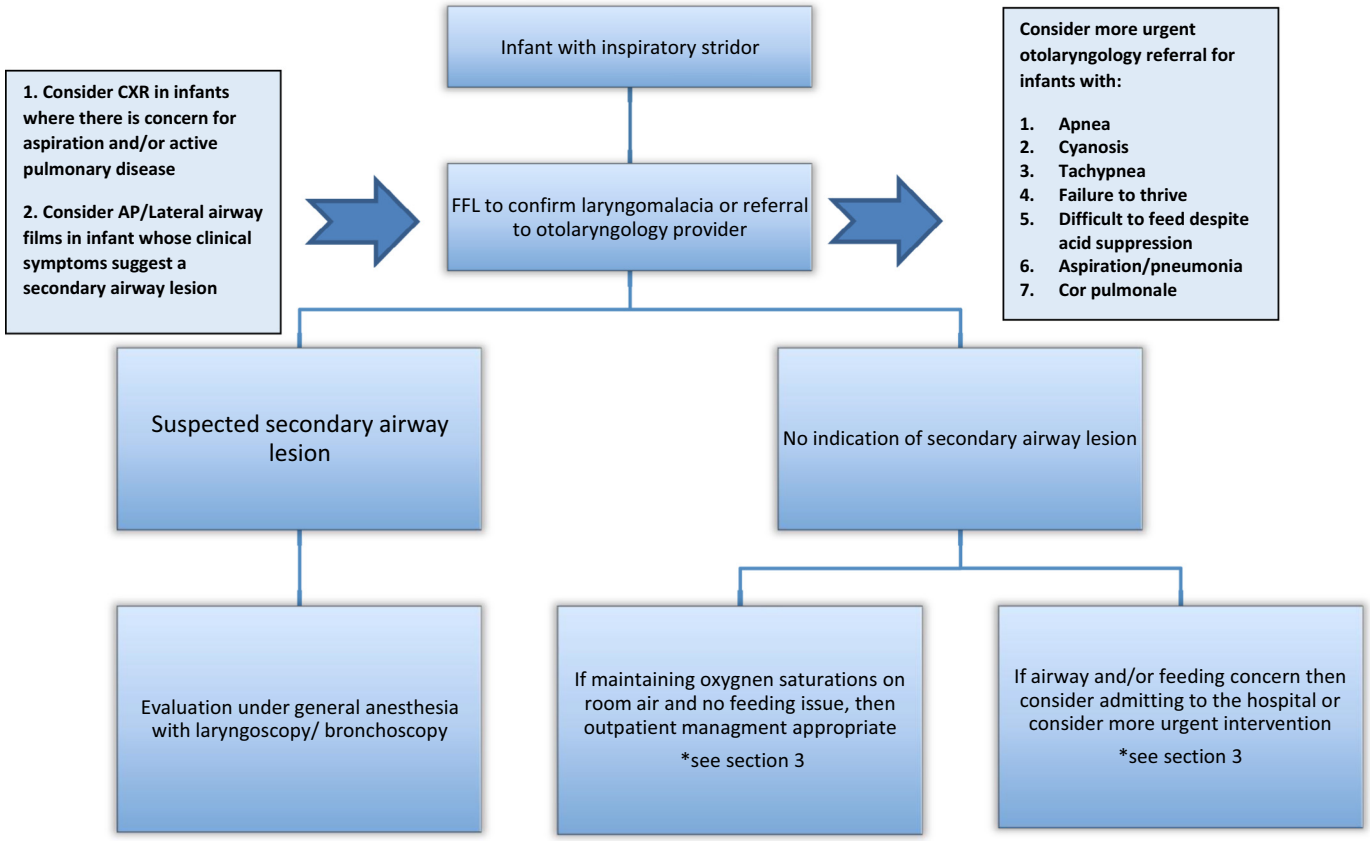

Fig. 1. Initial presentation algorithm.

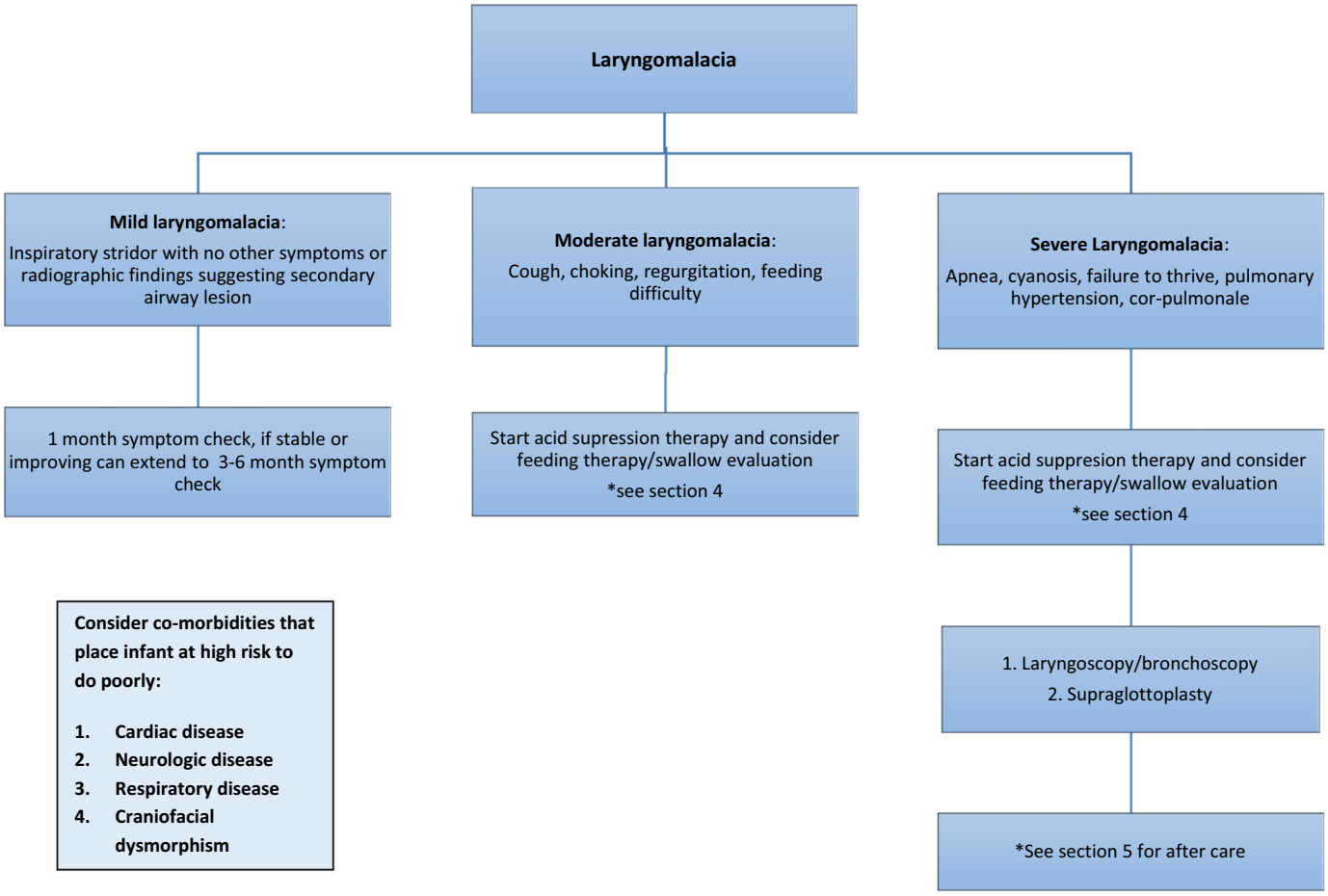

Fig. 2. Comprehensive care algorithm.

be made worse by surgery. Variation in practice among the current group members remains, and the purpose of this section is to provide a list of reasonable options based on expert opinion.

6.4. **Section 4:** *management of the difficult to feed infant with laryngomalacia*

This algorithm in Fig. 3 outlines a guide for managing infants who have been diagnosed with laryngomalacia and are having difficulty with effectively and/or safely feeding. The algorithm may be best performed in conjunction with feeding or speech therapy services when available to guide feeding recommendations and therapy (texture modification, bottle pacing, augmenting feeding schedule, etc.). Chest x-ray may be indicated in the infant if there are signs of respiratory compromise. Aspiration, pooling of secretions, and decreased supraglottic sensation may be seen during endoscopy in the setting of uncontrolled laryngopharyngeal reflux or neurologic disease. Persistence of symptoms despite maximal reflux suppression, especially in infants with hypotonia, should prompt work-up for neurologic causes prior or concurrent to surgical management. Neurologic disease is not a contraindication to supraglottoplasty, but the benefit of improving airway obstruction must be weighed with the risk of worsening aspiration in this scenario. Variation in practice among the current group members remains, and the purpose of this section is to provide a list of reasonable options based on expert opinion.

6.5. **Section 5:** *post-surgical treatment algorithm and persistent laryngomalacia*

The algorithm displayed in Fig. 4 is intended to guide management in infants who have undergone supraglottoplasty and is targeted toward those who have persistent laryngomalacia despite surgery. Time course for follow-up is variable among providers and is dictated by the severity of persistent symptoms in the patient. Persistent laryngopharyngeal reflux or undiagnosed eosinophilic esophagitis may drive persistent laryngeal edema leading to continued laryngomalacia. Confirming the presence or absence of obstructive sleep apnea may drive decision making toward surgical management vs. observation. Identifying and optimizing cardiac, neurologic, and pulmonary co-morbidities is paramount in managing the infant with persistent symptoms after supraglottoplasty, especially before considering revision surgery. Patients with multiple severe comorbidities or multilevel airway obstruction are less likely to succeed with supraglottoplasty alone and may require tracheostomy. Again, variation in practice among the current group members remains, and the purpose of this section is to provide a list of reasonable options based on expert opinion.

6.6. **Section 6:** *recommendations for acid suppression therapy*

Fig. 5 provides a “step-up” vs. a “step-down” regimen for managing acid suppression therapy. In a “step down” regimen, therapy

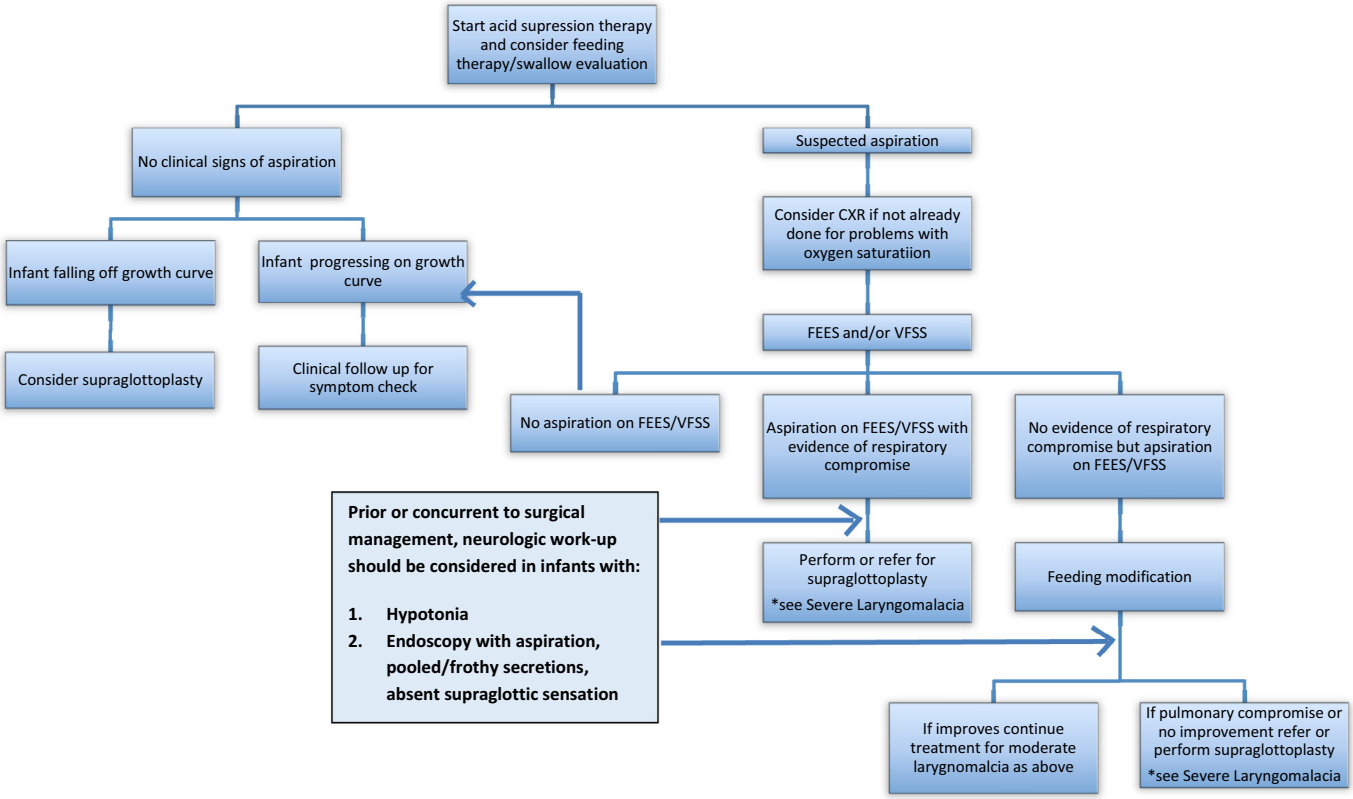

Fig. 3. Management of the difficult to feed infant with laryngomalacia.

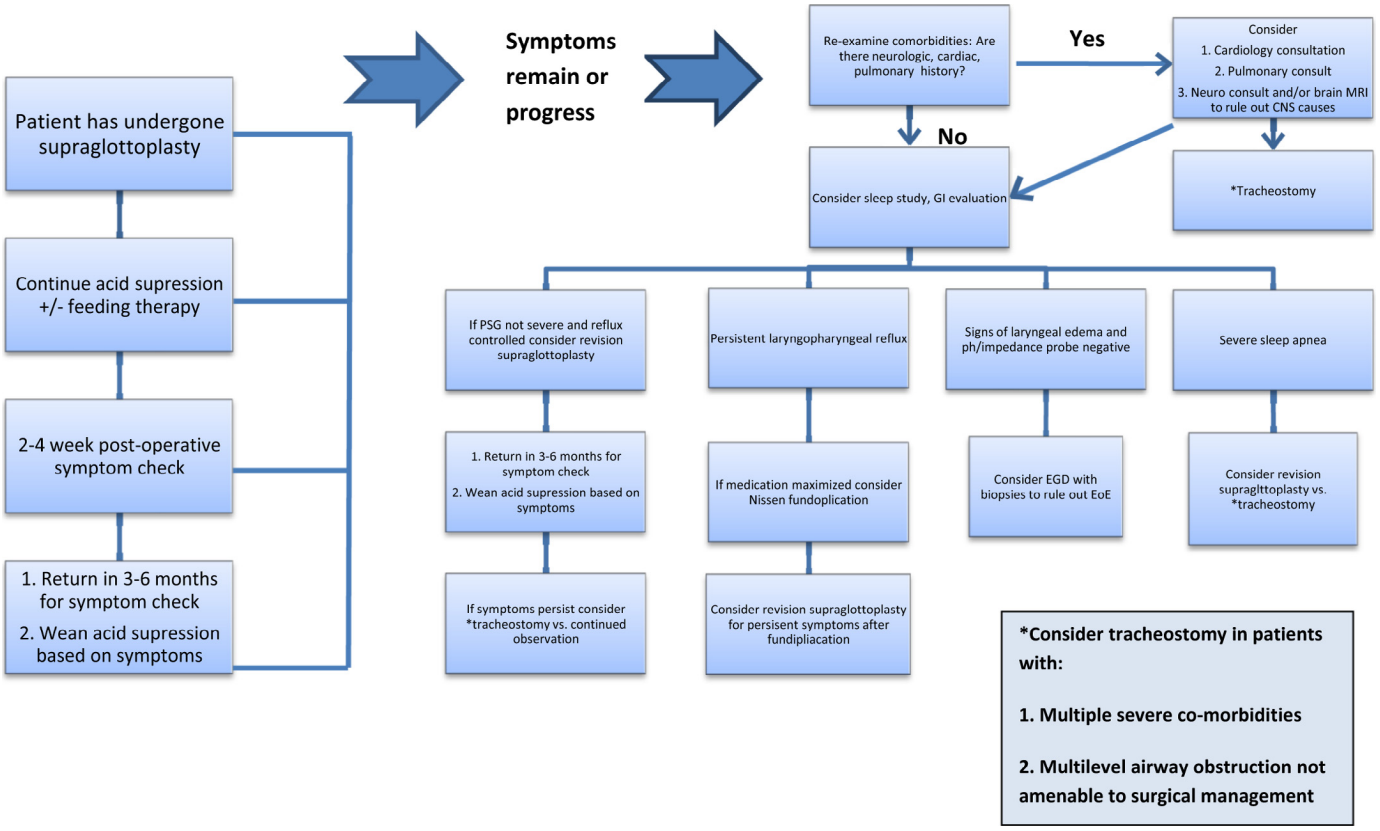

Fig. 4. Post-surgical treatment algorithm and persistent laryngomalacia.

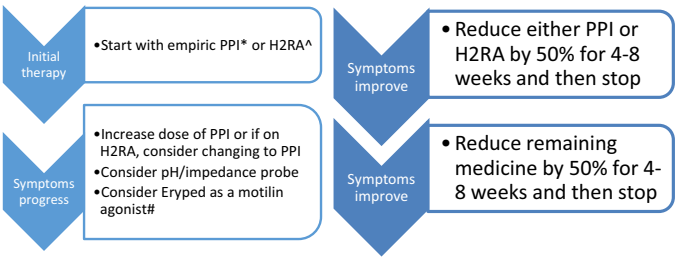

Fig. 5. Recommendations for acid suppression therapy.
* Preferred approach for children and adolescents, particularly when used empirically; QD dosing initially – AM dosing on empty stomach provides best acid suppression because H^+ pump is less activated nocturnally, use PM dosing for nocturnal symptoms.
^ Decrease acid production by 40–60% and well tolerated; use mandated before PPI trial by some insurance carriers; preferred for infants with non-life-threatening symptoms as H2RAs clinically better tolerated than PPIs.
# Low dose Erypred 200 (200 mg/5 ml) or Erypred 400 (400 mg/5 ml) at 1–2 mg/kg/dose, 15 min before meals, up to 6× per day as a motilin agonist to increase smooth muscle contraction.

can be started with both a proton pump inhibitor (PPI) and a histamine-2 blocker (H2RA) and then weaned to a single therapy if the patient improves. Conversely, the infant can be started conservatively on a single therapy and "stepped-up" to dual acid suppression if symptoms are not controlled. We suggest maintaining therapy for at least 3 months after initiation and a wean should not be considered until a diet can be safely tolerated from an aspiration standpoint. It should be noted that no PPI is FDA approved for use in patients younger than 1 year of age and debate exists concerning the efficacy of PPIs in infants. Consider gastroenterology evaluation and/or pH/impedance probe testing in those that are refractory to therapy. Additionally, prokinetic agents such as erythromycin ethylsuccinate (Eryped) can be considered to improve gastrointestinal motility in refractory cases. There is great variation in practice among the current group members, and the purpose of this section is to provide reasonable options to guide the practitioner when using acid suppression in the setting of laryngomalacia.

Conflict of interest

None.

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The Laryngoscope

Surveillance Direct Laryngoscopy and Bronchoscopy in Children With Tracheostomies

Amy Richter, MD; Diane Wenhua Chen, BS; Julina Ongkasuwan, MD, FAAP, FACS

Objectives/Hypothesis: To determine utility of surveillance direct laryngoscopy and bronchoscopy (DLB) in children with chronic tracheostomies by examining the frequency of operative intervention in children undergoing an annual DLB.

Study Design: Retrospective medical record review and analysis of operative findings and interventions.

Methods: A retrospective chart review was conducted of all children with tracheostomies who underwent surveillance DLB between 2003 and 2012 at a tertiary children's hospital. Charts were reviewed for demographics, indication for tracheotomy, symptoms prior to DLB, dates of DLB, and operative findings and interventions.

Results: A total of 489 patients underwent 1,094 DLBs. Two hundred fifty-three DLBs (23%) were accompanied by preprocedural symptoms including bleeding; increased secretions; infection; and changes in ventilation requirement, swallow, or voice. Six hundred nineteen procedures (58%) required 817 interventions. Common interventions performed included debridement of granulation tissue (41%), tracheostomy tube exchange (27%), and subglottic dilation (10%). The presence of preprocedural symptoms and indication for tracheostomy did not predict need for intervention during DLB ($P > .05$).

Conclusions: In pediatric tracheostomy patients undergoing surveillance DLB, most procedures (58%) required operative intervention for airway optimization. These data support our current practice of yearly surveillance DLB in asymptomatic pediatric tracheostomy patients and aim to facilitate the development of clinical practice guidelines regarding chronic tracheostomy care in pediatric patients.

Key Words: Pediatric tracheostomy, direct laryngoscopy and bronchoscopy, surveillance, suprastomal granulation.

Level of Evidence: 4

***Laryngoscope*, 125:2393–2397, 2015**

INTRODUCTION

Tracheotomy is a common procedure in otolaryngology. Indications for tracheostomy tube placement and the associated morbidity and mortality of adult and pediatric tracheostomies have been well documented. Compared to adult tracheostomies, pediatric tracheostomies are associated with greater risk of complications with higher morbidity and mortality.[1] Children with prolonged tracheostomy are at elevated risk for respiratory infections, airway bleeding, accidental decannulation, and death.[1–3] Screening direct laryngoscopy and bronchoscopy (DLB) may be used to detect lesions that may lead to eventual complications or decrease time to decannulation.[4] However, there is a general paucity of literature investigating current practice patterns for surveillance of patients with chronic tracheostomies, particularly in the pediatric population.

Practice patterns for screening endoscopy vary between institutions. Indications for DLB include bleeding, difficult tracheostomy tube changes, ventilator dependence, poor phonation, anatomic abnormalities, and preparation for laryngotracheal reconstruction.[4,5] A survey of pediatric otolaryngologists found that most practitioners perform at least yearly surveillance endoscopy in children under age 2 years, but many only perform endoscopy on patients prior to decannulation or in those experiencing difficulties.[6] Surveillance DLB in asymptomatic patients with chronic tracheostomies may result in documentation of an improved airway or no change in airway status, diagnosis of new tracheal lesion, including development of suprastomal granuloma, need for change in tracheostomy tube size, or decannulation. The goal of surveillance DLB is to optimize the airway, reduce the risk of accidental decannulation, and facilitate easier tracheostomy tube changes so that caregivers can manage the airway more easily at home. However, surveillance DLB is not without risks. These risks include the cardiopulmonary risks of general anesthesia, airway and oral cavity instrumentation, and prolonged hospitalization.

Despite the lack of current clinical practice guidelines for surveillance DLB, most practitioners agree that monitoring of children with tracheostomies in inpatient and outpatient settings is necessary to prevent tracheostomy-related complications.[4,6] In a survey of members of the American Academy of Otolaryngology–Head and Neck Surgery Foundation, most members agreed that a clinical practice guideline regarding tracheostomy care would be useful (54%).[7] Standardization of post-tracheostomy care in pediatric patients may help to improve the quality of

From the Bobby R. Alford Department of Otolaryngology–Head and Neck Surgery (A.R., J.O.), Baylor College of Medicine (D.W.C.), Texas Children's Hospital, Houston, Texas, U.S.A.

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Send correspondence to Julina Ongkasuwan, MD, 6701 Fannin, Suite 640, Houston, TX 77030. E-mail: julinao@bcm.edu

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TABLE I.
Demographic Data.

	Patients, No. (%), N = 489
Patients	
Male	279 (57%)
Female	210 (43%)
Indications for tracheostomy	
Congenital anomaly	240 (49%)
Neuromuscular disease	93 (19%)
Bronchopulmonary dysplasia	83 (17%)
Trauma	29 (6%)
Congenital anomaly and bronchopulmonary dysplasia	44 (9%)
Premature	200 (41%)

patient care, potentially reduce the risk of unnecessary procedures, and decrease the economic burden of chronic tracheostomy care. This study investigates the utility of surveillance DLB in pediatric tracheostomy patients to help facilitate the development of clinical practice guidelines regarding chronic tracheostomy care.

MATERIALS AND METHODS

Data Collection

The current practice of nine pediatric otolaryngologists at Texas Children's Hospital (TCH) is to perform annual surveillance DLB on all pediatric patients with tracheostomies. A retrospective chart review was conducted of all of the children <18 years of age with tracheostomies who underwent surveillance DLB between 2003 and 2012 at TCH, an academic tertiary referral center. Patients with existing tracheostomies who transferred care to TCH and underwent surveillance DLB at TCH were included in the study. The institutional review board at Baylor College of Medicine approved this study. Charts were reviewed for demographic data, date of tracheostomy, indication for tracheostomy, symptoms prior to surveillance DLB, dates of surveillance DLB, operative findings, and interventions. Indications for tracheostomy were categorized as congenital anomaly, neuromuscular disease, bronchopulmonary dysplasia, and trauma. Congenital anomalies included craniofacial dysmorphism, laryngeal anomalies, laryngomalacia, subglottic stenosis, hemangioma, tracheal anomaly, and other congenital syndromes. Interventions included debridement of suprastomal granulation tissue, change in tracheostomy tube size or type, tracheal dilation, and tracheostomy stoma revision. Charts were also reviewed for plans for decannulation or laryngotracheal reconstruction following surveillance DLB. Patients with incomplete medical records were excluded from this study. Those patients with subglottic hemangioma and recurrent laryngeal papillomatosis were excluded from this study, as these patients require serial DLB with planned intervention. Patients who underwent DLB in conjunction with a planned procedure, including intraoperative decannulation, laser cordotomy, or laryngotracheal reconstruction, were also excluded.

Surgical Technique

Yearly surveillance bronchoscopies are performed in all children with chronic tracheostomies. Patients were taken to the operating room, and general anesthesia was induced via tracheostomy, and spontaneous ventilation maintained. All patients received a dose of intravenous steroids. Direct laryngoscopy was performed with application of topical anesthesia to the glottis, and rigid tracheoscopy and bronchoscopy was performed. The tracheostomy tube was removed, allowing the surgeon to thoroughly examine the entire airway, supraglottis, glottis, subglottis, trachea, carina, and mainstem bronchi with photodocumentation of all subsites. When necessary, debridement of suprastomal or peristomal granulation tissue was performed with a combination of techniques depending on surgeon preference, including sharp dissection or microdebrider. Similarly, there were several techniques used for dilation of subglottic stenosis when indicated, including balloon dilation, microlaryngoscopy and CO_2 laser, serial dilation with rigid bronchoscopes, or a combination of techniques. The tracheostomy tube may have been exchanged with one of different type or size, depending on intraoperative findings. The patient was allowed to recover in the postanesthesia care unit and was typically discharged home the same day depending on the intraoperative findings and stability of the airway. Caregivers were provided photodocumentation of intraoperative findings, and outpatient follow-up was typically scheduled for 4 to 6 weeks in uncomplicated cases.

Data Analysis

Data analysis was performed with assistance from the Texas Children's Hospital Outcomes and Impact Service. Continuous variables were reported as medians with a minimum-maximum range or means with standard deviation (SD). Categorical variables were reported with frequencies and percentages. Statistical analysis was performed using logistic regression and multivariate analysis.

RESULTS

A total of 489 patients underwent 1,094 screening DLBs with a mean 2.3 procedures per patient (range, 1–14). Two hundred seventy-nine patients (57%) were males, and the mean age was 5.1 years (SD 4.9 years). The most common indication for tracheostomy was congenital anomaly (49%), followed by neuromuscular disease (19%), isolated bronchopulmonary dysplasia (17%), and trauma (6%). Nine percent of patients had congenital anomalies with bronchopulmonary dysplasia (9%). Forty-one percent of patients were premature (Table I). The mean interval time between surveillance DLB was 430 days. Two hundred fifty-three DLBs (23%) were accompanied by preprocedural symptoms. The most common complaint prior to DLB was increased tracheal secretions (78%). Other preoperative symptoms included bleeding from tracheostomy (8%), intermittent difficulties ventilating (7%), voice complaints (1%), aspiration of secretions (1%), tracheitis (1%), dysphagia (1%), and stoma erythema (1%) (Table II, Fig. 1).

There were a total of 619 procedures that required 817 interventions, accounting for 58% of the total number of DLBs. Two hundred sixty-six patients (54%) required an intervention during surveillance DLB. The most common intervention performed was debridement of suprastomal granulation tissue (41%), followed by tracheostomy tube exchange (27%), tracheal dilation (10%), and stoma revision (6%) (Table III, Fig. 1). Of the patients who had tracheostomy tube changes, 47% of

TABLE II.
Surveillance DLB Preoperative Findings.

	No. of Patients (%)
Surveillance DLB, n = 1,094	
Mean no. of DLBs per patient, median (range)	2.2, 2 (1–14)
No. of DLBs requiring intervention	639/1094 (58%)
No. of DLBs with preoperative symptoms	253/1094 (23%)
No. of DLBs with preoperative symptoms that required intervention	137/639 (54%)
No. of patients requiring multiple DLBs	156/489 (32%)
Preoperative symptoms, n = 253	
Tracheal secretions	197 (78%)
Bleeding from tracheostomy	20 (8%)
Difficulties with ventilation	17 (7%)
Voice complaints	2 (1%)
Aspiration of secretions	2 (1%)
Air leak surrounding tracheostomy tube	3 (1%)
Tracheitis	3 (1%)
Dysphagia	2 (1%)
Erythema surrounding tracheostomy stoma	3 (1%)

DLB = direct laryngoscopy and bronchoscopy.

patients had an increase in tracheostomy tube size, 51% of patients underwent decrease in tracheostomy tube size, and 2% of patients had tracheostomy tube exchange for a different style of tube in the same diameter. If a patient underwent tracheal dilation, balloon dilation was the most common technique used (50%), followed by use of microlaryngoscopy and carbon dioxide (CO_2) laser (23%), and serial dilation using rigid bronchoscopes (20%). The remaining tracheal dilations were performed using a combination of stellate CO_2 laser incisions with balloon or rigid dilation (7%). For those patients who presented with symptoms prior to DLB, 54% of those DLB required an intervention. This was not statistically significant compared to patients who were asymptomatic (77% of all patients) prior to surveillance DLB ($P > .05$). In addition, age at tracheostomy, duration of tracheostomy, interval time to DLB, prematurity, and indication for tracheostomy did not predict need for intervention ($P > .05$). There were no perioperative complications. One hundred sixty-seven patients (34%) were eventually decannulated, and 43 patients (9%) underwent laryngotracheal reconstruction.

DISCUSSION

There is no current consensus on endoscopic surveillance of children with chronic tracheostomies. At our institution, asymptomatic children with chronic tracheotomies undergo yearly surveillance DLB. The most common indication for tracheostomy was upper airway obstruction due to congenital anomaly and airway obstruction, including craniofacial dysmorphism, subglottic stenosis, vocal fold paralysis, and laryngomalacia. These findings are consistent with current literature that demonstrates a trend in indications for pediatric tracheostomies due to airway obstruction, rather than prolonged mechanical ventilation support.[2,8–10] Forty-one percent of patients in our study were premature, which is consistent with other international case studies.[11]

All patients with chronic tracheostomies at our institution are scheduled for yearly endoscopic evaluation with rigid bronchoscopy. Twenty-three percent of bronchoscopies were preceded by symptoms that were reported at the preoperative evaluation. The most common symptom was presence of tracheal secretions, intermittent difficulties with ventilation, voice complaints, tracheitis, dysphagia, or erythema surrounding the stoma. Of those patients with complaints prior to surveillance DLB, 54% required operative intervention compared to 58% of the entire cohort. This suggests that preoperative symptoms are not predictive for need for operative intervention. Over half of these children in this study, 58%, required operative intervention with debridement of granulation tissue, airway dilation, or tracheostomy tube exchange. This suggests that children are frequently asymptomatic from suprastomal granulation tissue, airway stenosis, or inappropriate tracheotomy tube size.

By addressing potential airway complications in advance, we hope to reduce the morbidity and mortality related to pediatric tracheostomies. According to a survey of the American Society of Pediatric Otolaryngology, a large portion (41%) of physicians only perform endoscopy on patients with difficulties ventilating.[6] Our study suggests this practice may overlook patients with asymptomatic suprastomal granulomas that may benefit from operative intervention to optimize the airway and prevent more dangerous complications in the future. The complication rate in tracheostomies ranges from 13% to 88%, and late complications are more common than perioperative complications related to tracheostomy.[1–3] Late complications include accidental decannulation, tube occlusion, suprastomal granulation, and tracheitis, which may be increased in patients with a history of prematurity and low body weight at the time of tracheotomy.[9,12,13]

Yearly surveillance DLB is not without risks, as the anesthetic risk and economic burden cannot be overlooked. The variability in current care practices according to institutional practices or geographic influence may affect reimbursement and variable quality in patient care.[7] This study demonstrates an opportunity to develop care practice guidelines for long-term surveillance of children with chronic tracheostomies to optimize patient care and reduce healthcare costs.

The American Thoracic Society (ATS) published consensus clinical practice guidelines for management of pediatric tracheostomies, and recommended routine rigid or flexible bronchoscopy every 6 to 12 months and further research to validate this recommendation.[4] In our study, the presence of preoperative symptoms, age at tracheostomy, prematurity, and presence of preoperative symptoms did not predict need for intervention. Based on this finding, the standard of care at our institution is to perform yearly surveillance DLB on all asymptomatic

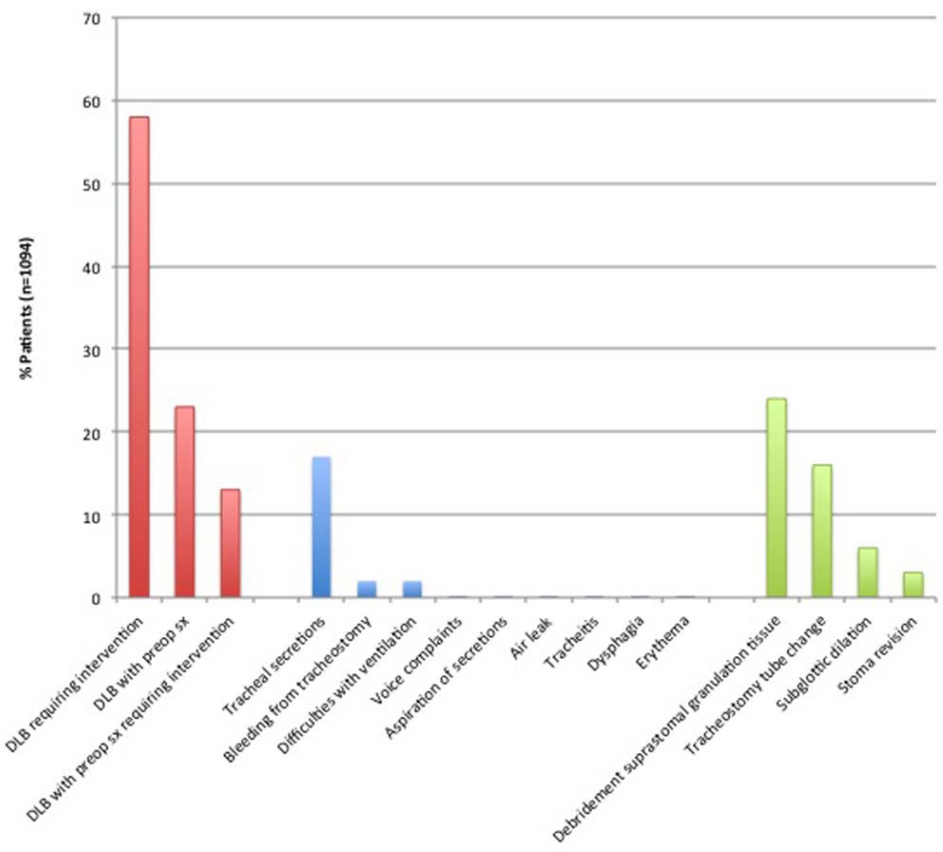

Fig. 1. Surveillance direct laryngoscopy and bronchoscopy (DLB) results. The percent of DLB requiring intervention, those with preoperative symptoms (sx), and those with symptoms requiring intervention are presented in red. The percent of patients with preprocedure symptoms are presented in blue. The operative interventions are presented in green. All percentages are reported with the total number of patients (N = 1,094) as the denominator. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

patients with chronic tracheostomies. However, this study is limited by its retrospective, single-institution design; further research may corroborate the ATS guidelines to establish a standardized clinical pathway for the care of pediatric tracheostomies. Further investigations are needed for multi-institutional prospective studies to include randomization to time to surveillance DLB interval, risk stratification, and cost analysis.

TABLE III.
Surveillance Direct Laryngoscopy and Bronchoscopy Operative Interventions.

	No. of Patients (%), n = 817
Intervention	
Debridement of suprastomal granulation tissue	334/817 (41%)
Tracheostomy tube change	221/817 (27%)
Subglottic dilation	83/817 (10%)
Balloon dilation	42/83 (50%)
Microlaryngoscopy and CO_2 laser excision	19/83 (23%)
Serial dilation with rigid bronchoscopes	16/83 (20%)
Laser and dilation with balloon or rigid bronchoscope	6/83 (7%)
Tracheostomy stoma revision	50/817 (6%)
Decannulation	167/489 (34%)
Laryngotracheal reconstruction	43/489 (9%)

CONCLUSION

In pediatric tracheostomy patients undergoing surveillance DLB, most procedures (58%) required operative intervention for airway optimization. These data support our current practice of yearly surveillance DLB in asymptomatic pediatric tracheostomy patients and our aim to facilitate development of clinical practice guidelines regarding chronic tracheostomy care in pediatric patients.

Acknowledgments

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BIBLIOGRAPHY

1. Goldenberg D, Ari EG, Golz A, Danino J, Netzer A, Joachims HZ. Tracheotomy complications: a retrospective study of 1130 cases. *Otolaryngol Head Neck Surg* 2000;123:495–500.
2. Mahadevan M, Barber C, Salkeld L, Douglas G, Mills N. Pediatric tracheotomy: 17 year review. *Int J Pediatr Otorhinolaryngol* 2007;71:1829–1835.
3. Tantinikorn W, Alper CM, Bluestone CD, Casselbrant ML. Outcomes in pediatric tracheotomy. *Am J Otolaryngol* 2003;24:131–137.

4. Sherman JM, Davis S, Albamonte-Petrick S, et al. Care of the child with a chronic tracheostomy: this official statement of The American Thoracic Society was adopted by the ATS Board of Directors. *Am J Respir Crit Care Med* 2000;161:297–308.
5. Lawrason A, Kavanagh K. Pediatric tracheotomy: are the indications changing? *Int J Pediatr Otorhinolaryngol* 2013;77:922–925.
6. Kraft S, Patel S, Sykes K, Nicklaus P, Gratny L, Wei J. Practice patterns after tracheotomy in infants younger than 2 years. *Arch Otolaryngol Head Neck Surg* 2011;137:670–674.
7. Zhu H, Das P, Brereton J, Roberson D, Shah RK. Surveillance and management practices in tracheostomy patients. *Laryngoscope* 2012;122: 46–50.
8. Carron JD, Derkay CS, Strope GL, Nosonchuk JE, Darrow DH. Pediatric tracheostomies: changing indications and outcomes. *Laryngoscope* 2000;110:1099–1104.
9. Ward RF, Jones F, Carew JF. Current trend in pediatric tracheotomy. *Int J Pediatr Otorhinolaryngol* 1995;32:233–239.
10. Ozmen S, Ozmen O, Unal O. Pediatric tracheotomies: a 37-year experience in 282 children. *Int J Pediatr Otorhinolaryngol* 2009;7:959–961.
11. De Trey L, Niedermann E, Ghelfi D, Gerber A, Gysin C. Pediatric tracheostomy: a 30-year experience. *J Pediatr Surg* 2013;48:1470–1475.
12. Kenna MA, Reilly JS, Stool SE. Tracheotomy in the preterm infant. *Ann Otol Rhinol Laryngol* 1987;96:68–71.
13. Carr MM, Poje CP, Kingston L, Kielma D, Heard C. Complications in pediatric tracheostomies. *Laryngoscope* 2001;111:1925–1928.

The Laryngoscope

Transoral Robotic Surgery for Upper Airway Pathology in the Pediatric Population

Carlton J. Zdanski, MD; Grace K. Austin, MD; Jonathan M. Walsh, MD; Amelia F. Drake, MD; Austin S. Rose, MD; Trevor G. Hackman, MD; Adam M. Zanation, MD

Objectives/Hypothesis: The purpose of this study is to present one of the largest case series of pediatric transoral robotic surgery (TORS) in the upper airway demonstrating a wide range of ages and indications.

Study Design: A retrospective case series at an academic tertiary referral center from August 2010 to September 2014.

Methods: The da Vinci surgical robot (Intuitive Surgical, Inc., Sunnyvale, CA) was used on 16 pediatric patients for 18 procedures. A variety of upper airway pathologies and reconstructions in children with a wide range of ages and weights were treated. No lingual tonsillectomies or base-of-tongue reductions were included.

Results: Sixteen children (6 males) underwent 18 TORS procedures, including resection of hamartoma (n = 1), repair of laryngeal cleft (n = 7), removal of saccular cyst (n = 2), release of pharyngeal or esophageal strictures (n = 2), and excision of lymphatic malformations (n = 4). Patient ages ranged from 14 days to 15 years. There were no intraoperative complications. All patients had successful robotic access, and no patients had conversions to open or traditional endoscopic surgery. Hospital courses varied with duration ranging from 1 to 20 days. The median follow up was 22 months.

Conclusion: Applying TORS to the pediatric population can be feasible and safe for appropriate airway pathologies. Because many patients are small in size, there is inherent risk in using robotic instruments and scopes transorally. Pearls in this series include a standardized two-robot experienced attending team and longitudinal airway follow-up.

Key Words: Laryngeal cleft, saccular cyst, lymphatic malformation, pediatric airway, transoral robotic surgery (TORS).

Level of Evidence: IV.

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INTRODUCTION

Transoral robotic surgery (TORS) for use in the pediatric airway is a recent application of this technology. Within a few years of descriptions of TORS in adults for head and neck surgery, animal studies investigating the feasibility of pediatric applications were published.[1] It was first described in human pediatric patients by Rahbar et al. with a case series of five patients in 2007.[2] Since that time, there have been seven case reports and case series presented in the literature; the largest describes 16 patients who underwent lingual tonsillectomy.[3–9] The role of TORS in the pediatric airway is still evolving. As the technology and tools advance, the indications and applications of TORS in the pediatric airway are being developed. We present one of the largest case series of pediatric TORS, detailing our experience with a wide range of patient ages and pathologic processes. The purpose of this report is to illustrate the potential and feasibility of TORS in the pediatric airway and complex reconstructions.

MATERIALS AND METHODS

The da Vinci surgical robot (Intuitive Surgical, Inc., Sunnyvale, CA) was used on 16 pediatric patients for 18 procedures at the University of North Carolina, Chapel Hill, North Carolina, from August 2010 to September 2014. Patients with pharyngeal and laryngeal pathology requiring either endoscopic or open surgical treatment were offered TORS as an alternative treatment option. For vascular malformations, this was limited to lymphangiomas for this series. Arteriovenous malformations, venous malformations, and other vascular tumors were excluded from consideration.

The da Vinci surgical robot has been U.S. Food and Drug Administration-approved for resection of T1 and T2 oropharyngeal cancers. We applied robotic technology for off-label use in pediatric airway procedures. Patients and families were offered traditional approaches and were also informed of the off-label application of TORS. All consent forms clearly stated that the robot would be utilized. The procedures were also preauthorized for insurance coverage.

There are special considerations of the pediatric procedures. Because many patients are small in size, there is inherent higher risk in introducing and manipulating robotic instruments and scopes transorally compared to adult patients.

From the Department of Otolaryngology/Head and Neck Surgery, University of North Carolina Hospitals (C.J.Z., G.K.A., A.F.D., A.S.R., T.G.H., A.M.Z.), Chapel Hill, North Carolina; and the Department of Otolaryngology/Head and Neck Surgery, Johns Hopkins University (J.M.W.), Baltimore, Maryland, U.S.A.

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Send correspondence to Carlton J. Zdanski, MD, Associate Professor, Department of Otolaryngology/Head and Neck Surgery, University of North Carolina, 170 Manning Drive, CB 7070, Physician's Office Building, Room G-190, Chapel Hill, NC 27599-7070.
E-mail: carlton_zdanski@med.unc.edu

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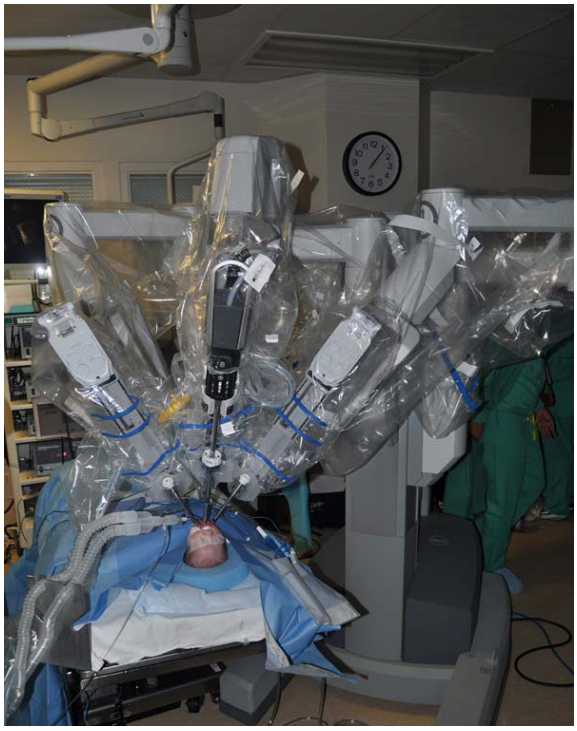

Fig. 1. Positioning of the robot and the patient. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

The operating room setup was similar to adult patients. All patients were placed in the supine position with the table top 180 degrees from the normal position; that is, the patient's head was placed at the foot of the bed. This allows for placement of the robot to be placed underneath the table and closer to the patient after rotating the bed (Fig. 1). The patients were induced by pediatric anesthesiologists, the airway was topically anesthetized with lidocaine, and the operating table was then rotated 90 degrees away from the anesthesiologist's field to deliver the patients toward the surgeon. The operating table is rotated a total of 90 degrees.

Direct laryngoscopy and bronchoscopy were performed prior to each procedure under the same anesthetic. When patients had existing tracheostomy tubes, these were replaced with laser-safe Jackson tracheostomy tubes for the duration of the procedure. In patients without tracheostomies, an appropriate laser-safe endotracheal tube (i.e., cuffless Mallinckrodt laser oral endotracheal tube, Magill tip; Covidien plc, Dublin, Ireland) was sized and placed when feasible.

A tooth guard was individually created and placed when teeth were present utilizing Aquaplast (Medline, Mundelein, IL). A variety of mouth gags were available for selecting appropriate fit. We found that a McIvor gag with a flat blade produced the best exposure of the posterior larynx for laryngeal cleft repair in most patients. A tongue stitch was utilized for retraction when a mouth gag was not necessary.

The articulating robotic arms were positioned intraorally with camera, typically utilizing a 30-degree anterior facing scope for hypopharyngeal and laryngeal pathology and a 0-degree scope for tongue base pathology. In all cases, 5-mm working ports and instruments were used.

There were two attending surgeons that were robot-credentialed during these cases. There is an internal hospital pathway for robotic surgery credentialing. Attending surgeons, as well as residents and fellows, have access to a robotic simulator and are at the console with simulation prior to participating in robotic surgery cases in general. However, the surgeons did not practice on a robot simulator for each patient immediately prior to surgery.

Two experienced robot-credentialed attending surgeons alternated positions between the robot console (i.e., the robotic surgeon) and the bedside (i.e., the bedside surgeon), as needed. A bedside surgeon participated in every case, utilizing a variety of standard laryngeal and pharyngeal surgical instruments including suction and cautery (Fig. 2). In addition, the bedside surgeon had the critical role of protecting the patient and maintaining the airway during the procedure.

RESULTS

Sixteen children (6 males) underwent 18 TORS procedures including resection of hamartoma (base of tongue) (n = 1), repair of laryngeal cleft (n = 7) (Fig. 3), removal of saccular cyst (n = 2), release of pharyngeal or esophageal strictures (n = 2), and excision of lymphatic malformations in the base of tongue (n = 1) or hypopharynx/supraglottis (n = 3) (Table I). Of the patients with lymphatic malformations, two patients received subsequent TORS procedures. Patients with lingual tonsillectomies or tongue base reductions were not included. The median follow-up from surgery was 22 months (range, 56 days to 44 months).

At the time of surgery, the median age of children was 4 years old (range, 14 days to 15 years). The median weight was 18.4 kg (range, 2.5 kg to 93.7 kg). The youngest patient was 14 days old and weighed 3.7 kg. The smallest patient was 26 days old and weighed 2.5 kg. Both had saccular cysts and successfully underwent robotic-assisted removal of these lesions (Fig. 4).

The median operating room (OR) elapsed time (time from patient entering the OR room to exiting the OR room, including time of anesthesia care and robot setup) was 3 hours, 17 minutes (range: 2 hours, 27 minutes to 5 hours, 37 minutes). The median surgery elapsed time (time for surgical procedure including laryngoscopy and bronchoscopy) was 2 hours and 24 minutes (range: 1 hour, 3 minutes to 4 hours, 38 minutes). The median setup time (patient release from anesthesia team to time out) was 8 minutes. The docking time, that is, the time used to position the robot, could not be determined or calculated from the retrospective review of the data.

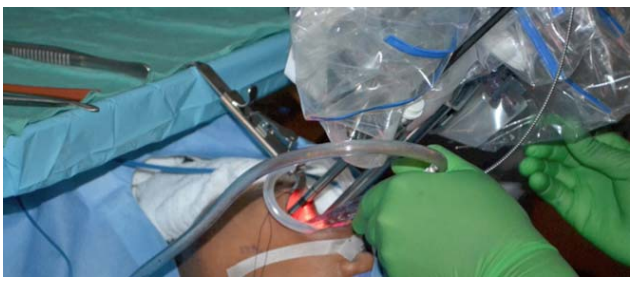

Fig. 2. The bedside surgeon utilizes standard laryngeal and pharyngeal surgical instruments, as well as having the critical role of protecting the patient and the airway. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

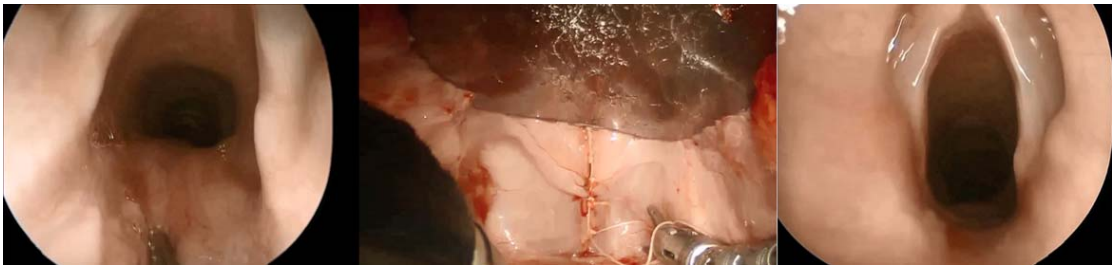

Fig. 3. Laryngeal cleft repair. (A) Palpation of the laryngeal cleft prior to repair; (B) close-up intraoperative view of the laryngeal cleft closure during repair; (C) intraoperative view of the luminal side of laryngeal cleft after repair. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

There were no intraoperative complications. The overall TORS completion rate was 100%. No procedures were converted to open or traditional endoscopic surgery. Estimated blood loss ranged from 0 to 25 mL.

The majority of patients had high-grade American Society of Anesthesiologists (ASA) classification: ASA I (n = 2), ASA 2 (n = 1), ASA 3 (n = 7), and ASA 4 (n = 6) (Table I). The reason many patients in this series had a high-grade ASA classification is related to their complex medical conditions, but ASA grade was not a criterion for eligibility. Three of 16 patients had a tracheostomy tube in place prior to the operative case. None of the patients required a new tracheostomy intraoperatively or postoperatively. Five patients were kept intubated after the procedure and were observed in the pediatric intensive care unit (PICU) (1–4 days) for protection of the airway.

There were three postoperative complications. The first patient was a 5-year old girl, ASA 3, who had a type 1 laryngeal cleft and sleep-disordered breathing (patient 8). On polysomnogram, the patient had an apnea-hypopnea index of 0.3 (no obstructive apneas, 2 central apneas, and 2 hypopneas). The patient was not treated surgically for the sleep-disordered breathing. The patient underwent a TORS-assisted laryngeal cleft repair and removal of supraglottic tissue using CO2 laser with FlexGuide ULTRA conduit (Omniguide, Lexington, MA). The patient had no intraoperative complications, but required immediate reintubation in the operating room at the end of the case due to copious secretions. The patient was extubated successfully in the PICU and discharged home on postoperative day 5.

The second patient was a 12-year-old girl who had a history of caustic ingestion and resultant pharyngeal, supraglottic, and esophageal strictures (patient 12). The patient had an existent tracheostomy tube in place and underwent multiple previous procedures addressing strictures at the oral aperture, hypopharynx, and esophagus. The patient underwent a TORS approach that included pharyngectomy, supraglottic laryngectomy, and base-of-tongue release. The surgical wound site was allowed to heal by granulation. The patient had no intraoperative complications but had poor tidal volumes after surgery. Despite perioperative antibiotics, the

TABLE I.
Patient Characteristics.

Patient	Gender	Weight (kg)	ASA	Indication
1	F	23.7	4	Supraglottic lymphatic malformation
2	F	44	3	Hypopharyngeal and supraglottic lymphatic malformation
3	F	10	3	Type I laryngeal cleft
4	M	30	1	Pharyngeal and esophageal stricture
5	M	3.7	4E	Saccular cyst
6	M	13.1	4	Type II laryngeal cleft
7	F	10.8	3	Type I laryngeal cleft
8	F	29.4	3	Type I laryngeal cleft
9	M	2.5	4	Saccular cyst
10	F	27.6	1	Base of tongue hamartoma
11	F	52.5	3	Hypopharyngeal lymphatic malformation
12	F	34.2	4	Pharyngeal and esophageal stricture
13	M	8	3	Type III laryngeal cleft
14	M	7.03	3	Type II laryngeal cleft
15	F	93.7	2	Base of tongue lymphatic malformation
16	F	11.2	4	Type I laryngeal cleft

ASA = American Society of Anesthesiologists; F = female; M = male.

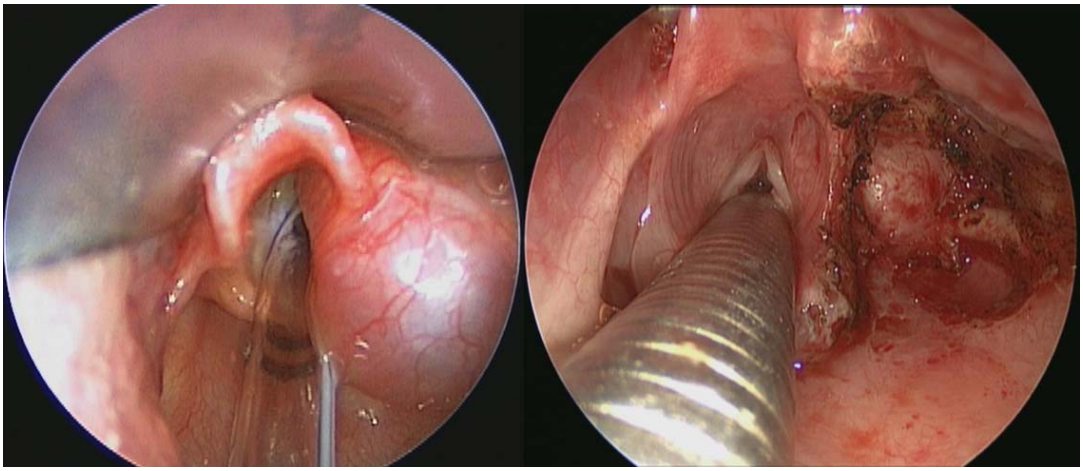

Fig. 4. Saccular cyst excision. (A) Visualization of the saccular cyst prior to excision; (B) intraoperative view after excision of saccular cyst. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

patient developed pneumonia and septic shock postoperatively that required broad-spectrum antibiotics and vasopressors. The patient underwent emergent bronchoscopy on postoperative day 2 for respiratory distress and copious secretions. The patient was found to have worsening right middle-lobe consolidation. By postoperative day 7, the patient was successfully weaned to tracheostomy collar and discharged home on postoperative day 8.

The third patient was a 3-year-old girl, ASA 4, with DiGeorge syndrome and subglottic stenosis who underwent repair of type 1 laryngeal cleft and excision of redundant glottic tissue (patient 16). The patient was kept intubated postoperatively but failed extubation under steroid coverage on postoperative day 3. The patient was successfully extubated on postoperative day 6. The patient's total hospital stay was 11 days.

The hospital duration for pediatric patients ranged from 1 to 20 days. The longest hospital stay was the 14-day-old patient, ASA 4E, with a right saccular laryngeal cyst who underwent TORS-assisted excision of the saccular cyst (patient 5). The patient was kept intubated after surgery, extubated on postoperative day 3, and received 5 days of perioperative steroids. Although the patient's procedure and hospital course were uncomplicated, the patient was monitored in the neonatal intensive care unit predominantly until per oral feeding status could be assured.

Three of the 16 patients had previous traditional surgical approaches prior to TORS. This includes a 2-year-old patient with a type 2 laryngeal cleft and redundant supraglottic tissue who has required no further surgery after subsequent successful TORS repair (patient 6); a 12-year-old patient with lymphangioma involving the left hypopharynx and tongue base who has undergone one additional TORS procedure (patient 11); and a 12-year-old patient with history of caustic ingestion with resultant pharyngeal, supraglottic, and esophageal strictures who has required multiple endoscopic procedures for dilation (patient 12).

To date, two of three patients who had a preexisting tracheostomy tube were successfully decannulated following their TORS procedure, with only the patient with a history of caustic ingestion and multiple levels of aerodigestive scarring remaining tracheostomy dependent.

DISCUSSION

Since Rahbar et al. first published the robotic-assisted repair of laryngeal clefts in pediatric patients, the technology and its applications have been advancing rapidly.[2] When analyzing robotic surgery in general, factors such as capital expense, instrument size, haptic feedback loss, docking time, operative time, simulation and training, complications, operative cost, and patient outcomes are a few considerations which have been evaluated.[10] Following the current debate regarding adult TORS, these same concerns regarding feasibility, teachability, safety, efficacy, and outcomes will need to be addressed for pediatric TORS. [11]

Many early reports have appropriately focused on safety, feasibility, operative time, and docking time.[3,5,6,8] Pediatric TORS is a clear example of early development and exploration phases of surgical innovation in both its application in the pediatric airway and description in the literature.[12–16] In attempts to have more evidence-based innovation, adopting the IDEAL model, as described by McCulloch, is helpful and recommended.[12] The IDEAL model is a descriptive model of surgical technique delineating the stages of Innovation, Development, Exploration, Assessment, and Long-term study. The model includes descriptive guidance on the types of expected studies in each stage, as well as the clinical and scientific goals to be accomplished in each stage.

Our case series adds to the literature in several ways. In representing one of the largest case series, it nearly doubles the number of cases presented in the literature to date. A wide range of pathologies was successfully and safely addressed, including hypopharyngeal and laryngeal lymphatic malformations, laryngeal clefts, saccular cysts, pharyngeal strictures, tongue base

masses, and cysts. The generalizability of this series is novel in that it lies outside of the range of most of the published literature that includes lingual tonsillectomies and tongue-base reductions. It also demonstrates safety and feasibility in a wide range of patient ages and weights, including the carefully selected neonates (a 2.5-kg 26 day old and a 3.7-kg 10 day old). Because of the wide range of procedure types and pathologies addressed, a significant trend of decreased operative or surgical time is not to be expected.

Our reported complications are within the expected complications for similar traditional transoral approaches in children with significant airway, respiratory, and comorbid pathologies. It is difficult to draw strict comparison of open or traditional transoral procedures in all cases because many of the cases do not have appropriate counterpart comparative procedures or data. The complications seen in this series, although not directly from robotic instrumentation or surgery, could be the result of prolonged mouth gag suspension times, more extensive tissue manipulation, or tissue effects of noncompliant armored endotracheal tubes. However, the advantages of wristed instrument control, three-dimensional visualization, and more precise surgery were affirmed in our qualitative experience in this series. For example, we believe that use of the robot allowed more sutures to be placed in small spaces; more precise control of the laser; and in some cases, multilayer closure with greater exposure than we typically experience in standard endoscopic procedures.

We believe there are several critical elements for success in this case series. First, we had a team with two robotic surgery experienced attending surgeons. Secondly, the experienced bedside surgeon facilitated patient safety, surgical access, and robotic surgeon. We also selected older, bigger children with relatively assessable pathology before attempting more challenging cases in younger, smaller children. We excluded patients with malignancy and vascular tumors (other than lymphangioma). We were also prepared to convert to traditional surgical methods if the procedure could not be safely and effectively addressed with the robot. With experience, we learned the importance of carefully selecting the appropriate endotracheal tube for the patient, resting the tongue (e.g., release from prolonged retraction), and consideration for overnight intubation in long surgical cases. We believe that surgeons can also decrease operative time with more experience.

These data help solidify our understanding of key challenges and future development of TORS for pediatric airway surgery: 1) securing the airway with the appropriate laser-safe endotracheal or tracheostomy tubes; 2) identifying the appropriate exposure; 3) obtaining surgical access with the robotic arms allowing for unrestricted mobility; 4) the critical role of the bedside surgeon in protecting the airway and the patient in addition to assisting the robotic surgeon. As the technology continues to advance with smaller instruments, arms, and optics, the initial challenges lessen and the potential applications widen. Because all of the surgical instruments adapted for use in pediatric TORS airway surgery were designed for general and urologic surgical applications, it is essential for the future innovation and advancement of pediatric robotic airway surgery to have specialized airway instrumentation. As safety concerns diminish and indications are being developed, critical assessment of the future clinical value pediatric TORS for airway surgery should be assessed.[10]

CONCLUSION

Transoral robotic surgery can be safe and feasible, even in very small neonates. A wide array of pathologies and sites, including the hypopharynx, larynx, and proximal trachea, can be successfully addressed. Whereas the diversity of procedures presented limits robust comparison to traditional procedures, this study demonstrates advancements in application, feasibility, and safety. Future advancements in technology, smaller instruments, specialized instruments, and airway-specific optics can help broaden robotic applications.

BIBLIOGRAPHY

1. Faust R, Kant A, Lorinez A, Younes A, Dawe E, Klein M. Robotic endoscopic surgery in a porcine model of the infant neck. *J Robotic Surg* 2007;1:75–83
2. Rahbar R, Ferrari L, Borer J, Peters C. Robotic surgery in the pediatric airway: application and safety. *Arch Otolaryngol Head Neck Surg* 2007; 133:46–50.
3. Mehta D, Duvvuri U. Robotic Surgery in Pediatric Otolaryngology: Emerging Trends. *Laryngoscope* 2012; 122:S105–S106.
4. Kayhan F, Kaya K, Koc A, Altintas A, Erdur O. Transoral Surgery for an infant thyroglossal duct cyst. *Int J Pediatr Otorhinolaryngol* 2013;77: 1620–1623.
5. Leonardis R, Duvvuri U, Mehta D. Transoral robotic-assisted lingual tonsillectomy in the pediatric population. *JAMA Otolaryngol Head Neck Surg* 2013;139:1032–1036.
6. Wine T, Duvvuri U, Maurer S, Mehta D. Pediatric transoral robotic surgery for oropharyngeal malignancy: A case report. *Int J Pediatr Otorhinolaryngol* 2013;77:1222–1226.
7. Kokot N, Mazhar K, O'Dell K, Huang N, Lin A, Sinha UK. Transoral robotic resection of oropharyngeal synovial sarcoma in a pediatric patient. *Int J Pediatr Otorhinolaryngol* 2013;77:1042–1044.
8. Leonardis R, Duvvuri U, Mehta D. Transoral robotic-assisted laryngeal cleft repair in the pediatric patient. *Laryngoscope* 2014;124:2167–2169.
9. Ferrell J, Roy S, Karni R, Yuksel S. Applications for transoral robotic surgery in the pediatric airway. *Laryngoscope* 2014;124:2630–2635.
10. Cundy T, Marcus H, Hughes-Hallet A, Najmaldin A, Yang G, Darzi A. International attitudes of early adopters to current and future robotic technologies in pediatric surgery. *J Pediatr Surg* 2014;29:1522–1526.
11. Weinstein G, O'Malley B, Desai S, Quon H. Transoral robotic surgery: does the ends justify the means? *Curr Opin Otolaryngol Head Neck Surg* 2009;17:126–131.
12. McCulloch P, Altman D, Campell B; Balliol Collaboration, et al. No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009;374:1105–1112.
13. Barkun JS, Aronson JK, Feldman LS; Balliol Collaboration, et al. Evaluation and stages of surgical innovations. *Lancet* 2009;374:1089–1096.
14. Ergina PL, Cook JA, Blazeby JM; Balliol Collaboration, et al. Challenges in evaluating surgical innovation. *Lancet* 2009;374:1097–1104.
15. Byrd JK, Leonardis RL, Bonawitz SC, Losee JE, Duvvuri U. Transoral robotic surgery for pharyngeal stenosis. *Int J Med Robot* 2014;10:418–422.
16. Thottam PJ, Govil N, Duvvuri U, Mehta D. Transoral robotic surgery for sleep apnea in children: is it effective? *Int J Pediatric Otorhinolaryngol* 2015;79:2234–2237.

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PEDIATRIC/CRANIOFACIAL

Principles for Management of Orbital Fractures in the Pediatric Population: A Cohort Study of 150 Patients

Devin Coon, M.D., M.S.E.
Martin Kosztowski, M.D.
Nicholas R. Mahoney, M.D.
Gerhard S. Mundinger, M.D.
Michael P. Grant, M.D., Ph.D.
Richard J. Redett, M.D.

Baltimore, Md.

Background: Pediatric orbital fractures represent a challenging and sometimes controversial clinical problem. Patients may present with clear indications for surgery, but most require balancing benefits against intraoperative and late complications. The authors assessed these fractures at a state-designated ophthalmology referral center to develop criteria for surgery.
Methods: Institutional review board approval was obtained to retrospectively analyze pediatric trauma registry patients with orbital fracture diagnoses at the Wilmer Eye Institute over 10 years. Patients were excluded if they did not undergo a full ophthalmologic examination, never followed up after their injury, or had significant facial fractures outside of the orbit.
Results: One hundred fifty patients met selection criteria; 116 patients (77 percent) completed all follow-up (average, 309 days). Two patients had 20/40 vision or worse at the end of follow-up. One hundred ten patients (71 percent) underwent surgery; 96 underwent acute repair (<3 weeks) and 11 underwent delayed repair (median, 49 days). Three patients required reoperation, two for plate infection and one for hyperglobus, with an overall complication rate of 4.7 percent.
Conclusions: The authors analyzed the largest series of operative pediatric orbital fractures to propose criteria for surgical intervention. There are four potential indications: (1) rectus muscle entrapment; (2) early enophthalmos; (3) central-gaze diplopia or extraocular movement restriction after the resolution of swelling; and (4) loss of orbital support likely to produce secondary changes in globe position and/or binocular stereo vision. In our series, application of these principles offered excellent long-term aesthetic and ophthalmic outcomes with an acceptably low complication profile. (*Plast. Reconstr. Surg.* 137: 1234, 2016.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

Isolated pediatric orbital fractures in the absence of other injuries warranting surgery represent a challenging and controversial area of management.[1–3] Some patients present with clear and absolute indications for reduction and internal fixation (e.g., restrictive strabismus with obvious muscle entrapment on imaging).[4] However, the majority of children will have a less clear clinical picture, with the risks of surgery balanced against the possibility of a secondary deformity that can be highly challenging to correct (i.e., globe malposition).[5,6] Plastic surgeons may understandably have a higher threshold for recommending surgery to prevent potential enophthalmos in the context of surgical disruption of an orbit with residual growth potential of not only bone but also soft tissue and extraocular muscle function.[7] We aimed to quantitatively assess our experience with isolated pediatric orbital fractures

From the Department of Plastic Surgery and the Division of Oculoplastic Surgery, Wilmer Eye Institute, Johns Hopkins Medical Institutions.
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at a high-volume ophthalmologic trauma referral center with the goal of analyzing outcomes and better understanding when intervention is warranted.

PATIENTS AND METHODS

Institutional review board approval was obtained to conduct a retrospective review of patients in the prospectively maintained pediatric trauma registry (0 to 18 years) at the Wilmer Eye Institute of Johns Hopkins Medical Institutions who were diagnosed with orbital fractures by *International Classification of Diseases, Ninth Revision* codes 802.4, 802.6, 802.7, and 802.8. The medical records were reviewed for each patient who was diagnosed with an orbital fracture between the years 2003 and 2013. Patients were excluded from this study if records did not include a full ophthalmologic examination immediately after presentation or if they did not follow-up after their injury. Data were extracted from each medical record for information about demographics, mechanism of injury, physical examination at presentation, surgical intervention, and final outcomes. Patients were excluded if they had any facial fractures outside of the orbit, with the exception of nondisplaced zygoma and frontal bone fractures representing the continuation of orbital fractures.

The *t* test and Mann-Whitney *U* test were used for statistical comparison of dichotomous groups for normally and nonnormally distributed variables, respectively. Univariate logistic regression was used to examine the impact of individual factors on the development of particular complications, with multivariate regression for possible confounders. All statistical tests were two-sided, and significance was set to the level of $p < 0.05$.

RESULTS

Demographics

One hundred fifty patients met the selection criteria. The average patient age at the time of trauma was 12.6 ± 4.3 years. One hundred sixteen patients (77 percent) completed all recommended follow-up and were discharged from care, with an average follow-up time of 309 days. The majority of patients were male [110 (73.3 percent)], and the most common causes were sports (34 percent) and assault (32 percent) (Table 1).

Fracture Characteristics

One hundred twenty-seven patients (85 percent) had orbital fractures including the orbital floor. Fifty-eight (39 percent) had medial wall involvement, 12 (8 percent) included the roof, and five (3 percent) had lateral wall involvement. The subset of patients without floor involvement ($n = 23$) was much less likely to undergo surgical management (30.4 percent versus 78.7 percent; $p < 0.001$). Similarly, patients with evidence of extraocular muscle restriction on examination were much likelier to have a floor component of their orbital fracture (OR, 5.2; $p = 0.001$).

Table 1. Mechanisms of Injury ($n = 150$)

	No. (%)
Sports	50 (33.8)
Assault	47 (31.8)
Play	18 (12.2)
Fall	13 (8.8)
Motor vehicle accident	10 (6.8)
ATV/motorbike	5 (3.4)
Other	5 (3.4)

ATV, all-terrain vehicle.

Twelve patients had extension of their fractures outside the orbit. Five had extension of a roof fracture into the frontal bone and four had zygoma involvement, all of which were nondisplaced. Three patients had nasoorbitoethmoid fractures: two with Markowitz-Manson type 1 fractures and one with a Markowitz-Manson type 2 fracture.

On presentation, 43 patients (29 percent) showed evidence of radiographic muscle entrapment (i.e., herniation of a portion of the inferior rectus muscle belly into the defect) on computed tomography. Lack of diplopia and extraocular movement restriction on initial presentation were relatively sensitive for ruling out muscle entrapment on imaging (sensitivity, 95 percent; specificity, 45 percent; 95 percent CI, 84.2 to 99.4 percent). Twenty-two patients (15 percent) showed evidence of enophthalmos preoperatively, 19 of whom developed it in the acute fracture period. Of the remaining three patients, two were initially managed conservatively but developed enophthalmos, and one had surgery delayed because of ophthalmologic sequelae (i.e., commotio retinae and traumatic iritis).

Surgical Cohort

Overall, 107 patients (71 percent) underwent surgery for their fracture. Of these, 96 (90 percent) underwent repair within the acute period (≤3 weeks), whereas 11 (10 percent) underwent delayed fracture repair (22 to 1399 days; median, 49 days). Thirty-nine patients (37 percent) had surgery within the first 48 hours after their injury. Patients received surgical or conservative treatment based on their relative indications (Fig. 1), with the exception of the previously mentioned patients presenting with major eye injuries.

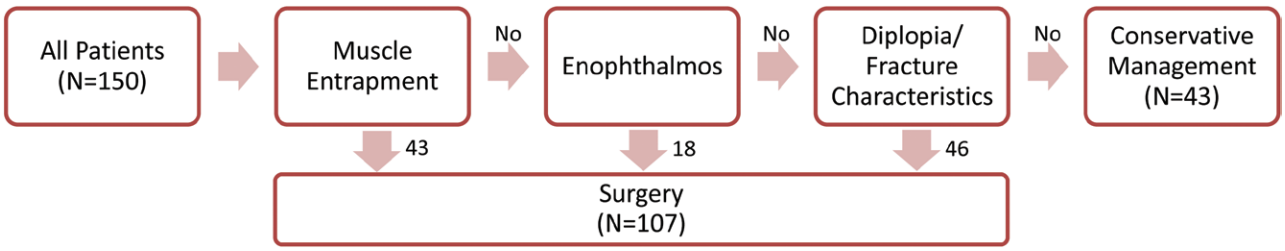

Fig. 1. Management algorithm for surgical decision-making in pediatric orbital fractures.

In 104 cases (97 percent), an implant was placed (i.e., porous polyethylene, porous polyethylene with titanium, or preformed anatomical titanium mesh). Of the three remaining cases, one involved a superomedial defect, one involved a very small floor defect with entrapped muscle that was felt to not require an implant, and one patient developed intraoperative mydriasis during posterior dissection and thus only a reduction after limited dissection was performed. The three patients with nasoorbitoethmoid fractures also had reduction of the medial canthal tendon–bearing bone fragment(s) with a titanium miniplate.

Nonoperative Cohort

The remaining 43 patients were managed nonoperatively because they did not have indications for surgery. Younger age was strongly correlated with a lower operative intervention rate ($p < 0.001$; OR, 1.15 per year; 95 percent CI, 1.06 to 1.25). Follow-up completion rates were comparable between surgical and conservatively managed patients (81 percent versus 76 percent; $p = 0.5$). Demographically, there were no significant differences compared with the operative group except for age (Table 2). There were no cases of globe malposition in conservatively managed patients.

Outcomes

Two patients had 20/40 vision or worse on the side of the fracture at the conclusion of follow-up. One patient had suffered a significant retinal injury and the other had suffered traumatic optic neuropathy caused by an orbital foreign body. In both cases, the final visual acuity was better than the preoperative visual acuity.

A total of three patients (2.8 percent) had complications requiring reoperation. Two cases involved plate infection that resolved after implant removal and antibiotics. One patient underwent plate removal in a successful attempt to correct hyperglobus and diplopia. Three patients experienced postoperative globe malposition, with one patient demonstrating mild residual enophthalmos and two patients (including the patient who underwent hardware removal) demonstrating mild hyperglobus. None of these patients demonstrated a functional impairment as a result of the globe malposition. There were no cases of eyelid malposition or unacceptable scarring. The overall complication rate was 4.7 percent.

DISCUSSION

Orbital fractures are among the most common facial fractures in the pediatric population.[8,9]

Table 2. Between-Cohort Differences

	Overall	Surgical ($n = 107$)	Nonoperative ($n = 43$)
Age, yr	12.6 ± 4.2	13.3 ± 3.4	10.7 ± 5.4
12 yr or younger, %	31	25	44
Male sex, %	73	75	70
Race, %			
Caucasian	52	46	69
African American	41	47	24
Other	7	7	7
Follow-up, mo	10.2	10.1	10.2
Diplopia, %*	51.5	62.5	22.2
Gaze restriction, %*	58.7	74.3	20.9
Initial VA worse than 20/40, %	16.8	20.6	7.5
Final VA worse than 20/40, %	1.4	2.0	0.0

VA, visual acuity.
*At the time of presentation.

Despite this, there is little in the way of consensus regarding the full breadth of indications that warrant surgical repair. At least four different surgical specialties manage these injuries, and recommendations for treatment vary across the literature. The greatest areas of disagreement focus on (1) optimal timing of surgery, for both entrapped and nonentrapped fractures; (2) ophthalmologic symptoms necessitating intervention; and (3) fracture characteristics that warrant early intervention before the development of globe malposition.

We sought to specifically answer the question of surgical intervention in orbital fractures with an emphasis on the outcomes of surgical versus conservative treatment. Although it represents the largest series of isolated pediatric orbital fractures and the largest operative series in the literature, our cohort is also unique in that we excluded patients with any other type of facial fracture or injury that could potentially confound the decision to operate. Thus, patients were stratified between surgery and conservative management cohorts based on their clinical indications. Both cohorts also included only patients who returned after their injury, with nearly 80 percent of patients completing their recommended follow-up visits and released to follow-up on an as-needed basis. Limitations of our study include the potential for bias by excluding patients who did not return for follow-up. Our results may also have limited generalizability to high-energy craniofacial trauma with multiple concomitant facial fractures.

We previously reported a large cohort of pediatric orbital roof fractures, with a significant rate of intracranial injury and multisystem trauma.[10] These patients (who were not included in this series) were admitted to the Johns Hopkins Pediatric Trauma Center and had high rates of multiple trauma by means of high-energy mechanisms. In contrast, the patients in this series were managed through the state-designated Wilmer Eye Institute Ocular and Orbital Trauma Center and were, by inclusion criteria, isolated injuries. This is congruent with the low incidence of roof fractures seen in this series. Examination of the demographics and fracture patterns of the two groups offers an interesting comparison between low- and high- energy facial injuries in the pediatric population. Unlike the high rate of operative repair in this series, less than 10 percent of patients with orbital roof fractures had surgery,[10] and their management is typically more analogous to a skull fracture than an orbital floor fracture. Trapdoor fractures are much less common in high-energy injuries, contributing to a paradoxically elevated rate of surgical intervention in orbital fracture patients with low energy mechanisms.

Losee et al. reported a series of 74 pediatric orbital fracture patients, 25 of which were isolated orbital fractures.[2] Only three of the 25 patients (12 percent) underwent surgical treatment, two of which were because of entrapment. Mild detectable enophthalmos was seen in one of the surgically treated fractures (33 percent) and three of the conservatively treated fractures (14 percent). However, among "significant fractures" (n = 12), defined as fractures that involved more than 50 percent of the area or displacement measuring greater than three times the cortex width, the enophthalmos rate was 30 percent with conservative treatment. The authors questioned the practical significance of mild enophthalmos and advocated a conservative approach to management in the absence of entrapment or early globe malposition. This is clearly an area where surgeon preference and informed consent by parents as to the risks and benefits of intervention versus observation is essential.

Attempts to correlate radiographic fracture size with the development of late complications began shortly after the widespread adoption of computed tomographic scanning. In 1983, Hawes and Dortzbach postulated that a greater than 50 percent defect of the orbital floor on computed tomographic scan was necessary to cause enophthalmos.[11] This number has been widely adopted as a standard for "critical fracture size" in the ophthalmology literature. For example, Hatton et al. published a series of 96 pediatric patients, inclusive of multiple facial fracture patterns, from the Massachusetts Eye and Ear Hospital following this criterion.[12] Forty-nine patients (51 percent) underwent surgery; however, only four patients (4 percent) had surgery based on the size of the fracture.

Bansagi and Meyer published a review of a 34-patient experience, of which eight were trapdoor fractures.[13] They noted that this subset of patients had better recovery of ocular motility if operated on immediately (within 48 hours) versus later (3 to 14 days after injury). Specifically, these patients demonstrated long-term limitation in supraduction. In contrast, Egbert et al.[14] concluded that delay of up to 1 week was acceptable. In our experience, these patients tend to do better the earlier they undergo reduction. Accordingly, our preference is to perform surgery for this subgroup within 24 hours of presentation whenever possible.

In the oral surgery literature, Gerber published a series of 24 patients, of which 22 were operated on (92 percent).[3] Seven patients (32 percent) had long-term gaze restriction or diplopia, with one case of enophthalmos. Based on these results, they proposed that all operative pediatric orbital fractures should be repaired within 3 days; however, we have not seen evidence that this is necessary to obtain good outcomes, and it may make the repair procedure unnecessarily difficult because of edema.

In any pediatric facial trauma cohort, there is always significant clinical heterogeneity between the extremes of infants with highly immature craniofacial skeletal structures and "nearly adult" 16-year-olds. If orbital fractures themselves were randomly distributed in our cohort by age, we would expect to see a roughly even distribution of fracture patients by each year of life; instead, there is a sharp increase in frequency after the age of 12. We hypothesize that this is a combination of increasing environmental exposure to trauma and increasing anatomical predilection to orbital (as opposed to skull or maxillary) fractures.[15] Even factoring this in, however, increasing age still correlated with a higher operative rate. We attribute this to a combination of a higher threshold for intervention in very young children with significant remaining orbital growth and a lower rate of symptomatic fractures in these patients.

Our patients who underwent surgery fell into three groups. Group I (n = 43) had definite evidence or suspicion of muscle entrapment based on a combination of clinical examination and computed tomographic imaging, a clear indication for early open reduction and internal fixation, which we try to accomplish as soon as possible. Of the patients who were not operated on for muscle entrapment, group II (n = 18) demonstrated early enophthalmos, typically from a relatively large defect, which represents a second generally accepted indication for surgery, although this can be performed in a more delayed fashion.

Group III (n = 46) included patients with neither entrapment nor acute globe malposition who required surgery for other reasons (Fig. 2). These patients represent the most challenging evaluation, and the main indications for surgery can broadly be divided into two categories: (1) to preserve conjugate gaze or (2) to avoid late enophthalmos or other sequelae resulting from changes in orbital anatomy. Persistent diplopia in central gaze or extraocular muscle movement restriction after 1 to 2 weeks when edema has mostly resolved will generally prompt us to intervene, especially when there is evidence of orbital fat herniation into the orbital defect on imaging.

The importance of ophthalmologic symptoms tends to be underestimated in patient evaluation. After swelling has largely abated at 1 to 2 weeks, the continued presence of diplopia in central gaze is concerning for alterations in orbital volume and structure. This is less concerning if computed tomographic imaging suggests the possibility of transient impairment of extraocular muscle function (e.g., an extremely swollen inferior rectus or intramuscular hematoma). Similarly, if the diplopia is not present on central gaze but only on vertical upgaze or downgaze, we have a greater tendency toward observation.

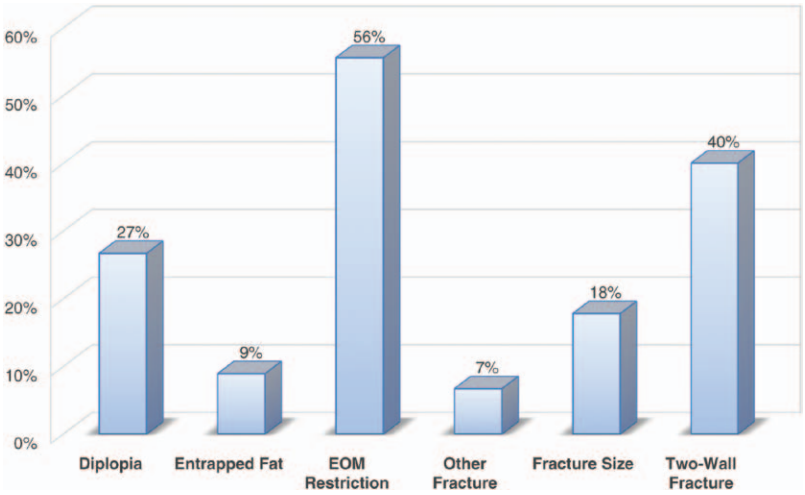

Fig. 2. Indications for surgery among group III patients (n = 46). Totals exceed 100 percent because some patients had two relative indications. "Other fracture" indicates nasoorbitoethmoid or orbital roof. *EOM*, extraocular movement.

Fracture characteristics that warrant acute repair are likely the area of greatest controversy in the management of these patients. Loss of support of the orbital contents is difficult to measure quantitatively, and we generally avoid applying a strict size measurement threshold except for the rare patient who presents with an extremely large defect where the majority of the orbital floor is gone. Instead, we assess the apparent structural changes (e.g., rounding of the inferior rectus muscle, significant fat herniation) and clinical symptoms coupled with the suspected structural instability from the fracture. Displaced two-wall fractures that include the medial transition zone can result in a defect that appears deceptively small. However, comparison to the opposite orbit often reveals that only a few millimeters of displacement of this large fragment can create a significant orbital volume increase, and we manage these operatively (Fig. 3). In these cases, we have had good results with the use of prefabricated anatomical titanium orbital plates.

Our absolute percentage rate of surgical intervention is significantly higher than in other series. As a state-designated ophthalmology referral center and the primary pediatric trauma center for the state of Maryland, there is undoubtedly a strong referral bias present in our series. We generally advise outside physicians that they do not need to transfer patients if the fracture is clearly nonoperative (e.g., small and nondisplaced), ocular motility is full, and the dilated ophthalmic examination is normal. In addition, focusing on isolated orbital fractures likely causes selection bias toward "symptomatic" orbital fractures by excluding incidental findings on patients imaged for other facial fractures. Although these factors prevent direct comparison of operative rates, they do offer the advantage of a uniquely higher acuity cohort with a greater proportion of cases where management is not obviously nonoperative.

Even with referral bias considered, our criteria still represent a lower threshold for operative repair of pediatric orbital fractures compared with most previous authors. As a high-volume center, routinely performing these procedures offers advantages in familiarity and favorable outcomes, with a less than 5 percent rate of complications. Importantly, in our experience, the long-term ocular outcomes of these patients tend to be superior when significant disturbances in the anatomy of the orbit are corrected.

Most series focus on the primary outcome of globe malposition, which is evident on routine

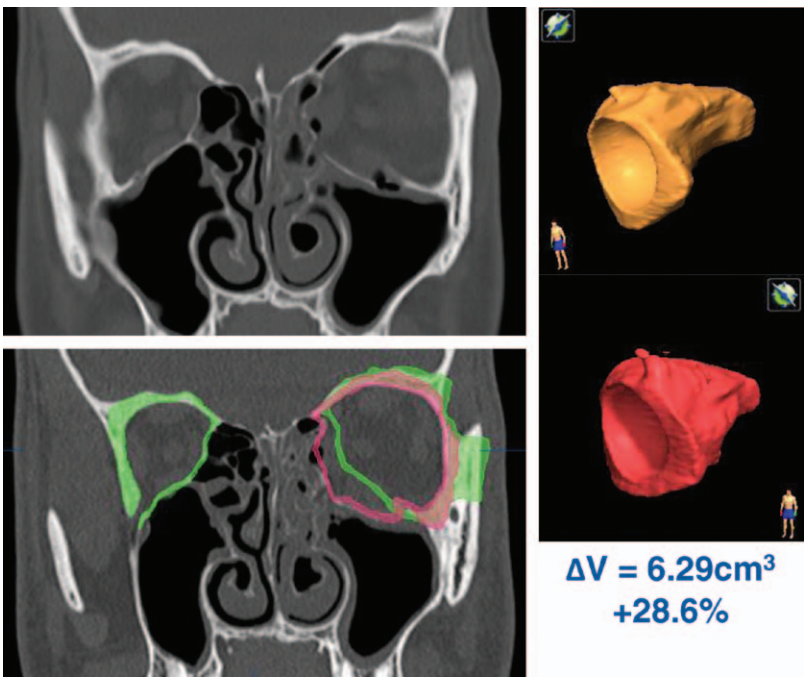

Fig. 3. A 14-year-old patient with a two-wall fracture that included the medial transition zone who was managed operatively. Despite a deceptive lack of comminution or severe displacement (*above*, *left*), the orbit is significantly enlarged compared with the uninjured side (*below*, *left*). Volumetric segmentation of the two orbits (*right*) shows that the overall volume of the orbit has increased 28.6 percent.

physical examination and important because late enophthalmos is a highly challenging problem. Less appreciated is extraocular muscle function and preservation of binocular stereo vision. Although it is not uncommon in the literature to see conclusions that "all diplopia resolved," continued diplopia in children can lead to the development of compensatory mechanisms that may go unappreciated. We have seen a number of secondary referral patients whose diplopia has resolved despite detectable heterotropia because they have suppressed vision from the affected eye. The development of strabismus can be particularly problematic in the context of younger children with a developing visual system and significant neuroplasticity.

All children in this series had routine ophthalmologic examinations, and only four patients had any detectable degree of heterotropia. By restoring orbital symmetry and addressing any restrictions in ocular movement, excellent visual acuity outcomes and maintenance of conjugate gaze can be obtained. Overall, operative intervention was well tolerated, with a 4.7 percent complication rate, including two patients with detectable hyperglobus and one that had inadequate enophthalmos correction. Two patients required reoperation for removal of infected hardware. Only one patient desired correction of their globe malposition, which was addressed by plate removal to improve hyperglobus. Equally important, although impaired visual acuity was common on initial presentation, nearly all patients recovered excellent vision by the conclusion of follow-up. Only two patients had worse than 20/40 visual acuity at the end of the follow-up, both of whom had sustained serious ophthalmologic injuries during their trauma (retinal injury and traumatic optic neuropathy, respectively) and had poor vision on initial presentation.

CONCLUSIONS

Orbital fractures are among the most common sequelae after blunt facial trauma in children. Many different criteria have been suggested to identify the need for operative intervention. In the largest series of isolated orbital fractures with good follow-up, we had a less than 5 percent complication rate from reduction and internal fixation. Concomitant ophthalmologic injuries can often be predicted based on associated fracture patterns and should prompt delay in intervention until surgery is unlikely to aggravate the condition. Indications for surgery can be divided into four main criteria: (1) entrapment of extraocular muscles; (2) early enophthalmos; (3) persistent restrictive strabismus or diplopia in central gaze suggestive of restriction of orbital contents; and (4) anatomically or functionally significant loss of orbital support. Using these principles, early intervention to restore normal orbital volume and support can provide good long-term outcomes in visual acuity, globe position, and binocular eye function, with an acceptably low complication profile.

Richard J. Redett, M.D.
Department of Plastic Surgery
Johns Hopkins Medical Institutions
1800 Orleans Street, 7314B
Baltimore, Md. 21287
rredett1@jhmi.edu

REFERENCES

1. Stotland MA, Do NK. Pediatric orbital fractures. *J Craniofac Surg.* 2011;22:1230–1235.
2. Losee JE, Afifi A, Jiang S, et al. Pediatric orbital fractures: Classification, management, and early follow-up. *Plast Reconstr Surg.* 2008;122:886–897.
3. Gerber B, Kiwanuka P, Dhariwal D. Orbital fractures in children: A review of outcomes. *Br J Oral Maxillofac Surg.* 2013;51:789–793.
4. Grant JH, Patrinely JR, Weiss AH, Kierney PC, Gruss JS. Trapdoor fracture of the orbit in a pediatric population. *Plast Reconstr Surg.* 2002;109:482–489; discussion 490–495.
5. Grant MP, Iliff NT, Manson PN. Strategies for the treatment of enophthalmos. *Clin Plast Surg.* 1997;24:539–550.
6. Wolfe SA, Ghurani R, Podda S, Ward J. An examination of posttraumatic, postsurgical orbital deformities: Conclusions drawn for improvement of primary treatment. *Plast Reconstr Surg.* 2008;122:1870–1881.
7. Escaravage GK Jr, Dutton JJ. Age-related changes in the pediatric human orbit on CT. *Ophthal Plast Reconstr Surg.* 2013;29:150–156.
8. Grunwaldt L, Smith DM, Zuckerbraun NS, et al. Pediatric facial fractures: Demographics, injury patterns, and associated injuries in 772 consecutive patients. *Plast Reconstr Surg.* 2011;128:1263–1271.
9. Chapman VM, Fenton LZ, Gao D, Strain JD. Facial fractures in children: Unique patterns of injury observed by computed tomography. *J Comput Assist Tomogr.* 2009;33:70–72.
10. Coon D, Yuan N, Jones D, Howell LK, Grant MP, Redett RJ. Defining pediatric orbital roof fractures: Patterns, sequelae, and indications for operation. *Plast Reconstr Surg.* 2014;134:442e–448e.
11. Hawes MJ, Dortzbach RK. Surgery on orbital floor fractures: Influence of time of repair and fracture size. *Ophthalmology* 1983;90:1066–1070.
12. Hatton MP, Watkins LM, Rubin PA. Orbital fractures in children. *Ophthal Plast Reconstr Surg.* 2001;17:174–179.
13. Bansagi ZC, Meyer DR. Internal orbital fractures in the pediatric age group: Characterization and management. *Ophthalmology* 2000;107:829–836.
14. Egbert JE, May K, Kersten RC, Kulwin DR. Pediatric orbital floor fracture: Direct extraocular muscle involvement. *Ophthalmology* 2000;107:1875–1879.
15. Koltai PJ, Amjad I, Meyer D, Feustel PJ. Orbital fractures in children. *Arch Otolaryngol Head Neck Surg.* 1995;121:1375–1379.

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Defining failure and its predictors in mandibular distraction for Robin sequence

Roberto L. Flores [1], S. Travis Greathouse [2], Melinda Costa [2], Youssef Tahiri [2], Tahereh Soleimani [2], Sunil S. Tholpady[*, 2]

Riley Hospital for Children, Indiana University School of Medicine, 705 Riley Hospital Drive, Indianapolis, IN 46202, USA

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ABSTRACT

Introduction: Robin sequence (RS) is defined as the triad of micrognathia, glossoptosis and airway obstruction. A popular surgical treatment is mandibular distraction osteogenesis (MDO). In this study, it is demonstrated that the associated variables change, dependent on the manner in which failure is defined. These multiple failure outcomes are used to construct a scoring system to predict MDO failure.
Methods: A retrospective database of neonatal MDO patients was constructed. Failure outcomes studied included tracheostomy; a decrease in the apnea-hypopnea index (AHI) but an AHI >20; and death. A combination of bivariate and regression analysis was used to produce significantly associated variables and a scoring system.
Results: Statistical analysis demonstrated the association of gastroesophageal reflux; age >30 days; neurologic anomaly; airway anomalies, other than laryngomalacia; an intact palate; and pre-operative intubation on the outcome variables studied. Multiple scoring systems were produced with reasonable sensitivity, specificity, and positive and negative predictive value.
Conclusions: When reporting surgical outcomes of MDO in the setting of RS, it is important to consider the AHI as well as avoidance of tracheostomy as an outcome variable. Incomplete amelioration of AHI accounts for half of the patients with a problem after MDO. The predictive scores presented will be used and validated on a larger, prospectively collected dataset.

1. Introduction

Upper airway obstruction caused by micrognathia and subsequent glossoptosis with or without cleft palate defines the triad of Robin sequence (RS) (Robin, 1929, 1934). Affected patients may present with airway obstruction causing detriment to breathing, growth, neurocognitive development and, in advanced cases, life threatening airway stenosis. Indeed mortality associated with Robin sequence is reported to be between 1.7 and 65% (Costa et al., 2014). Surgical intervention has been reserved for patients with severe airway obstruction in which conservative treatment has been unsuccessful. Mandibular distraction osteogenesis (MDO) is the first line of surgical therapy at many craniofacial centers treating Robin sequence. MDO has been demonstrated as a more functional and cost-effective alternative to tracheostomy (Kohan et al., 2010; Hong et al., 2012) and a more effective intervention compared with tongue-lip adhesion in the treatment of isolated Robin sequence (Flores et al., 2014).

Several investigators have reported on the efficacy of MDO in relieving airway obstruction in the RS population (Denny et al., 2001; Denny and Kalantarian, 2002; Monasterio et al., 2002; Denny, 2004; Mandell et al., 2004; Wittenborn et al., 2004; Burstein and Williams, 2005; Dauria and Marsh, 2008; Iatrou et al., 2010; Cascone et al., 2014). Critical appraisal of the literature demonstrates that the definition of successful distraction varies across studies (Denny et al., 2001; Denny and Kalantarian, 2002; Monasterio et al., 2002; Denny, 2004; Mandell et al., 2004; Wittenborn et al., 2004; Burstein and Williams, 2005; Dauria and

* Corresponding author. Division of Plastic Surgery, Riley Hospital for Children, 705 Riley Hospital Drive, RI 2514, Indianapolis, IN 46202, USA. Tel.: +1 317 274 2430; fax: +1 317 2780 0939.
E-mail address: stholpad@iupui.edu (S.S. Tholpady).
[1] Present address: Department of Plastic Surgery, NYU Langone Medical Center, 307 East 33rd Street, New York, NY 10016, USA.
[2] Present address: Division of Plastic Surgery, Riley Hospital for Children, Indiana University School of Medicine, 705 Riley Hospital Drive, Indianapolis, IN 46202, USA.

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Marsh, 2008; Paes et al., 2013; Flores et al., 2014; Lam et al., 2014; Murage et al., 2014; Rachmiel et al., 2014; Runyan et al., 2014; Tahiri et al., 2014) and can include resolution of apnea by clinical exam or polysomnogram (PSG) improvement; avoidance of tracheostomy; changes in airway obstruction patterns; or mortality. Unfortunately, this variation in definitions creates a confounder in determining patient characteristics leading to favorable or unfavorable results and is problematic to formulating definitive treatment protocols of care.

The main hypothesis of this study is that the variables associated with MDO failure depend on the definition of success for this patient population. A total institutional outcomes analysis for the treatment of MDO was performed with regard to the varying dependent definitions of success. These variables were then used to construct a tool with which failure could be predicted. This information will provide greater clarity in the analysis of surgical outcomes of MDO and draws attention to the need for standardized assessment of surgical outcomes in this challenging patient population. It also provides a set of pre-operative variables that can assist the clinician in patient counseling.

2. Material and methods

Institutional Review Board approval was obtained prior to the start of this study. A 10-year retrospective review was conducted of all patients with RS treated with MDO at a single tertiary care children's hospital between 2003 and 2012. RS was defined as micrognathia, glossoptosis, and airway obstruction with or without cleft palate. Study patients required a clinical follow-up of at least one year, pre-operative laryngoscopy/bronchoscopy, and pre-operative and postoperative PSGs, unless precluded by tracheostomy, intubation, or other airway intervention. Patients were not excluded based on secondary diagnosis or age at the time of distraction.

Work up and indication for distraction was based on a previously described, institutionally-derived protocol (Murage et al., 2013, 2014; Flores et al., 2014). A multidisciplinary team with members from plastic surgery, neonatology, genetics, pulmonology, otolaryngology, and nursing participated in patient assessment and surgical indications. Briefly, patients with airway obstruction unresponsive to conservative airway interventions were assessed by PSG. Those patients with an apnea/hypopnea index (AHI) >20 or significant CO_2 retention were considered for MDO unless central sleep apnea was noted. Prior to surgery, non-contrast computed tomography (CT) of the maxillofacial skeleton was obtained to assess mandibular form, bone quality, associated malformations of the condyle, or TMJ ankylosis. A laryngoscopy and bronchoscopy was also obtained prior to distraction to rule out secondary airway anomalies which could preclude successful MDO. Laryngomalacia was not a contraindication to distraction.

Mandibular distraction was performed using a Risdon incision placed 1 cm inferior to the mandibular border. A vertical ramus osteotomy was performed with a sagittal saw in combination with a coronoidectomy. A micro Zurich mandibular distractor (KLS Martin, Jacksonville, FL, USA) was then applied using a horizontal vector. The activation arm exited anteriorly or posteriorly according to each surgeon's preference. After a latency period of 5 days, activation commenced at a rate of 1 mm/day to the maximal allowable length of the distraction device (20–30 mm). Devices were removed in a second operation after 8 weeks of consolidation.

Multiple patient variables were recorded to correlate with the surgical outcomes of MDO. These included: sex, age, low birth weight (LBW, defined as <2500 g), intrauterine growth retardation (IUGR), prematurity (defined as <37 weeks gestation), age at the time of surgery, presurgical intubation, presence of a cleft palate, syndromic or genetic anomaly, cardiac anomaly, central nervous system (CNS) anomaly, respiratory anomaly excluding laryngomalacia, gastrointestinal (GI) anomaly, gastroesophageal reflux (GER), genitourinary (GU) anomaly, or other system anomaly. Outcome variables defining failure were: a decrease in AHI but still above 20, the need for post-intervention tracheostomy, and death. Repeat distraction was considered under the same paradigm but not considered to be a failure unless it led to no further reduction in AHI, tracheostomy, or death.

Statistical analysis was performed using SAS for Windows (SAS Institute, Cary, NC, USA). Changes in AHI in response to surgery were assessed using a paired *t*-test. A chi-square test was used to analyze each dependent variable's effect on the failure of MDO as classified by: an AHI not decreasing below 20; the need for tracheostomy; or death. Statistical significance was defined as $p \leq 0.05$. Identified variables that had a statistically significant association with failure were then used to construct a scoring system that was tested for the best sensitivity, specificity, and positive and negative predictive value. The receiver operating characteristic (ROC) curves for each was then calculated in order to stratify well-performing predictive tests from poorly performing ones.

3. Results

3.1. Study demographics

Eighty-one patients met the inclusion criteria for this study. Patient characteristics included a mean age of 33.5 days at operation, a mean birth weight of 2.92 kg, and a mean operative weight of 3.36 kg. Other systemic anomaly data was collected as per previous studies. All demographic data is represented in Table 1. These variables include: male sex (58.02%); LBW (29.63%); premature (24.69%); GER (41.98%); Nissen (14.81%); gastrostomy tube (67.9%); laryngomalacia (25.93%); syndromic (30.86%); cleft palate (83.75%); isolated RS (20.99%); CNS anomaly (22.22%); cardiac anomaly (24.69%); GI anomaly (2.47%); GU anomaly (14.81%); airway anomaly (other than laryngomalacia) (34.57%); other

Table 1
Pre-operative demographics of mandibular distraction osteogenesis study patients.

	Mean, *n* (%)
Age (days)	33.49
Birth weight (kg)	2.92
Weight (kg)	3.36
Male	47 (58.02)
Female	34 (41.98)
LBW	24 (29.63)
IUGR	24 (29.63)
Premature	20 (24.69)
GER	34 (41.98)
Nissen	12 (14.81)
Gastrostomy tube	55 (67.9)
Laryngomalacia	21 (25.93)
Syndromic	25 (30.86)
Cleft palate	67 (83.75)
Isolated RS	17 (20.99)
CNS anomaly	18 (22.22)
Cardiac anomaly	20 (24.69)
GI anomaly	2 (2.47)
GU anomaly	12 (14.81)
Other airway anomaly	28 (34.57)
Other anomaly	21 (25.93)
Intubated	6 (7.41)

CNS: central nervous system; GER: gastroesophageal reflux; GI: gastrointestinal; GU: genitourinary; IUGR: intrauterine growth restriction; LBW: low birth weight; RS: Robin sequence.

congenital anomaly (25.93%); and pre-operatively intubated (7.41%).

3.2. Bivariate and regression analysis of variables associated with failure

Failure was defined as follows, with parenthesized numbers indicating the number of patients within that group: need for tracheostomy (7), death due to apneic disease (1), AHI >20 after distraction (6), failure due to tracheostomy or insufficient reduction in AHI (12), any of these failures (13), and all failures as well as all-cause mortality (16). These failures were then analyzed in a bivariate fashion to reveal variables that were specifically associated with each cluster of failure variables. Table 2 outlines all variables in this analysis. Values in bold indicate variables significantly associated with failure.

In this analysis of specific causes of failure, certain variables were important across all types of failure. These include **G**ER, **A**ge >30 days, **N**eurologic anomaly, airway anomalies **O**ther than laryngomalacia, **I**ntact palate, and pre-operative in**T**ubation. Paired *t*-test analysis for numeric variables demonstrated an age of approximately 30 days as being significant in failure by tracheostomy, AHI, and any failure (Table 3). Interestingly, there was a trend towards failure in children below 2.5 kg birth weight, but this only reached significance in the failure by tracheostomy or AHI >20 group.

3.3. Construction of a tool to predict failure in the MDO population

Elucidation of variables associated with failure provided the material with which to create a scoring system for the prediction of failure of MDO. The variables assessed were **G**ER, **A**ge >30 days, **N**eurologic anomaly, airway anomalies **O**ther than laryngomalacia, **I**ntact palate, and pre-operative in**T**ubation. Scores were created for every variation possible for these variables. A sample of the analysis is demonstrated in Table 4. The top eight scores by ROC curve analysis were listed for each mode of failure. ROC curve analysis was performed for the outcome variable denoting failures due to all causes (Fig. 1).

4. Discussion

There have been multiple publications demonstrating the effectiveness of MDO in relieving airway obstruction in patients affected by severe airway stenosis secondary to Robin sequence (Denny et al., 2001; Denny and Kalantarian, 2002; Denny, 2004). As a result MDO is increasingly used as a first line intervention for the surgical treatment of MDO. Unfortunately, standardized protocols of assessment and intervention have not yet been formulated to treat this challenging patient population. To construct these standardized care plans, a consistent means of assessing surgical outcomes needs to be defined. The current literature demonstrates varying definitions of 'failure' of MDO including: the clinical presence of apnea; an objective drop in AHI; the need for tracheostomy, redistraction, or other airway procedures; and death (Dauria and Marsh, 2008; Paes et al., 2013; Papoff et al., 2013; Flores et al., 2014; Lam et al., 2014; Tahiri et al., 2014). Agreement on the definition of failure is critical to assessing differing patient variables associated with successful and unsuccessful distraction and is ultimately required to create definitive treatment protocols.

In this study it is shown that differing definitions of successful distraction not only have an effect on the success rate of distraction but also implicate differing sets of patient variables associated with unsuccessful distraction (Table 2). An almost equal number of patients were characterized as failures by need for tracheostomy ($n = 7$) and inadequate improvement of AHI ($n = 6$). Furthermore, an additional patient died from apnea-related disease. Commonly, the success rate is defined as avoidance of tracheostomy; if this measure is used, only 50% of patients with a problem would be identified.

The variables associated with failure of distraction are also affected by the definitions of failure. This can most clearly be seen in Table 2. The table provides an easily visualized data representation of important variables of failure across differing definitions. When failure is defined by avoidance of tracheostomy, the previously described standard variables appear as important: CNS

Table 2
Bivariate analysis of pre-operative demographic variables against all causes of failure.

	% (*p* value)			
	Failure by tracheostomy	Failure by AHI	Any failure	Any failure + deceased
Total	8.64%	8.11%	16.67%	19.75%
Male	12.77 (0.229)	9.3 (1)	21.74 (0.219)	23.4 (0.405)
Female	2.94 (0.229)	6.45 (1)	9.38 (0.219)	14.71 (0.405)
LBW	16.67 (0.187)	5.26 (1)	23.81 (0.32)	33.33 (0.066)
IUGR	4.17 (0.668)	14.29 (0.343)	18.18 (1)	25 (0.543)
Premature	20 (0.059)	11.76 (0.616)	31.58 (0.073)	30 (0.206)
Isolated RS	0 (0.335)	5.88 (1)	5.88 (0.277)	5.88 (0.171)
CNS anomaly	**22.22 (0.04)**	13.33 (0.595)	29.41 (0.143)	**38.89 (0.039)**
Cardiac anomaly	10 (1)	5.26 (1)	15 (1)	20 (1)
GI anomaly	50 (0.166)	0 (1)	50 (0.307)	50 (0.358)
GU anomaly	8.33 (1)	0 (0.588)	9.09 (0.68)	8.33 (0.443)
Other anomalies	4.76 (0.67)	5.88 (1)	15.79 (1)	23.81 (0.751)
GER	**17.65 (0.038)**	13.79 (0.202)	**28.13 (0.032)**	29.41 (0.09)
NISSEN	**41.67 (<0.0001)**	22.22 (0.153)	**54.55 (0.002)**	**50 (0.011)**
Gastrostomy	12.73 (0.09)	12.24 (0.091)	**23.08 (0.05)**	25.45 (0.077)
Other airway anomalies	**17.86 (0.045)**	11.54 (0.659)	28.57 (0.055)	28.57 (0.158)
Laryngomalacia	19.05 (0.07)	10 (0.659)	28.57 (0.1)	28.57 (0.339)
Syndromic	8 (1)	4.76 (0.668)	16.67 (1)	20 (1)
Intact palate	**30.77 (0.012)**	16.67 (0.249)	**41.67 (0.024)**	38.46 (0.122)
Age >30 days	**19.23 (0.031)**	12.50 (0.38)	26.92 (0.11)	**34.62 (0.034)**
Intubated	**50 (0.007)**	50 (0.15)	**80 (0.002)**	**66.67 (0.012)**

AHI: apnea-hypopnea index; CNS: central nervous system; GER: gastroesophageal reflux; GI: gastrointestinal; GU: genitourinary; IUGR: intrauterine growth restriction; LBW: low birth weight; RS: Robin sequence.
Significant values ($p < 0.05$) are listed in bold.

Table 3
Paired *t*-test of numeric variables between mandibular distraction osteogenesis successes and failures.

	Failure by tracheostomy			Failure by AHI			Any failure			Any failure + deceases		
	No	Yes	*p* value	No	Yes	*p* value	No	Yes	*p* value	No	Yes	*p* value
n	74	7	–	68	6	–	65	13	-	64	16	–
Birth weight (kg)	2.97	2.46	0.067	3.00	2.69	0.307	3.02	2.61	0.053	**3.03**	**2.50**	**0.006**
Age (days)	**29.9**	**70.5**	**0.001**	32.2	43.0	0.423	**30.8**	**51.7**	**0.037**	**29.6**	**49.3**	**0.031**
Weight (kg)	3.33	3.75	0.417	3.43	3.16	0.419	3.39	3.44	0.898	3.38	3.28	0.707

AHI: apnea-hypopnea index.
Significant values ($p < 0.05$) are listed in bold.

anomalies, GER, intact palate, airway anomalies, and pre-operative intubation. However, when failure is defined as limited improvement in AHI, there are no variables statistically associated with failure. This suggests that multifactorial or unanalyzed variables are influencing failure in this unanalyzed and previously unreported sub-population.

As reported previously, laryngomalacia is not associated with failure of MDO across any of the analyzed variables ($p < 0.05$) (Tholpady et al., 2015). When this supraglottic disease is separated from other airway anomalies, a clear difference can be seen between the two variables. Non-laryngomalacia airway anomalies are associated with failure by tracheostomy and so should still be approached with the knowledge that MDO will not be successful at a higher rate.

The analysis of this patient population provides the basis for score creation, much like the GILLS score (Rogers et al., 2011; Abramowicz et al., 2012). The score is a well-known predictor of success of tongue-lip adhesion (TLA) in the RS population. It has identified **G**ER, **I**ntubation pre-operatively, **L**ate operation, **L**ow birth weight, and **S**yndromic diagnosis as important predictors of success; fewer than three of these predicts a 100% successful TLA. Of these variables GER and intubation pre-operatively were identified as being important in this mandibular distraction study. Low birth weight was not shown to be significant, but approached significance in the deceased population ($p < 0.06$). Syndromic status was not significant.

Interestingly, using paired *t*-test analysis, a breakpoint was identified between successful and unsuccessful MDO with regard to the age at performance of distraction. RS patients below 30 days of age at the time of distraction were more likely to be successful than children older than 2 months. The reasons for this age difference could be many, but this is similar to the GILLS score in that

Table 4
Sensitivity, specificity, positive and negative predictive value for the combinations of the six variables with corresponding receiver operating characteristic curve scores.

Combination of variables analyzed[a]	GAITO	GIANTO	GIT	OAINT	OTIG	TINGO	TING	TONI
Failure by tracheostomy								
Specificity	100	100	85.7	100	100	100	85.7	100
Negative predictive value	22.6	19.4	54.5	28	31.8	25	31.6	43.8
Positive predictive value	100	100	98.6	100	100	100	98.4	100
Sensitivity	67.6	60.8	93.2	75.7	79.7	71.6	82.4	87.8
Area under ROC curve	0.93 (0.86–1)	0.94 (0.87–1)	0.93 (0.86–1)	0.94 (0.88–1)	0.95 (0.9–1)	0.96 (0.9–1)	0.92 (0.82–1)	0.96 (0.92–0.99)
Failure by AHI								
Specificity	83.3	83.3	33.3	66.7	83.3	83.3	50	50
Negative predictive value	18.5	16.1	28.6	18.2	27.8	21.7	21.4	23.1
Positive predictive value	97.9	97.7	94	96.2	98.2	98	95	95.1
Sensitivity	67.6	61.8	92.6	73.5	80.9	73.5	83.8	85.3
Area under ROC curve	0.75 (0.5–1)	0.75 (0.49–1)	0.73 (0.53–0.94)	0.71 (0.47–0.96)	0.77 (0.53–1)	0.75 (0.51–1)	0.72 (0.5–0.95)	0.72 (0.5–0.94)
Any failure								
Specificity	84.6	84.6	53.8	76.9	84.6	84.6	61.5	69.2
Negative predictive value	36.7	32.4	70	40	52.4	42.3	47.1	56.3
Positive predictive value	95.8	95.5	91.2	94.3	96.5	96.2	91.8	93.5
Sensitivity	70.8	64.6	95.4	76.9	84.6	76.9	86.2	89.2
Area under ROC curve	0.8 (0.64–0.97)	0.8 (0.63–0.97)	0.8 (0.66–0.95)	0.79 (0.63–0.95)	0.83 (0.67–0.99)	0.81 (0.65–0.98)	0.78 (0.63–0.94)	0.81 (0.66–0.96)
Any failure including all deaths								
Specificity	75	81.3	43.8	68.8	68.8	68.8	50	56.3
Negative predictive value	38.7	36.1	63.6	44	50	39.3	42.1	56.3
Positive predictive value	92	93.3	87.1	91.1	91.5	90.6	87.1	89.2
Sensitivity	70.8	64.6	93.8	78.5	83.1	73.8	83.1	89.2
Area under ROC curve	0.74 (0.58–0.91)	0.77 (0.63–0.92)	0.72 (0.57–0.87)	0.77 (0.63–0.91)	0.73 (0.56–0.9)	0.76 (0.61–0.9)	0.75 (0.62–0.88)	0.75 (0.61–0.9)

AHI: apnea-hypopnea index; ROC: receiver operating characteristic.
[a] The combinations of variables analyzed are drawn from the following: **G**astroesophageal reflux; **A**ge >30 days; **N**eurologic anomaly; airway anomalies **O**ther than laryngomalacia; **I**ntact palate; and pre-operative intubation.

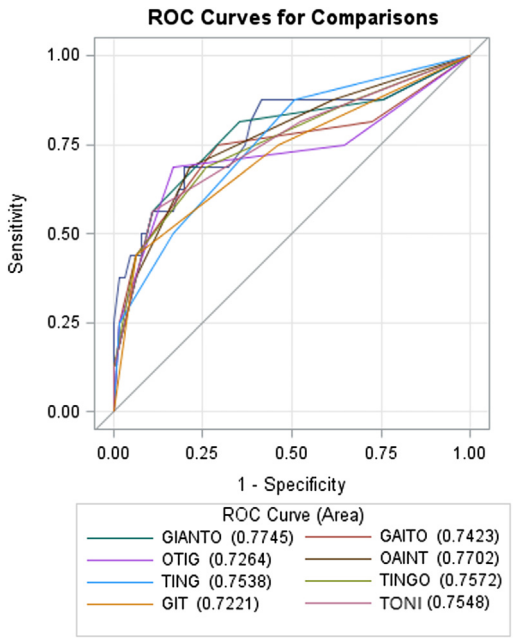

Fig. 1. Receiver operating characteristic (ROC) curve analysis for the top eight predictor variable groupings for outcome variable denoting all failures.

there is a critical period during which an operation has a better chance of success. In the GILLS score, late operation is defined as two weeks; in this study it is 30 days. This indicates there may be physiological changes that become ingrained and are irreversible past a certain age even with intervention.

This report does identify the following patient variables associated with failure of distraction as defined by post-procedure tracheostomy, limited improvement in AHI, or death by apnea: **G**ER, **A**ge >30 days, **N**eurologic anomaly, airway anomalies **O**ther than laryngomalacia, **I**ntact palate, and pre-operative in**T**ubation. Gastrostomy tube and fundoplication were eliminated from the score construction because they are usually procedures that occur after distraction, and so are not useful for prospectively identifying failures of distraction.

These scores were most simply chosen by evaluation of the ROC curves. These are graphical plots that illustrate the performance of a binary classifier system (will MDO work or not) as the discrimination values are varied. It is created by plotting the true positive rate against the false positive rate over differing threshold values. In this case, 0.5 indicates what would be seen when guessing, 1 indicates a perfectly discriminative test, and 0 is completely incorrect. Although no score is perfect, ROC values ranged between 0.7 and 0.9 for all failure variables (Fig. 1).

Depending on the question asked, each score has a differing value. A comparison of the GIT and GIANTO scores illustrate this point. If a score with a high sensitivity is required, the GIT score demonstrates a higher sensitivity and positive predictive value than the GIANTO score. As more variables are added to the score, the specificity increases, at the expense of sensitivity. No score has a 100% specificity and sensitivity, and the needs of the patient and provider determine which test will be useful (Loong, 2013).

These data suggest that a unified definition of successful distraction should be established for consistent assessment of surgical outcomes of MDO as applied to RS patients. The authors suggest this definition would be the tripartite avoidance of tracheostomy, improvement in AHI, and avoidance of mortality associated with airway obstruction. The avoidance of tracheostomy and mortality are commonly used measures; however, these outcomes fail to identify patients who avoid tracheostomy and are still affected by severe airway obstruction.

Decrease in AHI is a metric that requires further attention. AHI measurement requires the use of polysomnography as an assessment tool for quantifying surgical outcomes, and is not consistently used across and within all studies (Denny, 2004; Schaefer et al., 2004; Dauria and Marsh, 2008; Cicchetti et al., 2012). Furthermore, the requirement of an improvement in AHI may identify patients who have avoided tracheostomy but still have a high degree of airway obstruction (AHI >5–10) and as a result, require major supplemental airway support such as continuous positive airway pressure (CPAP) or home oxygen. This scenario demonstrates an incomplete beneficial effect of MDO and therefore cannot be considered a completely successful distraction. The specific definition of 'improvement in AHI' is subject to debate and limited clinical data exists suggesting a normal acceptable range.

An AHI below 5 would be considered acceptable by most specialists treating airway obstruction. The authors, however, would urge caution in following this definition based on their clinical experience in treating Robin sequence. Certainly patients with RS that is isolated or lacks an additional craniofacial anomaly can be expected to respond favorably to mandibular distraction, when indicated. However, patients with severe Treacher Collins or Nager syndrome uncommonly achieve AHI below 5, even in the best of circumstances, precluding them from any possibility of achieving a successful distraction as defined by a 'normal' AHI. Further complicating the issue of a 'normal' AHI is the recent report of isolated cleft lip/palate patients having AHIs above 20 in infancy that then rapidly ameliorate without any intervention except growth (Smith et al., 2014). Defining the normal/acceptable range of airway obstruction in the RS population after MDO is beyond the scope of this report. Based on the clinical data presented, and to improve the classification of successful and unsuccessful operations, the authors suggest an AHI below a certain threshold should be considered as an indicator of successful MDO for the relief of airway obstruction in the RS population.

This study is limited by the retrospective design and single-institutional experience which includes the collective surgical outcomes of multiple surgeons over many years. The patients in this report were treated following a previously published, institutionally derived, treatment protocol (Flores et al., 2014; Murage et al., 2014). It is certainly possible that other surgeons, following different indications for intervention would produce different surgical outcomes.

5. Conclusion

In conclusion, variables significantly associated with failure of distraction are shown to be **G**ER, **A**ge >30 days, **N**eurologic anomaly, airway anomalies **O**ther than laryngomalacia, **I**ntact palate, and pre-operative in**T**ubation. Failure can be defined as: the need for tracheostomy, an incomplete amelioration in AHI, or any cause of death; these dependent outcome variables have different contributing independent variables, with no variable appearing to significantly contribute in patients where there is incomplete amelioration of AHI. The variables allow score construction with varying levels of specificity and sensitivity, depending on the needs of the treating physician and the question asked. These variables will be studied along with others in a larger prospective study on this patient population.

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References

Abramowicz S, Bacic JD, Mulliken JB, Rogers GF: Validation of the GILLS score for tongue–lip adhesion in Robin sequence patients. J Craniofac Surg 23: 382–386, 2012

Burstein FD, Williams JK: Mandibular distraction osteogenesis in Pierre Robin sequence: application of a new internal single-stage resorbable device. Plast Reconstr Surg 115: 61–67, 2005

Cascone P, Papoff P, Arangio P, Vellone V, Calafati V, Silvestri A: Fast and early mandibular osteodistraction (FEMOD) in severe Pierre Robin sequence. J Craniomaxillofac Surg 42: 1364–1370, 2014

Cicchetti R, Cascone P, Caresta E, Papoff P, Miano S, Cerasaro C, et al: Mandibular distraction osteogenesis for neonates with Pierre Robin sequence and airway obstruction. J Matern Fetal Neonatal Med 25: 141–143, 2012

Costa MA, Tu MM, Murage KP, Tholpady SS, Engle WA, Flores RL: Robin sequence: mortality, causes of death, and clinical outcomes. Plast Reconstr Surg 134: 738–745, 2014

Dauria D, Marsh JL: Mandibular distraction osteogenesis for Pierre Robin sequence: what percentage of neonates need it? J Craniofac Surg 19: 1237–1243, 2008

Denny AD: Distraction osteogenesis in Pierre Robin neonates with airway obstruction. Clin Plast Surg 31: 221–229, 2004

Denny A, Kalantarian B: Mandibular distraction in neonates: a strategy to avoid tracheostomy. Plast Reconstr Surg 109: 896–904, 2002

Denny AD, Talisman R, Hanson PR, Recinos RF: Mandibular distraction osteogenesis in very young patients to correct airway obstruction. Plast Reconstr Surg 108: 302–311, 2001

Flores RL, Tholpady SS, Sati S, Fairbanks G, Socas J, Choi M, et al: The surgical correction of Pierre Robin sequence: mandibular distraction osteogenesis versus tongue-lip adhesion. Plast Reconstr Surg 133: 1433–1439, 2014

Hong P, Bezuhly M, Mark TS, Hart RD, Kearns DB, Corsten G: Tracheostomy versus mandibular distraction osteogenesis in Canadian children with Pierre Robin sequence: a comparative cost analysis. J Otolaryngol Head Neck Surg 41: 207–214, 2012

Iatrou I, Theologie-Lygidakis N, Schoinohoriti O: Mandibular distraction osteogenesis for severe airway obstruction in Robin sequence. Case report. J Craniomaxillofac Surg 38: 431–435, 2010

Kohan E, Hazany S, Roostaeian J, Allam K, Head C, Wald S, et al: Economic advantages to a distraction decision tree model for management of neonatal upper airway obstruction. Plast Reconstr Surg 126: 1652–1664, 2010

Lam DJ, Tabangin ME, Shikary TA, Uribe-Rivera A, Meinzen-Derr JK, de Alarcon A, et al: Outcomes of mandibular distraction osteogenesis in the treatment of severe micrognathia. JAMA Otolaryngol Head Neck Surg 140: 338–345, 2014

Loong T-W: Understanding sensitivity and specificity with the right side of the brain. BMJ 327: 716–719, 2013

Mandell DL, Yellon RF, Bradley JP, Izadi K, Gordon CB: Mandibular distraction for micrognathia and severe upper airway obstruction. Arch Otolaryngol Head Neck Surg 130: 344–348, 2004

Monasterio FO, Drucker M, Molina F, Ysunza A: Distraction osteogenesis in Pierre Robin sequence and related respiratory problems in children. J Craniofac Surg 13: 79–83, 2002

Murage KP, Costa MA, Friel MT, Havlik RJ, Tholpady SS, Flores RL: Complications associated with neonatal mandibular distraction osteogenesis in the treatment of Robin sequence. J Craniofac Surg 25: 383–387, 2014

Murage KP, Tholpady SS, Friel M, Havlik RJ, Flores RL: Outcomes analysis of mandibular distraction osteogenesis for the treatment of Pierre Robin sequence. Plast Reconstr Surg 132: 419–421, 2013

Paes E, Molen A, Muradin MM, Speleman L, Sloot F, Kon M, et al: A systematic review on the outcome of mandibular distraction osteogenesis in infants suffering Robin sequence. Clin Oral Investig 178: 1807–1820, 2013

Papoff P, Guelfi G, Cicchetti R, Caresta E, Cozzi DA, Moretti C, et al: Outcomes after tongue-lip adhesion or mandibular distraction osteogenesis in infants with Pierre Robin sequence and severe airway obstruction. Int J Oral Maxillofac Surg 42: 1418–1423, 2013

Rachmiel A, Emodi O, Rachmiel D, Aizenbud D: Internal mandibular distraction to relieve airway obstruction in children with severe micrognathia. Int J Oral Maxillofac Surg 43: 1176–1181, 2014

Robin P: La chute de la base de la langue consideree comme une nouvelle cause de gene dans la respiration naso-pharyngienne. Bull Acad Med Paris 89: 37–41, 1929

Robin P: Glossoptosis due to atresia and hypotrophy of the mandible. Am J Dis Child 48: 541–547, 1934

Rogers GF, Murthy AS, LaBrie RA, Mulliken JB: The GILLS score: part I. Patient selection for tongue-lip adhesion in Robin sequence. Plast Reconstr Surg 128: 243–251, 2011

Runyan CM, Uribe-Rivera A, Karlea A, Meinzen-Derr J, Rothchild D, Saal H, et al: Cost analysis of mandibular distraction versus tracheostomy in neonates with Pierre Robin sequence. Otolaryngol Head Neck Surg 151: 811–818, 2014

Schaefer RB, Stadler 3rd JA, Gosain AK: To distract or not to distract: an algorithm for airway management in isolated Pierre Robin sequence. Plast Reconstr Surg 113: 1113–1125, 2004

Smith CB, Walker K, Badawi N, Waters KA, MacLean JE: Impact of sleep and breathing in infancy on outcomes at three years of age for children with cleft lip and/or palate. Sleep 37: 919–925, 2014

Tahiri Y, Viezel-Mathieu A, Aldekhayel S, Lee J, Gilardino M: The effectiveness of mandibular distraction in improving airway obstruction in the pediatric population. Plast Reconstr Surg 133: 352e–359e, 2014

Tholpady SS, Costa MA, Hadad I, Havlik RJ, Socas J, Matt BH, et al: Mandibular distraction for Robin sequence associated with laryngomalacia. J Craniofac Surg 26: 826–830, 2015

Wittenborn W, Panchal J, Marsh JL, Sekar KC, Gurley J: Neonatal distraction surgery for micrognathia reduces obstructive apnea and the need for tracheotomy. J Craniofac Surg 15: 623–630, 2004

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Examination of Life-Threatening Injuries in 431 Pediatric Facial Fractures at a Level 1 Trauma Center

Ian C. Hoppe, MD, Anthony M. Kordahi, BA, Angie M. Paik, BA, Edward S. Lee, MD, and Mark S. Granick, MD

Purpose: Pediatric facial fractures represent a challenge in management due to the unique nature of the growing facial skeleton. Oftentimes, more conservative measures are favored to avoid rigid internal fixation and disruption of blood supply to the bone and soft tissues. In addition, the great force required to fracture bones of the facial skeleton often produces concomitant injuries that present a management priority. The purpose of this study was to examine a level 1 trauma center's experience with pediatric facial trauma resulting in fractures of the underlying skeleton with regards to epidemiology and concomitant injuries.

Methods: A retrospective review of all facial fractures at a level 1 trauma center in an urban environment was performed for the years 2000 to 2012. Patients aged 18 years or younger were included. Patient demographics were collected, as well as location of fractures, concomitant injuries, and surgical management strategies. A significance value of 5% was used.

Results: During this period, there were 3147 facial fractures treated at our institution, 353 of which were pediatric patients. Upon further review, 68 patients were excluded because of insufficient data for analysis, leaving 285 patients for review. The mean age of patients was 14.2 years with a male predominance (77.9%). The mechanism of injury was assault in 108 (37.9%), motor vehicle accident in 68 (23.9%), pedestrian struck in 41 (14.4%), fall in 26 (9.1%), sporting accident in 20 (7.0%), and gunshot injury in 16 (5.6%). The mean Glasgow Coma Scale (GCS) on arrival to the emergency department was 13.7. The most common fractures were those of the mandible (29.0%), orbit (26.5%), nasal bone (14.4%), zygoma (7.7%), and frontal bone/frontal sinus (7.5%). Intracranial hemorrhage was present in 70 patients (24.6%). A skull fracture was present in 50 patients (17.5%). A long bone fracture was present in 36 patients (12.6%). A pelvic or thoracic fracture was present in 30 patients (10.5%). A cervical spine fracture was present in 10 patients (3.5%), and a lumbar spine fracture was present in 11 patients (3.9%). Fractures of the zygoma, orbit, nasal bone, and frontal sinus/bone were significantly associated with intracranial hemorrhage ($P < 0.05$). Fractures of the zygoma and orbit were significantly associated with cervical spine injury ($P < 0.05$). The mean GCS for patients with and without intracranial hemorrhages was 11.0 and 14.6, respectively ($P < 0.05$). The mean GCS for patients with and without cervical spine fractures was 11.2 and 13.8, respectively ($P < 0.05$).

Conclusions: Pediatric facial fractures in our center are often caused by interpersonal violence and are frequently accompanied by other more life-threatening injuries. The distribution of fractures parallels previous literature. Midface fractures and a depressed GCS showed a strong correlation with intracranial hemorrhage and cervical spine fracture. A misdiagnosed cervical spine injury or intracranial hemorrhage has disastrous consequences. On the basis of this study, it is the authors' recommendation that any patient sustaining a midface fracture with an abnormal GCS be evaluated for the aforementioned diagnoses.

Key Words: Adolescent, child, facial bones/injuries, infant, humans, multiple trauma/epidemiology/etiology/mortality, skull fractures/epidemiology/etiology/mortality, violence/statistics & numerical data

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Pediatric facial fractures are a fairly uncommon injury, representing less than 15% of all facial fractures,[1] and present a challenge in management. The goal of management in all pediatric patients presenting with facial fractures is anatomic reduction and healing without complication. Before treatment of the facial fracture, it is essential to identify concomitant injuries, such as intracranial injury and spine injury, that may pose a threat to life or quality of life if not identified and appropriately treated. A large retrospective study found that almost 65% of pediatric patients with a facial fracture exhibited associated injury.[2] A recent study concluded that a concussion was documented in almost one third of all pediatric patients presenting with a facial fracture, with an increased risk if the skull, orbit, or maxilla were involved.[3] A related study determined that more than half of all pediatric patients diagnosed with a facial fracture also presented with a serious associated trauma of a vital organ system.[4] In a survey of the National Trauma Data Bank, it was found that pediatric patients with facial fractures exhibited a higher injury severity, longer length of hospital stay, longer time spent in an intensive care setting, increased number of days on a ventilator, and increased hospital charges compared with those without facial fractures.[5] Other studies show varying degrees of concomitant injuries.[6–14]

It has been suggested that the presence of facial fractures actually represents a protective mechanism for the brain to reduce intracranial injury due to the force absorbing characteristics of the facial skeleton.[15] A multicenter study examined this protective mechanism in injured bicyclists and discovered that facial fractures are actually associated with an increased risk for brain injury.[16] The

From the Division of Plastic Surgery, Department of Surgery, New Jersey Medical School, Rutgers University, Newark, NJ.
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Address correspondence and reprint requests to Ian C. Hoppe, MD, Division of Plastic Surgery, Department of Surgery, New Jersey Medical School, Rutgers University, Ambulatory Care Center, Suite E1620, 140 Bergen St., Newark, NJ 07103; E-mail: ianhoppe@gmail.com; hoppeic@njms.rutgers.edu
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TABLE 1. Distribution of Fractures Observed

	Male	Female	Total
Number of patients	222	63	285
Mean age, y	14.7	12.7	14.2
Number of fractures	328	103	431
Mandible fractures	118	21	139
Orbital fractures	92	33	125
Zygoma fractures	26	9	35
Nasal fractures	48	21	69
Frontal bone/sinus fractures	21	15	36
Palate fractures	5	2	7
Le Fort variant fractures	18	2	20

reason for this is likely related to the high-energy mechanism often associated with fracture of the facial skeleton.

The objective of this study is to examine associations between modes of presentation, fracture patterns, and concomitant life-threatening injuries in all facial fractures diagnosed via a radiographic study at a level 1 trauma center during a predetermined period.

METHODS

After institutional review board approval, all facial fractures occurring at a level 1 trauma center (University Hospital, Newark, NJ) between January 2000 and December 2012 were collected based on International Classification of Disease, Revision 9, codes. These results were further refined to include only those patients in the pediatric population (age of 18 years or younger). Patient demographics were collected as well as mechanism of injury, Glasgow Coma Scale (GCS) on presentation, fracture locations, concomitant injuries, and fracture management strategies. Comparisons were made between type of fracture, mechanism of injury, GCS on presentation, length of hospital stay, and life-threatening injuries such as cervical spine injury and intracranial hemorrhage. A significance value of 5% was used.

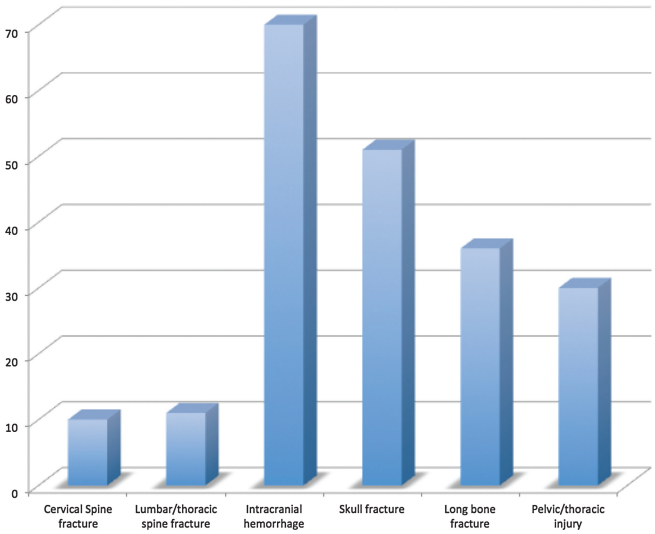

FIGURE 1. Concomitant injuries.

RESULTS

During this period, there were 3147 patients with facial fractures treated at our institution, 353 of which were pediatric patients. Upon further review, 68 patients were excluded because of insufficient data for analysis, leaving 285 patients for review, with a total of 431 fractures. The mean age of patients was 14.2 years with a strong male predominance (78%). The mandible was the most common bone fractured followed by fractures of the orbit (Table 1). Figure 1

TABLE 2. Fracture Types and Concomitant Injuries

	Cervical Spine Fracture	No Cervical Spine Fracture	Odds Ratio (95% CI)	Lumbar/ Thoracic Spine Fracture	No Lumbar/Thoracic Spine Fracture	Odds Ratio	ICH	No ICH	Odds Ratio
Mandible fracture	3	136	NS	3	136	NS	16	123	0.22 (0.12–0.41)*
Palatal fracture	1	6	NS	2	5	11.9 (2.0–70.1)†	3	4	NS
Zygoma fracture	4	33	4.9 (1.3–18.2)†	2	35	NS	16	21	2.7 (1.3–5.6)
Orbital fracture	8	119	5.2 (1.1–25.1)†	8	119	NS	48	79	3.8 (2.1–6.7)*
Nasal fracture	5	64	NS	6	63	4.0 (1.2–13.6)†	30	39	3.4 (1.9–6.1)*
Frontal bone/sinus fracture	3	33	NS	3	33	NS	25	11	10.3 (4.7–22.5)*
Le Fort fracture	2	18	NS	1	19	NS	8	12	NS
	Skull Fracture	No Skull Fracture	Odds Ratio	Long Bone Fracture	No Long Bone Fracture	Odds Ratio	Abdominal/Pelvic/ Thoracic Injury	No Abdominal/Pelvic/ Thoracic Injury	Odds Ratio
Mandible fracture	14	125	0.33 (0.17–0.64)*	14	125	NS	12	126	NS
Palatal fracture	4	3	6.6 (1.4–30.2)*	4	3	10.3 (2.2–47.9)*	2	5	NS
Zygoma fracture	10	27	NS	5	32	NS	6	31	NS
Orbital fracture	38	89	4.8 (2.4–9.4)*	19	108	NS	16	111	NS
Nasal fracture	16	53	NS	10	59	NS	12	57	2.3 (1.0–5.1)†
Frontal bone/sinus fracture	26	10	23.3 (10.1–53.9)*	5	31	NS	7	29	NS
Le Fort fracture	8	12	3.4 (1.3–8.9)*	4	16	NS	6	14	4.3 (1.5–12.2)*

*$P < 0.01$; †$P < 0.05$.

CI, confidence interval; ICH, intracranial hemorrhage; NS, not significant.

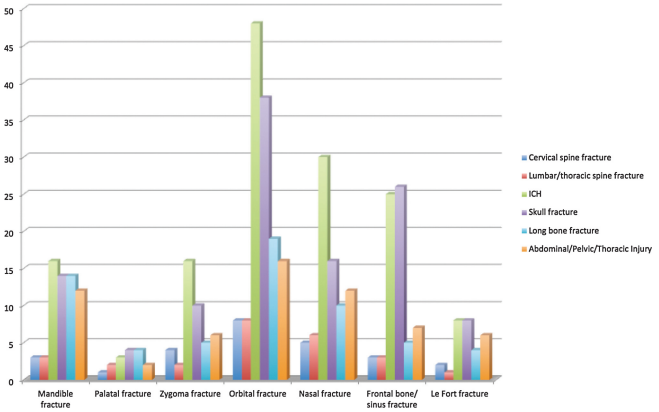

FIGURE 2. Concomitant injuries and type of fracture.

depicts the concomitant injuries observed in our series. The relationship between type of fracture and concomitant injuries is presented in Table 2 and Figure 2.

Loss of consciousness with injury was significantly associated with thoracic/lumbar spine fracture, intracranial hemorrhage, skull fracture, long bone fracture, abdominal/pelvic/thoracic injury, and death. Those patients intubated in the emergency department were significantly more likely to have a cervical spine fracture, thoracic/lumbar spine fracture, intracranial hemorrhage, skull fracture, and abdominal/pelvic/thoracic injury. In addition, intubation in the emergency department was significantly associated with death. The mean GCS for patients sustaining a cervical spine fracture was 11.2, compared with 13.8 for those without a cervical spine fracture ($P < 0.05$, Fig. 3). The mean GCS for patients with an intracranial hemorrhage was 11.0, compared with 14.6 for those without an intracranial hemorrhage ($P < 0.01$, Fig. 4). The mean age of patients experiencing an intracranial hemorrhage was significantly lower than those without (12.8 versus 14.7 years old, $P < 0.01$). The total hospital length of stay was increased for patients experiencing an intracranial hemorrhage (11.2 versus 3.7 days, $P < 0.01$).

DISCUSSION

Facial fractures in the pediatric population are associated with severe concomitant injuries. Similar to previous studies, there was a strong male preponderance,[12,17–19] and the mandible was

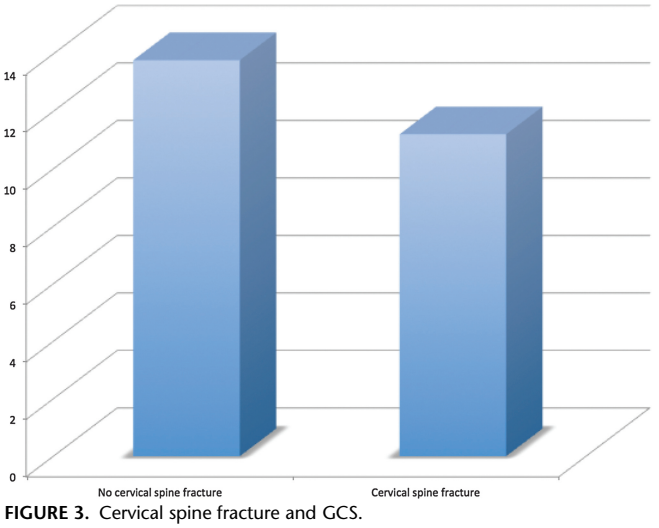

FIGURE 3. Cervical spine fracture and GCS.

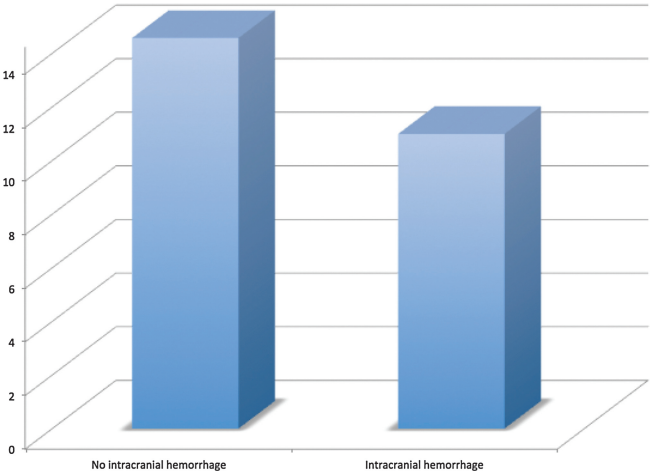

FIGURE 4. Intracranial hemorrhage and GCS.

the most common bone fractured.[17–19] Interestingly, in female patients in our series, the orbit was the most common bone fractured. The most common etiology of fractures in our series was interpersonal violence overall, interpersonal violence in men, and motor vehicle accident in women. The preponderance of interpersonal violence likely reflects the population treated at our institution, notably urban, often gang-affiliated males.

One hundred twenty-seven patients (44.6%) had some form of concomitant multisystem injury. These injuries are likely a reflection of the degree of force required to fracture the facial skeleton. In our study, mandible fractures seem to portend a protective mechanism from several serious injuries: intracranial hemorrhages and skull fractures. Fracture of the mandible may represent a force absorbing mechanism, thus sparing the cranium and its contents from injury. Palatal fractures were associated with an increased rate of thoracolumbar spine fractures, skull fractures, and long bone fractures. Palatal fractures usually are due to a strong force, and the association of long bone fractures and thoracolumbar spine fractures likely reflects this. Fractures of the zygoma were associated with cervical spine injuries and intracranial hemorrhage. As the force is transmitted in a more cranial direction on the facial skeleton, the cervical spine and intracranial contents may be more likely to be traumatized. Orbital fractures were associated with cervical spine fractures, intracranial hemorrhage, and skull fractures. This is similar to the patterns seen with fractures of the zygoma in that there is likely more force transmitted to the cervical spine and intracranial contents. Nasal bone fractures were associated with thoracolumbar spine fractures, intracranial hemorrhage, and abdominal/pelvic injuries. The reason for these associations is unclear and may represent an anomaly due to the prominent position of the nose. Frontal bone/sinus fractures were associated with intracranial hemorrhage and skull fractures. Again, the tremendous force required to fracture the frontal bone places the intracranial contents at greater risk. Le Fort variant fractures were associated with skull fractures and abdominal/pelvic injuries.

Cervical spine fractures and intracranial hemorrhages were associated with a lower GCS score. This is a logical association considering the severity of these injuries.

CONCLUSIONS

A large proportion of facial fractures in the pediatric population are associated with severe concomitant injuries. In general, as fractures move in a more cranial direction, there is an increased risk

for intracranial injuries and cervical spine fractures. A lower GCS on presentation portends a higher association with cervical spine injury and intracranial hemorrhage. The failure to identify these associated and serious injuries could have disastrous consequences, and every practitioner involved in treating facial fractures must be aware of this risk.

REFERENCES

1. Vyas RM, Dickinson BP, Wasson KL, et al. Pediatric facial fractures: current national incidence, distribution, and health care resource use. *J Craniofac Surg* 2008;19:339–349
2. Ferreira PC, Amarante JM, Silva PN, et al. Retrospective study of 1251 maxillofacial fractures in children and adolescents. *Plast Reconstr Surg* 2005;115:1500–1508
3. Afrooz PN, Grunwaldt LJ, Zanoun RR, et al. Pediatric facial fractures: occurrence of concussion and relation to fracture patterns. *J Craniofac Surg* 2012;23:1270–1273
4. Grunwaldt L, Smith DM, Zuckerbraun NS, et al. Pediatric facial fractures: demographics, injury patterns, and associated injuries in 772 consecutive patients. *Plast Reconstr Surg* 2011;128:1263–1271
5. Imahara SD, Hopper RA, Wang J, et al. Patterns and outcomes of pediatric facial fractures in the United States: a survey of the National Trauma Data Bank. *J Am Coll Surg* 2008;207:710–716
6. Gassner R, Tuli T, Hachl O, et al. Craniomaxillofacial trauma in children: a review of 3,385 cases with 6,060 injuries in 10 years. *J Oral Maxillofac Surg* 2004;62:399–407
7. Thoren H, Schaller B, Suominen AL, et al. Occurrence and severity of concomitant injuries in other areas than the face in children with mandibular and midfacial fractures. *J Oral Maxillofac Surg*. 2012;70:92–96
8. Thaller SR, Mabourakh S. Pediatric mandibular fractures. *Ann Plast Surg* 1991;26:511–513
9. Eggensperger Wymann NM, Holzle A, Zachariou Z, et al. Pediatric craniofacial trauma. *J Oral Maxillofac Surg* 2008;66:58–64
10. Grisoni ER, Pillai SB, Volsko TA, et al. Pediatric airbag injuries: the Ohio experience. *J Pediatr Surg* 2000;35:160–162
11. Holland AJ, Broome C, Steinberg A, et al. Facial fractures in children. *Pediatr Emerg Care* 2001;17:157–160
12. Kim SH, Lee SH, Cho PD. Analysis of 809 facial bone fractures in a pediatric and adolescent population. *Arch Plast Surg* 2012;39:606–611
13. MacIsaac ZM, Berhane H, Cray JJr, et al. Nonfatal sport-related craniofacial fractures: characteristics, mechanisms, and demographic data in the pediatric population. *Plast Reconstr Surg* 2013; 131:1339–1347
14. Mericli AF, DeCesare GE, Zuckerbraun NS, et al. Pediatric craniofacial fractures due to violence: comparing violent and nonviolent mechanisms of injury. *J Craniofac Surg* 2011;22:1342–1347
15. Lee KF, Wagner LK, Lee YE, et al. The impact-absorbing effects of facial fractures in closed-head injuries. An analysis of 210 patients. *J Neurosurg* 1987;66:542–547
16. Keenan HT, Brundage SI, Thompson DC, et al. Does the face protect the brain? A case–control study of traumatic brain injury and facial fractures. *Arch Surg* 1999;134:14–17
17. Munante-Cardenas JL, Olate S, Asprino L, et al. Pattern and treatment of facial trauma in pediatric and adolescent patients. *J Craniofac Surg* 2011;22:1251–1255
18. Singh G, Mohammad S, Pal US, et al. Pediatric facial injuries: it's management. *Natl J Maxillofac Surg* 2011;2:156–162
19. Qing-Bin Z, Zhao-Qiang Z, Dan C, et al. Epidemiology of maxillofacial injury in children under 15 years of age in southern China. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;115:436–441

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Speech Outcomes After Clinically Indicated Posterior Pharyngeal Flap Takedown

Evan B. Katzel, MD, Sameer Shakir, MD, Sanjay Naran, MD, Zoe MacIsaac, MD, Liliana Camison, MD, Matthew Greives, MD, Jesse A. Goldstein, MD, Lorelei J. Grunwaldt, MD, Matthew D. Ford, MS, CCC-SLP, and Joseph E. Losee, MD

Background: Velopharyngeal insufficiency affects as many as one in three patients after cleft palate repair. Correction using a posterior pharyngeal flap (PPF) has been shown to improve clinical speech symptomatology; however, PPFs can be complicated by hyponasality and obstructive sleep apnea. The goal of this study was to assess if speech outcomes revert after clinically indicated PPF takedown.

Methods: The cleft-craniofacial database of the Children's Hospital of Pittsburgh at the University of Pittsburgh Medical Center was retrospectively queried to identify patients with a diagnosis of velopharyngeal insufficiency treated with PPF who ultimately required takedown. Using the Pittsburgh Weighted Speech Score (PWSS), preoperative scores were compared to those after PPF takedown. Outcomes after 2 different methods of PPF takedown (PPF takedown alone or PPF takedown with conversion to Furlow palatoplasty) were stratified and cross-compared.

Results: A total of 64 patients underwent takedown of their PPF. Of these, 18 patients underwent PPF takedown alone, and 46 patients underwent PPF takedown with conversion to Furlow Palatoplasty. Patients averaged 12.43 (range, 3.0–22.0)(SD: 3.93) years of age at the time of PPF takedown, and 58% were men. Demographics between groups were not statistically different. The mean duration of follow-up after surgery was 38.09 (range, 1–104) (SD, 27.81) months. For patients undergoing PPF takedown alone, the mean preoperative and postoperative PWSS was 3.83 (range, 0.0–23.0) (SD, 6.13) and 4.11 (range, 0.0–23.0) (SD, 5.31), respectively ($P = 0.89$). The mean change in PWSS was 0.28 (range, −9.0 to 7.0) (SD, 4.3). For patients undergoing takedown of PPF with conversion to Furlow palatoplasty, the mean preoperative and postoperative PWSS was 6.37 (range, 0–26) (SD, 6.70) and 3.11 (range, 0.0–27.0) (SD, 4.14), respectively ($P < 0.01$). The mean change in PWSS was −3.26 (range, −23.0 to 4.0) (SD, 4.3). For all patients, the mean preoperative PWSS was 5.66 (range, 0.0–26) (SD, 6.60) and 3.39 (range, 0.0–27) (SD, 4.48), respectively ($P < 0.05$). The mean change in PWSS was −2.26 (range, −23.0 to 7) (SD, 5.7). There was no statistically significant regression in PWSS for either surgical intervention. Two patients in the PPF takedown alone cohort demonstrated deterioration in PWSS that warranted delayed conversion to Furlow palatoplasty. Approximately 90% of patients, who undergo clinically indicated PPF takedown alone, without conversion to Furlow Palatoplasty, will show no clinically significant reduction in speech.

Conclusions: Although there is concern that PPF takedown may degrade speech, this study finds that surgical takedown of PPF, when clinically indicated, does not result in a clinically significant regression of speech.

Key Words: cleft lip, cleft palate, velopharnygeal insufficiency, sleep apnea, craniofacial, Furlow plasty, pharyngoplasty, double opposing z-plasty, VPI

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From the Division of Pediatric Plastic Surgery, Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA.
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Reprints: Evan B. Katzel, MD, Division of Pediatric Plastic Surgery, Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA. E-mail: katzeleb@upmc.edu.

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The velopharyngeal valve separates the oral and nasal pharynx during swallowing and speaking. It is created by the lateral pharyngeal walls, the posterior pharyngeal wall, and the velum, and selectively allows and resists airflow during normal speech production. Velopharyngeal insufficiency (VPI) is the inability to completely occlude the velopharyngeal port during speech and can be an unfortunate complication seen in approximately 30% of palatal surgery.[1] Data suggest that straightline palatoplasty without intravelar veloplasty or with incomplete intravelar veloplasty place patients at a greater risk for VPI.[2] Sphincterplasty, fat grafting, or filler injection to the posterior pharynx and/or obturators can be used to treat VPI; however, the gold standard treatment of VPI after cleft palate repair is pharyngoplasty, and the posterior pharyngeal flap (PPF) is one of the most frequently performed procedures.

The PPF was initially described for the treatment of VPI in 1865 by Passavant.[3] Creation of a PPF is often used to treat VPI and is well established to improve clinical speech symptomatology.[4–7] Long-term success rates with PPF range from 74% to 98%.[1,8–11] However, PPFs are accompanied by the potential morbidity of hyponasality and postoperative obstructive sleep apnea (OSA), with OSA reported in as many as 40% of the cases.[12,13] Although, a large body of literature exists regarding the identification, prevention, and management of OSA in this population, studies have yet to answer whether speech symptomatology suffers as a consequence of PPF takedown.[8,14–19] There is also a lack of literature exploring conversion of previous straightline palatoplasties to Furlow palatoplasty for these patients. The treatment of these patients is controversial, given the challenge of treating the OSA *caused by the PPF* while maintaining the improvement in speech *owed to the PPF*. Given the lack of existing literature, the study aims to assess speech outcomes after clinically indicated PPF takedown alone or when performed with conversion to Furlow palatoplasty. This study hypothesizes that PPF takedown or PPF takedown with conversion to Furlow palatoplasty can be performed for the treatment of OSA without deleterious effects on speech outcomes.

METHODS

The study was approved by the Institutional Review Board at the University of Pittsburgh Medical Center. The Cleft-Craniofacial Database of the Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center was queried from 1992 to 2012 to identify patients with a diagnosis of VPI treated with PPF and eventual PPF takedown. All patients who fit these criteria were included in this study. No patients who had a diagnosis of VPI treated with PPF and eventual PPF takedown were excluded. Demographic, operative, and speech data were stratified based on treatment modality (ie, PPF takedown alone versus PPF takedown with conversion to Furlow palatoplasty) and compared. Demographic data included sex and age at time of PPF takedown. Operative data included surgical complications and postoperative length of follow-up.

The Pittsburgh Weighted Speech Score (PWSS) was used to quantify preoperative and postoperative speech changes. The PWSS is a validated measure of clinical speech outcomes that rates 5 components of

TABLE 1. Pittsburgh Weighted Speech Score

Nasal Emission (0–3, Highest Value)	**Right**	**Left**
Not present	0	0
Inconsistent, visible	1	1
Consistent, visible	2	2
Audible	3	3
Turbulent	3	3
Facial Grimace (0/2, Presence)	2	
Nasality (0–4, Highest Value)		
Normal	0	
Mild hypernasality	1	
Moderate hypernasality	23	
Severe hypernasality	4	
Hypo-/hypernasality	2	
Cul de sac	2	
Hyponasality	0	
Phonation (0–3, Highest Value)		
Normal	0	
Mild hoarseness/breathiness	1	
Moderate hoarseness/breathiness	2	
Severe hoarseness/breathiness	3	
Reduced loudness	2	
Tension in system	3	
Articulation (0–23, Summative)		
Normal	0	
Developmental errors	0	
Errors not related to VPI	0	
Errors related to dentition	0	
Reduced intraoral pressure from sibilants	1	
Reduced intraoral pressure for fricatives	2	
Reduced intraoral pressure for plosives	3	
Omission of fricatives or plosives	2	
Omission of fricatives or plosives plus hard glottal attack for vowels	3	
Lingual-palatal sibilants	2	
Pharyngeal fricatives or plosives, "backing", snorting, inhalation or exhalation substitutions	3	
Glottal stops	3	
Nasal substitutions for pressure sounds	4	

speech: nasality, nasal emission, facial grimace, phonatory characteristics, and compensatory misarticulations (Table 1).[20] The complete PWSS assessments as evaluated by the speech pathologists at every visit, were reviewed. A lower PWSS denotes better speech than a higher PWSS.

Patients underwent OSA screening and counseling regarding signs/symptoms at initial evaluation. Clinical suspicion (ie, breath-holding spells, snoring) warranted further evaluation including diagnostic sleep studies. After surgical intervention, parents were questioned and counseled at every postoperative visit regarding the persistence or development of OSA. Further diagnostic studies were ordered as warranted.

Clinical indications for PPF takedown included: (1) OSA, (2) OSA and deterioration of speech (ie, worsening PWSS), (3) borderline adequate speech and possible midface advancement with or without OSA, and/or (4) recurrent VPI and possible conversion Furlow palatoplasty.

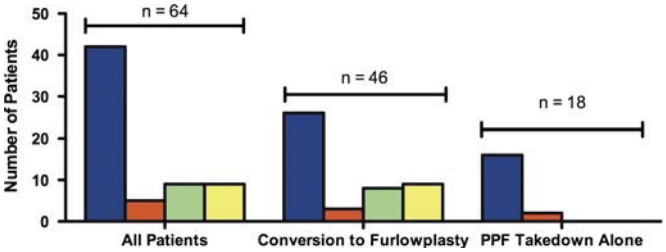

FIGURE 1. Clinical indications for PPF takedown are obstructive sleep apnea (black), obstructive sleep apnea with deterioration of speech (dark grey), borderline adequate speech and the plan for midface advancement with or without OSA (light grey), and recurrent VPI with plans for conversion to Furlow palatoplasty (white).

Statistical Analysis

Data were analyzed with unpaired, 2-tailed *t* tests with a significance level of *P* less than 0.05 using Prism GraphPad 5.0 (GraphPad Software, Inc., La Jolla, Calif.) statistical software.

RESULTS

Sixty-four patients with a history of VPI who underwent PPF takedown were identified during a 20-year period from 1992 to 2012. Forty-two patients (65.6%) underwent PPF takedown for OSA, 5 (7.8%) for OSA and deterioration of speech, 8 (12.5%) for borderline adequate speech and possible midface advancement with or without OSA, and 9 (14.1%) for recurrent VPI and possible conversion Furlow palatoplasty (Fig. 1). All PPFs were in place for greater than 5 years before takedown.

Thirty-seven patients (57.8%) were men. Eighteen patients (28.1%) underwent PPF takedown alone, and 46 patients (71.9%) underwent PPF takedown with conversion to Furlow palatoplasty. Mean length of postoperative follow-up period was 38.1 ± 27.8 months (range 1–104). Mean age at time of intervention was 12.4 ± 3.9 years (3–22). Mean age for patients undergoing PFF takedown with conversion to Furlow palatoplasty was 12.3 ± 3.9 years (3-20) compared to 12.8 ± 4.2 years (7–22) for those undergoing PPF takedown alone ($P = 0.63$).

For all patients, mean preoperative PWSS was 5.7 ± 6.6 (range, 0–26) compared to 3.4 ± 4.5 (range, 0–27) after PPF takedown. No statistically significant regression in PWSS occurred after PPF takedown ($P < 0.05$). For patients undergoing PPF takedown alone, mean preoperative (3.8 ± 6.1 [range, 0–23]) and postoperative PWSS (4.1 ± 5.3 [range, 0–23]) were not significantly different ($P = 0.89$)

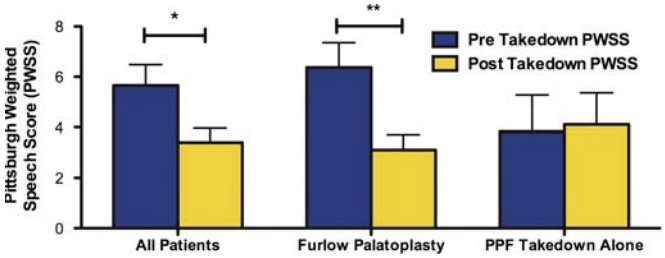

FIGURE 2. Pittsburgh weighted speech scores pre-takedown (black) and post-takedown (white) for all patients, PPF takedown with conversion to Furlow palatoplasty, and PPF takedown alone. All figures denote means with error bars reflecting standard error of the mean. ** represents a *P* value less than 0.01 and * represents a *P* value less than 0.05.

TABLE 2. Patients Who Had a Regression in PWSS After PPF Takedown

Pt	Pretakedown PWSS	Posttakedown PWSS	Delta PWSS	Reason for Takedown	Sex	Age at Takedown, y	Surgery	Additional Speech Surgery (Operation: PWSS Postoperatively)	Follow-up, mo
1	3	5	2	OSA/Lefort I	Male	16	PPF takedown + Conversion Furlow	No	29
2	2	5	3	OSA	Male	15	PPF takedown + Conversion Furlow	No	26
3	3	4	1	OSA	Female	10	PPF takedown + Conversion Furlow	No	53
4	0	1	1	Recurrent VPI	Male	9	PPF takedown + Conversion Furlow	No	49
5	23	27	4	OSA	Male	17	PPF takedown + Conversion Furlow	No	28
6	0	3	3	OSA/Lefort I	Male	20	PPF takedown + Conversion Furlow	No	55
7	0	4	4	OSA	Female	19	Takedown alone	No	10
8	0	7	7	OSA	Male	11	Takedown alone	Yes (delayed conversion Furlow Palatoplasty: 3)	60
9	0	3	3	OSA/hyponasal	Female	10	Takedown alone	No	78
10	0	3	3	OSA	Female	12	Takedown alone	No	16
11	0	1	1	OSA	Male	8	Takedown alone	No	53
12	0	1	1	OSA	Male	15	Takedown alone	No	1
13	0	3	3	OSA	Female	9	Takedown alone	No	19
14	4	10	6	OSA/hyponasal	Female	7	Takedown alone	Yes (delayed conversion Furlow Palatoplasty: 4)	104
15	2	3	1	OSA	Male	19	Takedown alone	No	2
16	3	4	1	OSA	Male	11	Takedown alone	No	2

(Fig. 2). For patients undergoing PPF takedown with conversion to Furlow palatoplasty, PWSS significantly improved postoperatively (3.1 ± 4.1 [range, 0–27]) compared to preoperative PWSS (6.4 ± 6.7 [range, 0–26]). When stratified by surgical intervention, no significant deterioration in postoperative PWSS occurred ($P = 0.79$).

No surgical complications occurred after PPF takedown. Sixteen (25.0%) patients had deterioration in PWSS after PPF takedown (n = 10 [55.6%] in the PPF takedown alone group versus 6 [13.0%] in the conversion to Furlow palatoplasty group) (Table 2). For patients whose speech deteriorated, mean deterioration in PWSS was 2.8 ± 1.8 (range, 1–7) (Fig. 3). For patients who had deterioration after PPF takedown alone, mean deterioration in PWSS was 3.0 ± 2.2 (range, 1–7). For patients who had deterioration after PPF takedown with conversion to Furlow palatoplasty, the mean deterioration in PWSS was 2.2 ± 1.3 (range, 1–4). Two patients (3.1%) in the study, representing 11.1% of the PFF takedown alone cohort, experienced *clinically* significant (defined as affecting intelligibility) deterioration in PWSS that required further speech resonance surgery after PPF takedown. These patients (patients 8 and 14) (Table 2) progressed to delayed conversion to Furlow palatoplasty. No patients required readmission for surgical-related or OSA-related complications after PPF takedown or PPF takedown with conversion to Furlow palatoplasty.

DISCUSSION

This study suggests clinically indicated PPF takedown results in minimal deleterious speech outcomes, highlighting its potential efficacy in the treatment of PPF-related OSA. The retrospective nature of the study results in potential limitations that must be addressed. Speech pathologists were not blinded to their patients, which may introduce a degree of rater bias when comparing preoperative and postoperative speech scores. Additionally, although blinded listener ratings of preoperative and postoperative speech samples do not exist, the speech rating reliability of the institution's speech pathologists has been previously validated and published.[21] Additionally, as our institution did not perform all initial surgeries, data regarding the initial PPF surgeries remain inaccessible. However, based on chart reviews from the authors' institution, all PPFs were in place for at least 5 years before takedown. Additionally, the mean age at takedown in this study was 12.4 years, and most PPFs are placed when the child is between the ages of 3 and 4 years. Thus, we can conclude that the flaps in this study were in place for at least 5 years and on average closer to 10 years.

The OSA rates have been reported to be as high as 30% after PPF surgery.[4,12,19,22,23] The proper treatment of OSA in these patients is controversial, and there is no established treatment algorithm or

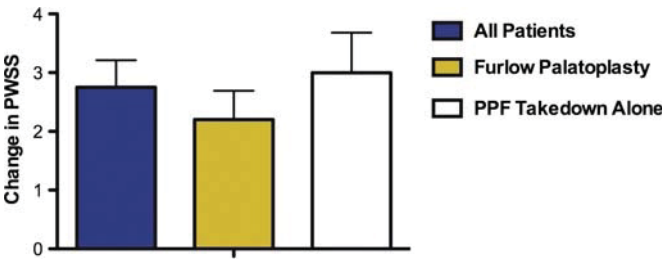

FIGURE 3. Change in PWSS for the 16 patients who had a regression in PWSS following PPF takedown. A positive score indicates a regression in PWSS from pre-takedown to post-takedown.

protocol.[1,8,13–19,24] Although there is concern that PPF takedown in these patients may lead to speech deterioration and recurrent VPI, to date, there are no studies in the literature that investigate outcomes after clinically indicated PPF takedown.

It can be rationalized that speech could be maintained in patients undergoing PPF takedown with conversion to Furlow palatoplasty. For example, a patient who initially underwent straightline palatoplasty and later developed VPI requiring a PPF to improve speech. If this patient developed subsequent sleep apnea, he could be treated with PPF takedown and conversion to Furlow palatoplasty with minimal speech change because of palatal lengthening due to the conversion to Furlow palatoplasty.

However, it remains unclear why a patient would not experience a clinically significant deterioration in speech with a PPF takedown alone when that patient previously required the PPF for speech correction. Several theories for conserved speech gains after PPF takedown alone can be presented in an additive fashion. First, the authors hypothesize that PPFs likely work in part by permanently altering the anatomy of the upper airway by secondary scarring and narrowing of the velopharyngeal port. Despite the PPF takedown, there may exist residual bulk on the posterior velum and posterior pharyngeal wall. Second, as most PPFs are placed during growth of the velum and pharynx, their tethering nature may result in an expansion effect on the velum that may allow for preserved speech function after flap takedown. Third, learned speech mechanisms and techniques may also aid in preserving speech function after flap division.

When analyzing data for the patients in the PPF takedown alone cohort, 10 (56%) experienced a regression in PWSS, with a mean change of only 0.28; and, 49% of patients experienced an improvement in their PWSS. Importantly, only 2 patients (3%) of the entire study and 10% of the PPF takedown alone cohort had a clinically significant deterioration in speech and progressed to a delayed conversion to Furlow palatoplasty. In these select patients (n = 2), delayed conversion to Furlow palatoplasty, improved speech scores from 7 to 3 and 10 to 4 (patients 8 and 14, respectively) (Table 2). A third patient (patient 5) (Table 2) who underwent PPF takedown and conversion Furlow palatoplasty demonstrated a clinically insignificant regression in PWSS from 23 to 27. This syndromic patient had significant developmental, and expressive delays, and the family elected not to have a secondary pharyngoplasty. In the 20-year experience of our institution, approximately 90% of patients experienced no clinically significant regression in speech after undergoing PPF takedown alone, with or without conversion to Furlow palatoplasty,

Given the efficacy of clinically indicated PPF takedown in the preservation of speech, we highlight the protocol used at the Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center that has produced consistent results (Table 3). Based on a single institutional experience that performs over 100 PPFs yearly, clinical indications for takedown alone include: (1) malpositioned and/or inferiorly tethered PPF, (2) hyponasality, (3) OSA, and (4) history of previous Furlow palatoplasty. Indications for PPF takedown with conversion to Furlow palatoplasty include: (1) malpositioned and/or inferiorly tethered PPF, (2) hypernasality/hyponasality, (3) OSA, (4) history of a straightline palatoplasty, and (5) plan for midface advancement.

TABLE 3. The Current Indications at Our Institution for PPF Takedown Alone and Takedown With Conversion to Furlow Palatoplasty

Indications for PPF Takedown Alone	Indications for Takedown With Conversion to Furlow Palatoplasty
Malposition and/or inferiorly tethering PPF	Malposition and/or inferiorly tethering PPF
Hyponasality	Hypernasality/hyponasality
OSA	OSA
History of previous Furlow palatoplasty	History of a straight-line palatoplasty
	Plan for midface advancement

CONCLUSIONS

This study presents a quaternary care institution's 20-year experience in critically analyzing speech changes after clinically indicated PPF takedown. Not only does the study quantify speech changes using the validated PWSS, but it also demonstrates the efficacy of performing PPF takedown procedures in the treatment of PPF-related OSA. Neither PPF takedown alone nor PPF takedown with conversion to Furlow palatoplasty significantly worsened speech outcomes. Specifically, PPF takedown with conversion to Furlow palatoplasty resulted in significantly improved PWSS postoperatively. The data collectively suggest that speech outcomes do not regress after clinically indicated PPF takedown.

REFERENCES

1. Sullivan SR, Marrinan EM, Mulliken JB. Pharyngeal flap outcomes in nonsyndromic children with repaired cleft palate and velopharyngeal insufficiency. *Plast Reconstr Surg*. 2010;125:290–298.
2. Noorchashm N, Dudas JR, Ford M, et al. Conversion Furlow palatoplasty: salvage of speech after straight-line palatoplasty and "incomplete intravelar veloplasty". *Ann Plast Surg*. 2006;56:505–510.
3. Passavant G. Ueber die Beseitigung der naselnden Sprache bei angeborenen Spalten des harten und weichen Gaumens. *Arch Klin Chir*. 1865: 333–349.
4. Morris HL, Bardach J, Jones D, et al. Clinical results of pharyngeal flap surgery: the Iowa experience. *Plast Reconstr Surg*. 1995;95:652–662.
5. Rudnick EF, Sie KC. Velopharyngeal insufficiency: current concepts in diagnosis and management. *Curr Opin Otolaryngol Head Neck Surg*. 2008;16: 530–535.
6. Shprintzen RJ, Marrinan E. Velopharyngeal insufficiency: diagnosis and management. *Curr Opin Otolaryngol Head Neck Surg*. 2009;17:302–307.
7. Sloan GM. Posterior pharyngeal flap and sphincter pharyngoplasty: the state of the art. *Cleft Palate Craniofac J*. 2000;37:112–122.
8. Abyholm F, D'Antonio L, Davidson Ward SL, et al. Pharyngeal flap and sphincterplasty for velopharyngeal insufficiency have equal outcome at 1 year postoperatively: results of a randomized trial. *Cleft Palate Craniofac J*. 2005;42: 501–511.
9. Argamaso RV, Shprintzen RJ, Strauch B, et al. The role of lateral pharyngeal wall movement in pharyngeal flap surgery. *Plast Reconstr Surg*. 1980;66: 214–219.
10. Cable BB, Canady JW, Karnell MP, et al. Pharyngeal flap surgery: long-term outcomes at the University of Iowa. *Plast Reconstr Surg*. 2004;113:475–478.
11. Canady JW, Cable BB, Karnell MP, et al. Pharyngeal flap surgery: protocols, complications, and outcomes at the University of Iowa. *Otolaryngol Head Neck Surg*. 2003;129:321–326.
12. Agarwal T, Sloan GM, Zajac D, et al. Speech benefits of posterior pharyngeal flap are preserved after surgical flap division for obstructive sleep apnea: experience with division of 12 flaps. *J Craniofac Surg*. 2003;14:630–636.
13. Sirois M, Caouette-Laberge L, Spier S, et al. Sleep apnea following a pharyngeal flap: a feared complication. *Plast Reconstr Surg*. 1994;93:943–947.
14. Dudas JR, Deleyiannis FW, Ford MD, et al. Diagnosis and treatment of velopharyngeal insufficiency: clinical utility of speech evaluation and videofluoroscopy. *Ann Plast Surg*. 2006;56:511–517; discussion 517.
15. Wells MD, Vu TA, Luce EA. Incidence and sequelae of nocturnal respiratory obstruction following posterior pharyngeal flap operation. *Ann Plast Surg*. 1999; 43:252–257.
16. Sipp JA, Ashland J, Hartnick CJ. Injection pharyngoplasty with calcium hydroxyapatite for treatment of velopalatal insufficiency. *Arch Otolaryngol Head Neck Surg*. 2008;134:268–271.
17. Kummer AW, Clark SL, Redle EE, et al. Current practice in assessing and reporting speech outcomes of cleft palate and velopharyngeal surgery: a survey of cleft palate/craniofacial professionals. *Cleft Palate Craniofac J*. 2012;49: 146–152.
18. Liao YF, Noordhoff MS, Huang CS, et al. Comparison of obstructive sleep apnea syndrome in children with cleft palate following Furlow palatoplasty or

pharyngeal flap for velopharyngeal insufficiency. *Cleft Palate Craniofac J*. 2004; 41:152–156.

19. Madrid JR, Eduardo Nieto L, Gomez V, et al. Palatoplasty as the technique of choice for prevention of obstructive sleep apnea secondary to surgery for velopharyngeal insufficiency. *Cleft Palate Craniofac J*. 2011;48:145–149.
20. McWilliams B, Philps B. *Velopharyngeal incompetence audio seminars in speech pathology.* Philadelphia: W.B Saunders; 1979.
21. Marazita ML. Subclinical features in non-syndromic cleft lip with or without cleft palate (CL/P): review of the evidence that subepithelial orbicularis oris muscle defects are part of an expanded phenotype for CL/P. *Orthod Craniofac Res*. 2007;10:82–87.
22. Chegar BE, Shprintzen RJ, Curtis MS, et al. Pharyngeal flap and obstructive apnea: maximizing speech outcome while limiting complications. *Arch Facial Plast Surg*. 2007;9:252–259.
23. Dailey SA, Karnell MP, Karnell LH, et al. Comparison of resonance outcomes after pharyngeal flap and Furlow double-opposing z-plasty for surgical management of velopharyngeal incompetence. *Cleft Palate Craniofac J*. 2006;43: 38–43.
24. Trigos I, Ysunza A, Gonzalez A, et al. Surgical treatment of borderline velopharyngeal insufficiency using homologous cartilage implantation with videonasopharyngoscopic monitoring. *Cleft Palate J*. 1988;25:167–170.

Review

Treatment of Prominent Ears and Otoplasty
A Contemporary Review

Sachin S. Pawar, MD; Cody A. Koch, MD, PhD; Craig Murakami, MD

Prominent ears affect approximately 5% of the population and can have a significant psychological impact on patients. A wide variety of otoplasty techniques have been described, all sharing the goal of re-creating the normal appearance of the ear and achieving symmetry between the 2 sides. Recent trends in otoplasty techniques have consistently moved toward less invasive options, ranging from nonsurgical newborn ear molding to cartilage-sparing surgical techniques and even incisionless, office-based procedures. Herein, we review anatomy of the external ear, patient evaluation, the evolution of nonsurgical and surgical otoplasty techniques, otoplasty outcomes, and future trends for treatment of prominent ears.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Sachin S. Pawar, MD, Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53226 (spawar@mcw.edu).

Prominent ears, or prominauris, are defined as the abnormal protrusion of the ears from the head. It has been estimated that approximately 5% of the population are affected by this condition to varying degrees.[1] While the physiologic effects of the condition are negligible, the psychological impact, as a result of decreased self-esteem and teasing by peers, can be severe.[2]

Treatment of prominent ears is primarily surgical except in newborns. Hundreds of surgical techniques have been published in the past century describing the correction of prominent ears. While no one technique is universally favored in all cases, they all share the same goals of re-creating the normal appearance of the auricle and achieving symmetry between the 2 sides.

Anatomy

The appropriate diagnosis and treatment of prominent ears relies on a detailed knowledge of auricular development and anatomy. The length of the adult auricle measures approximately 5.5 to 6.5 cm while the width is normally 50% to 60% of the length. The auricle develops quickly after birth, reaching 90% of the adult width within the first year of life and 97% to 99% of the adult width by 10 years of age.[3] The length of the auricle develops more slowly and reaches 75% of the adult length by 1 year of age and 93% by 10 years of age. The auricle rotates slightly posteriorly at an angle of 15° to 30°.

The projection of the ear from the head is measured by the conchomastoid angle. Normal values for the conchomastoid angle are approximately 25° in males and 20° in females. Larger conchomastoid angles are commonly encountered in patients with prominent ears.

The auricular cartilage provides support and definition for the skin and soft tissue of the auricle. The gentle curves of the normal auricle create multiple different named convexities and concavities in the normally developed ear, as illustrated in **Figure 1**. These structures may be underdeveloped or absent in the prominent ear and must be re-created during surgery to obtain satisfactory results.

Two auricular structures of particular importance for otoplasty include the antihelix and conchal bowl. The antihelix parallels the helical rim and splits near the superior pole of the auricle into the superior and inferior crus. The conchoscaphal angle defines the antihelix and is approximately 90°, with more obtuse angles being encountered in patients with prominent ears. The conchal bowl is a depression of cartilage at the entrance to the external auditory canal and is divided by the helical crus into the concha cavum inferiorly and concha cymba superiorly. The average depth of the conchal bowl is less than 1.5 cm but is frequently enlarged in patients with prominent ears.[3]

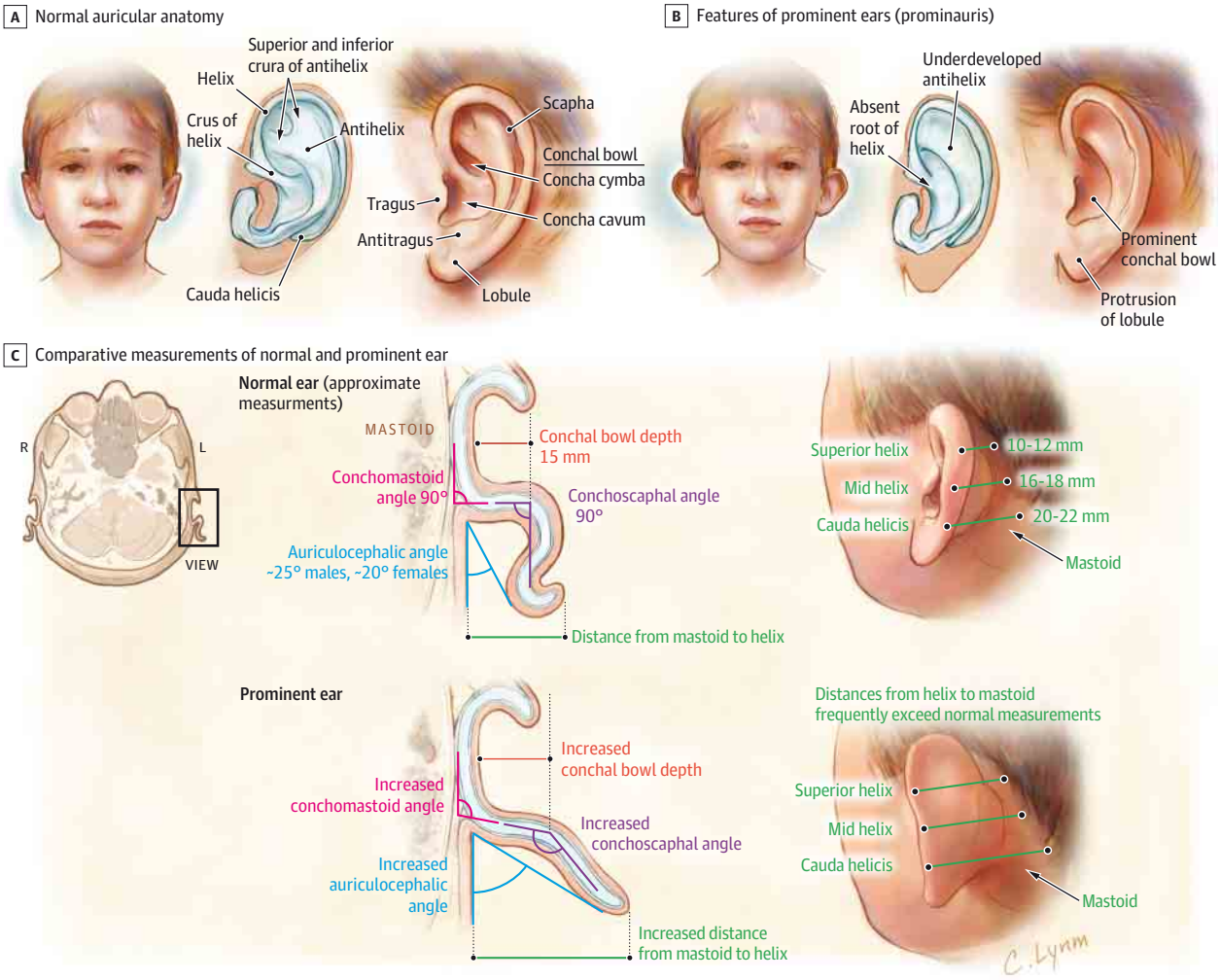
Patient Evaluation

Age is a critical factor in the evaluation and surgical decision-making regarding prominent ears. During the first several weeks of life, nonsurgical ear-molding options may be able to successfully correct a variety of auricular deformities. Beyond this period, surgical correction of prominent ears can be undertaken when the patient is as young as 5 years. The normal auricle reaches approximately 90% of adult size by 3 years of age.

Initial concerns that operating on patients before the auricle is fully grown will lead to growth restriction have been unfounded. For example, Balogh and Millesi[4] studied 76 patients who underwent otoplasty at ages 5 to 8 years and who had auricular measurements available both preoperatively and at ages 20 to 30 years. The authors[4] found that the size of the auricles in patients undergoing otoplasty were similar to those in controls who had not undergone otoplasty. Thus, undertaking otoplasty when the patient is approximately 5 to 6 years of age has been considered optimal owing to most auricular growth being achieved, maintenance of pliability of cartilage, and intervening prior to significant psychological damage secondary to teasing by peers.

In addition to age, the surgeon should pay close attention to the morphologic characteristics of the auricle. In particular, the conchomastoid and conchoscaphal angles should be estimated and re-

Figure 1. Auricular Anatomy of Normal and Prominent Ears



corded. Measurements from the superior helical rim, mid helical rim, and cauda helicis to the mastoid should also be recorded. Normal values for these measurements are typically 10 to 12 mm superiorly, 16 to 18 mm at the middle third, and 20 to 22 mm at the cauda helicis.[1] Patients with prominent ears frequently exceed these measurements. The position of the lobule in relation to the helical rim should also be noted; this position determines whether repositioning of the lobule will be required during surgery. Finally, the stiffness of the auricular cartilage should be noted. The auricular cartilage becomes less pliable with age and may dictate the surgical maneuvers required to achieve a satisfactory result.

Treatment of Prominent Ears

The fact that hundreds of techniques for the correction of prominent ears have been described over the past 50 years attests to no 1 technique being effective in all cases. While nonsurgical correction of prominent ears can be effective in some newborn patients, treatment after the first few weeks is primarily surgical. Surgical techniques to correct prominent ears can be divided into categories based on the deformity addressed, such as excess conchal cartilage or the underdevelopment of the antihelix. The appropriate technique to correct the deformity relies on an accurate preoperative physical examination, and more than 1 technique may be necessary to achieve optimal results.

Ear Splinting and/or Molding

The newborn period is unique owing to the ability to correct auricular deformities using nonsurgical techniques. The incidence of auricular deformities has been estimated to be as low as 11.5 per 10 000 live births[5] and as high as 47% of all births.[5] Only about one-third of the auricular deformities noted at birth will self-correct within the first week.[6]

The pliability of auricular cartilage in the newborn period is believed to be secondary to the high levels of circulating maternal estrogens. Maternal estrogens reach their peak in the fetus just before birth and quickly dissipate to normal levels at approximately 6 weeks to 3 months of age, paralleling the time frame during which nonsurgical treatment of auricular deformities is most successful. The high levels of maternal estrogens are believed to promote higher levels of proteoglycans within cartilage further promoting its pliability.[7]

The nonsurgical correction of auricular deformities was first reported in the literature in the 1980s. Kurozumi et al[8] reported the successful correction of a child with lop ear deformity after splinting of the ear with foam. Matsuo et al[7] reported their experience with 150 patients with auricular deformities who were treated with nonsurgical taping and molding during the first year of life. The authors[7] reported excellent results when patients were treated within the first 6 weeks of life; however, patients treated after 6 weeks of life rarely achieved correction of their deformity.

Many methods of surgical splinting and/or molding have been reported in the literature. These include the use of readily available materials, such as dental rolls and surgical tape, to prefabricated, commercially available systems. Historically, defects of the conchal bowl were more difficult to correct with molding compared with abnormalities of the helix and antihelix. For example, van Wijk et al[9] reported their experience with 132 patients with auricular deformities who were treated with ear molding and/or splinting. The authors reported that 69.8% of antihelical rim deformities were satisfactorily corrected compared with only 26.8% of conchal deformities.

Conchal bowl abnormalities can contribute to a prominent ear deformity by increasing the conchomastoid angle.[6] A commercially available device (EarWell Infant Ear Correction System; Becon Medical) has been developed that addresses some of the limitations of more basic splinting techniques. In their initial series, Byrd et al[6] reported a success rate higher than 90%, with good to excellent results in newborns after a 6-week treatment period. This treatment system has also been successful in addressing conchal bowl deformities, including a prominent conchal crus. In another recent study, Doft et al[10] reported their experience with early treatment (before 2 weeks of life) using the EarWell system. With early initiation of treatment, they were able to use a 2-week duration of therapy (as opposed to 6 weeks) and achieved outcomes reported as excellent or greatly improved by 96% of parents. Successful ear molding outcomes in the neonatal period may prevent the need for future surgery to correct these auricular deformities.

Techniques to Address Underdevelopment of the Antihelix

The appropriate technique to address the underdevelopment of the antihelix is perhaps the most debated topic in otoplasty. Techniques to address the antihelix are divided broadly into cartilage sparing vs cartilage cutting based on whether the auricular cartilage is incised during the procedure. Multiple techniques have been described within each group, each with purported advantages and disadvantages. A detailed review of all techniques is beyond the scope of this article; however, the most popular techniques in each category will be discussed.

Cartilage-Sparing Techniques

Cartilage-sparing techniques are the most frequently used procedures to address the underdevelopment of the antihelix and are ideal in patients with pliable cartilage and in patients with mild to moderate antihelical deformities. Cartilage-sparing techniques often require less undermining of the auricular skin, yielding a decreased risk of postoperative hematoma; require less operative time; and do not injure the native cartilage.

The most cited cartilage-sparing technique in otoplasty is that described by Mustarde,[11] who first described silk mattress sutures in 1963. The mattress sutures were placed through a postauricular excision of skin and were described as passing through both the anterior and posterior auricular perichondrium. While many authors describe the use of methylene blue or similar dyes to mark the planned location of the horizontal mattress sutures, the senior author (C.M.) prefers to use the technique described by Hilger et al[12] (**Figure 2**). They described using temporary marking horizontal mattress sutures placed through the anterior auricular skin and cartilage to give the desired auricular contour. Once the contour is secured with temporary anterior sutures, permanent clear nylon sutures are placed through the posterior surface of the cartilage. The anterior marking sutures are then removed, leaving the corrected auricle. One criticism of the Mustarde technique is that it addresses only the superior third of the auricle. We have not found this to be true and consistently use Mustarde sutures to correct deformities in the superior two-thirds of the auricle. Additional sutures can also be placed to independently enhance the superior and inferior crus.

Cartilage-Cutting Techniques

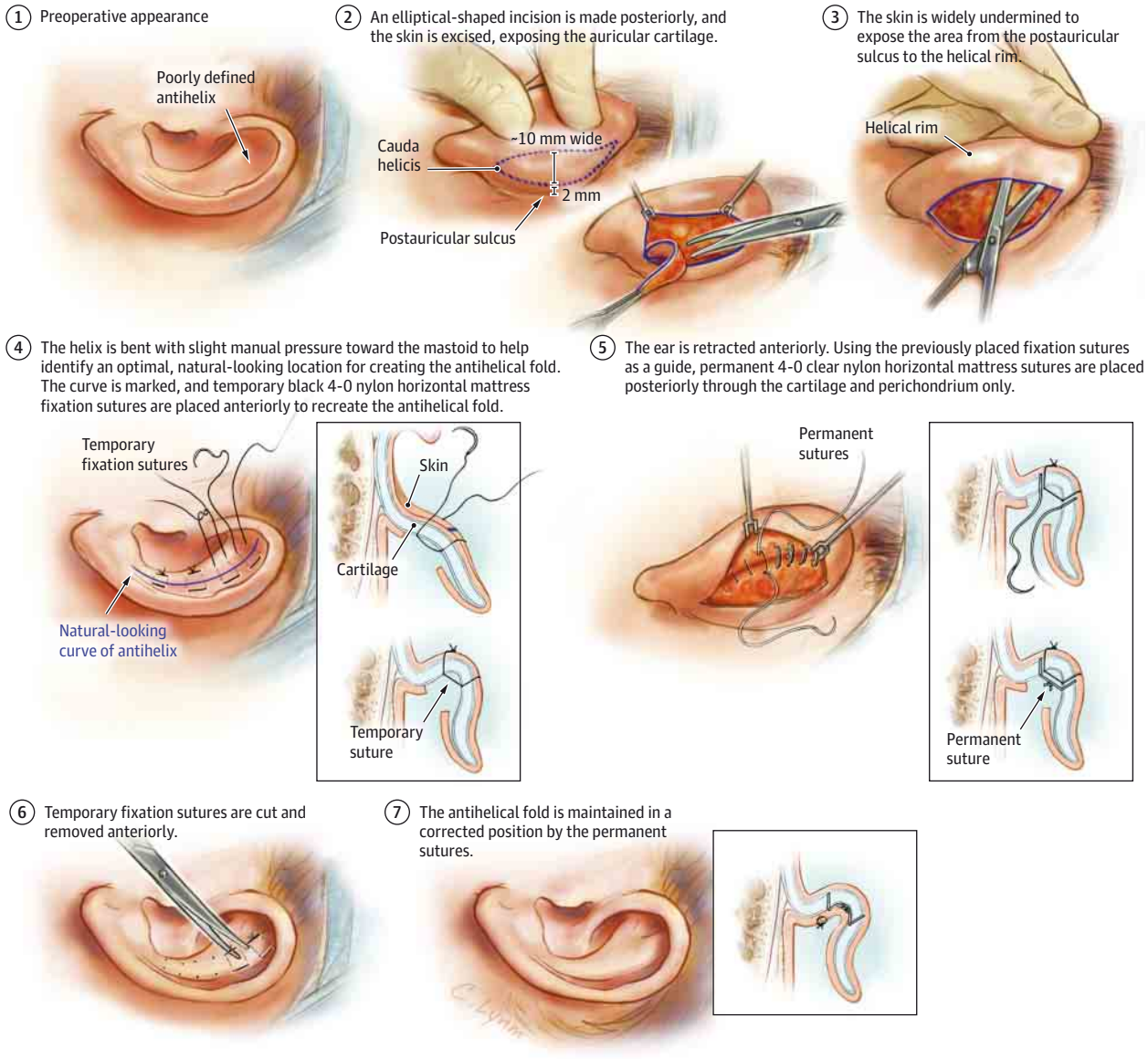
Otoplasty techniques that involve cutting the cartilage are most appropriate for stiff cartilage that is commonly encountered in adult patients. The cartilage in these patients requires the elastic spring of the cartilage to be broken to achieve a satisfactory result and reduced risk of recurrence over time. There have been many approaches to cartilage-cutting techniques described in the literature. These techniques vary based on whether cartilage is incised full thickness vs partial thickness and whether they involve an anterior vs posterior approach.

One example of a cartilage-cutting technique is that described by Converse et al.[13] In this method, full-thickness incisions are made through the cartilage along the area where the desired antihelical fold will be formed as well as at the conchal rim. This creates an island of cartilage, which can then be tubed to form the neoantihelical fold. Pitanguy and Rebello[14] described a similar method, which they called the "island technique," in which full-thickness incisions are also made on either side of the new antihelical fold. Sutures are then used to approximate the cartilage on the sides of the incision, which causes protrusion of the cartilage island and formation of the antihelical fold. Farrior[15] described another cartilage-cutting technique in which both partial-thickness and full-thickness incisions are used. Partial-thickness incisions are made along the conchal rim, whereas full-thickness excisions of cartilage are performed along the superior crus and the desired antihelical fold to give a gentle contour.

In a recent article, Obadia et al[16] described a cartilage-splitting technique, initially described by Jost,[17] that does not rely on sutures but rather on a complete separation of the helix and antihelix followed by scoring of the antihelical cartilage under direct visualization to facilitate folding. More than 90% of the patients in their series reported satisfactory outcomes.

While cartilage-cutting techniques can be powerful tools in patients with stiff cartilage, they are not without their disadvantages. Contour irregularities, such as unnatural-appearing postoperative prominences and angulations, are thought to be more prevalent in patients who have undergone cartilage-cutting techniques. In addition, revision surgery is more difficult in patients who have previously undergone cartilage-cutting procedures owing to the injury of the cartilage inherent in these techniques.

Figure 2. Technique to Re-create the Antihelical Fold



Techniques to Address Conchal Excess

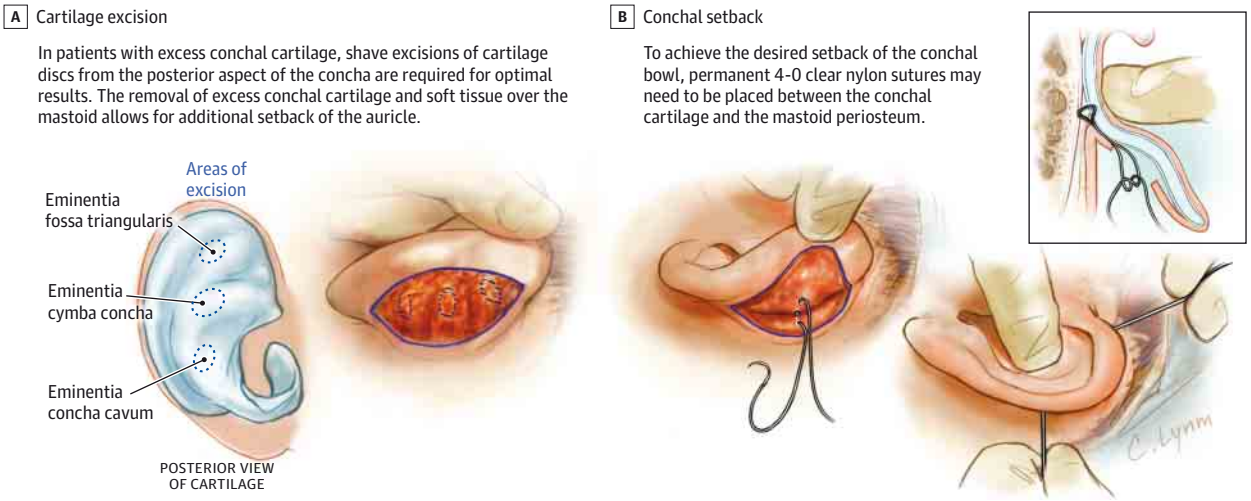
Multiple techniques have been described to address conchal excess. These include suture techniques and excision of cartilage with or without skin and scoring. The techniques are further modified by whether they are performed by a posterior or anterior approach.

Early attempts at treatment of conchal excess and cupping relied solely on the excision of skin. Dieffenbach[18] reported the resection of postauricular skin in an effort to correct a posttraumatic auricular deformity. Limited success encouraged the development of additional techniques. Morestin[19] described the first attempt at the correction of excess conchal cartilage by excising an oval of cartilage from the base of the conchal bowl without the use of sutures. The otoplasty described by Luckett[20] was one of the first to address deficiencies of the antihelix; however, the author also addressed conchal excess by excising conchal cartilage adjacent to the antihelix. These early attempts were often limited by the amount of cartilage that could be excised and frequently did not adequately correct the deformity.

Decades would pass until suture techniques would be used in addition to cartilage resection. Owens and Delgado[21] are credited as the first to use sutures to increase correction of conchal excess and deformity. The authors[21] described placing sutures that penetrated only the posterior conchal perichondrium and were anchored to the fascia, but not the periosteum overlying the mastoid. This technique led to early recurrence of the auricular deformities in a large number of patients, making future modifications necessary.

The most frequently cited modification of the technique reported by Owens and Delgado[21] was described by Furnas,[22] who described the use of nonabsorbable mattress sutures placed through both the perichondrium and conchal cartilage and secured to the more resilient mastoid periosteum. This technique provided for a long-lasting correc-

Figure 3. Techniques to Correct Conchal Excess



tion with a low rate of recurrence. While the procedure afforded a powerful technique, Furnas also noted its drawbacks; sutures placed too far anteriorly on the mastoid or posteriorly on the conchal cartilage will cause exaggeration of the rotation of the ear and could lead to narrowing of the external auditory canal. Sie and Ou[23] pointed out that the prominent conchal bowl also lacks the root of the helix that divides the concha into the concha cavum and the concha cymba. They suggested additional permanent sutures on the posterior conchal bowl to re-create the root of the helix and reduce the prominent conchal bowl.

Frequently, optimal results are obtained by combining the techniques of shaving conchal cartilage from the posterior aspect of the conchal bowl and the use of conchomastoid sutures as described herein. Our preferred technique involves resection of an ellipse of postauricular skin, removal of an ellipse of conchal cartilage at the 3 eminentia, followed by the use of nonabsorbable mattress sutures placed through the conchal cartilage and secured to the mastoid periosteum (**Figure 3**).

In some cases, the amount of excess conchal cartilage requires more aggressive techniques to achieve a satisfactory result. In rare instances, excision of conchal cartilage and skin may be necessary in cases in which the conchal cartilage joins the antihelix. If only cartilage is to be resected, it can be performed via a posterior approach. Resecting only cartilage near the conchoscaphal angle may leave redundant skin that results in a noticeable deformity. Therefore, in most cases of severe conchal excess, both cartilage and skin are resected through an anterior approach. Excessive resection of skin should be avoided to minimize the risk of creating hypertrophic scars. It should be noted that we have not found it necessary to use the techniques described herein in our own practice.

Incisionless Otoplasty

As with the trend in other facial plastic surgery procedures, the desire to have a less invasive otoplasty method prompted Fritsch[24] to publish his first description of an incisionless otoplasty technique in 1995. Since that time, he has published subsequent revisions to the original technique that have incorporated modifications in the suture placement procedure and application of the technique to other deformities other than the absent antihelical fold. The most recent revision, published in 2012,[25] incorporates incisionless cartilage scoring and retention suture placement for correction of the antihelical fold, conchal bowl, and lobule. Since Fritsch[24] published his initial description of the incisionless otoplasty technique, others have described their own modifications to the procedure.[26]

Outcomes of the incisionless otoplasty technique have been very favorable when compared with traditional open techniques. Mehta and Gantous[27] published a retrospective series of 72 adult and pediatric patients who underwent incisionless otoplasty and found it to be an effective technique with a low complication rate. Some of the complications seen with this approach were suture failure, suture exposure, granuloma formation, and antibiotic ointment reaction. Their revision rate was 13%, but Mehta and Gantous[27] noted that many revisions could be performed with local anesthesia in the clinic and that most needed only a single suture. They found that this technique was reliable, safe, and had longevity comparable with the more traditional techniques. In another recent study,[28] 2 different incisionless techniques were compared. The authors found similar outcomes and complication rates between their modified technique when compared with that described by Fritsch.[24]

Outcomes

Specific objective or patient-reported outcomes studies are relatively limited for otoplasty. As with other aesthetic procedures, patient-reported quality-of-life (QOL) outcomes are typically considered to be the most important measures. In 2010, Braun et al[29] reported one of the first retrospective studies looking at health-related quality-of-life (HRQOL) outcomes in 62 adult and pediatric patients who underwent otoplasty with suture techniques. They used the Glasgow Benefit Inventory, a validated retrospective questionnaire that is used to measure the effect of otolaryngology- and facial plastic surgery–related procedures on HRQOL. They reported that the primary reasons their patients underwent otoplasty were teasing, aesthetic impairment, reduced self-confidence, and prevention of teasing. Nearly two-thirds of their patients reported having been teased about their

ears, and about the same number reported attempting to cover their protruding ears with various hairstyles or headwear. They found a significant increase in the HRQOL following otoplasty in approximately 95% of both adults and children. In addition, both groups (including parents) reported a high satisfaction rate following the procedure. Since Braun et al[29] published their initial study, other authors have found very similar QOL results after otoplasty.[30,31]

Future Trends

Recently, electromechanical reshaping (EMR) has been studied as a way to reshape auricular cartilage. Using an in vivo rabbit ear model, Yau et al[32] studied the degree of shape change and histological findings after EMR and splinting. They found a dose-dependent relationship between the voltage applied and the degree of shape change and histologic findings showing areas of tissue injury, which were limited to a small area around the needle insertion sites. This type of technology has potential application as a minimally invasive technology that could be used for office-based otoplasty; however, further clinical studies in humans will be necessary.

Conclusions

Prominent ears are frequently treated by facial plastic surgeons. An intricate knowledge of normal auricular anatomy is required to develop an appropriate operative plan to address the deformed ear. The trend in otoplasty techniques has consistently moved toward less invasive options, ranging from nonsurgical newborn ear molding to cartilage-sparing surgical techniques and even incisionless, office-based procedures. While most surgeons who treat auricular deformities will develop preferences and expertise in a few techniques, they must remain flexible in order to deal with the variety and complexity of deformities that exist. Both surgical and nonsurgical otoplasty techniques continue to evolve and future advancements in minimally invasive technologies and tissue engineering will likely create even more possibilities to address auricular deformities.

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Author Affiliations: Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, Milwaukee (Pawar); Koch Facial Plastic Surgery and Spa, West Des Moines, Iowa (Koch); Division of Facial Plastic Surgery, Department of Otolaryngology–Head and Neck Surgery, Virginia Mason Medical Center, Seattle, Washington (Murakami).

Author Contributions: Dr Pawar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Koch, Murakami.
Acquisition, analysis, or interpretation of data: Pawar, Koch.
Drafting of the manuscript: Koch, Murakami.
Critical revision of the manuscript for important intellectual content: Pawar, Koch.
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REFERENCES

1. Adamson PA, Litner JA. Otoplasty technique. *Otolaryngol Clin North Am*. 2007;40(2):305-318.

2. Macgregor FC. Ear deformities: social and psychological implications. *Clin Plast Surg*. 1978;5(3):347-350.

3. Janis JE, Rohrich RJ, Gutowski KA. Otoplasty. *Plast Reconstr Surg*. 2005;115(4):60e-72e.

4. Balogh B, Millesi H. Are growth alterations a consequence of surgery for prominent ears? *Plast Reconstr Surg*. 1992;90(2):192-199.

5. Matsuo K, Hayashi R, Kiyono M, Hirose T, Netsu Y. Nonsurgical correction of congenital auricular deformities. *Clin Plast Surg*. 1990;17(2):383-395.

6. Byrd HS, Langevin CJ, Ghidoni LA. Ear molding in newborn infants with auricular deformities. *Plast Reconstr Surg*. 2010;126(4):1191-1200.

7. Matsuo K, Hirose T, Tomono T, et al. Nonsurgical correction of congenital auricular deformities in the early neonate: a preliminary report. *Plast Reconstr Surg*. 1984;73(1):38-51.

8. Kurozumi N, Ono S, Ishida H. Non-surgical correction of a congenital lop ear deformity by splinting with Reston foam. *Br J Plast Surg*. 1982;35(2):181-182.

9. van Wijk MP, Breugem CC, Kon M. A prospective study on non-surgical correction of protruding ears: the importance of early treatment. *J Plast Reconstr Aesthet Surg*. 2012;65(1):54-60.

10. Doft MA, Goodkind AB, Diamond S, DiPace JI, Kacker A, LaBruna AN. The newborn butterfly project: a shortened treatment protocol for ear molding. *Plast Reconstr Surg*. 2015;135(3):577e-583e.

11. Mustarde JC. The correction of prominent ears using simple mattress sutures. *Br J Plast Surg*. 1963;16:170-178.

12. Hilger P, Khosh MM, Nishioka G, Larrabee WF. Modification of the Mustardé otoplasty technique using temporary contouring sutures. *Plast Reconstr Surg*. 1997;100(6):1585-1586.

13. Converse JM, Nigro A, Wilson FA, Johnson N. A technique for surgical correction of lop ears. *Plast Reconstr Surg (1946)*. 1955;15(5):411-418.

14. Pitanguy Y, Rebello C. Ansiform ears-correction by "island" technique. *Acta Chir Plast*. 1962;4:267-277.

15. Farrior RT. A method of otoplasty: normal contour of the antihelix and scaphoid fossa. *AMA Arch Otolaryngol*. 1959;69(4):400-408.

16. Obadia D, Quilichini J, Hunsinger V, Leyder P. Cartilage splitting without stitches: technique and outcomes. *JAMA Facial Plast Surg*. 2013;15(6):428-433.

17. Jost J. *Atlas of Aesthetic Plastic Surgery*. Paris, France: Masson; 1975.

18. Dieffenbach JF. *Die Operative Chirurgie*. Leipizig, Germany: F. A. Brockhaus; 1845.

19. Morestin M. De la reposition et du plissement cosmetiques du pavillon de l'oreille. *Revue d'orthopedie*. 1903;14.

20. Luckett W. A new operation for prominent ears based on the anatomy of the deformity. *Surg Gynec Obst*. 1910;10.

21. Owens N, Delgado DD. The management of outstanding ears. *South Med J*. 1965;58:32-33.

22. Furnas DW. Correction of prominent ears by conchamastoid sutures. *Plast Reconstr Surg*. 1968;42(3):189-193.

23. Sie KC, Ou H. Otoplasty: an alternative approach to management of the deep conchal bowl. *Laryngoscope*. 2006;116(11):2092-2094.

24. Fritsch MH. Incisionless otoplasty. *Laryngoscope*. 1995;105(5, pt 3)(suppl 70):1-11.

25. Fritsch MH. Incisionless otoplasty with conchal bowl recession [in German]. *HNO*. 2012;60(10):856-861.

26. Haytoglu S, Haytoglu TG, Yildirim I, Arikan OK. A modification of incisionless otoplasty for correcting the prominent ear deformity [published online October 14, 2014]. *Eur Arch Otorhinolaryngol*. doi:10.1007/s00405-014-3329-3.

27. Mehta S, Gantous A. Incisionless otoplasty: a reliable and replicable technique for the correction of prominauris. *JAMA Facial Plast Surg*. 2014;16(6):414-418.

28. Haytoglu S, Haytoglu TG, Bayar Muluk N, Kuran G, Arikan OK. Comparison of two incisionless otoplasty techniques for prominent ears in children. *Int J Pediatr Otorhinolaryngol*. 2015;79(4):504-510.

29. Braun T, Hainzinger T, Stelter K, Krause E, Berghaus A, Hempel JM. Health-related quality of life, patient benefit, and clinical outcome after otoplasty using suture techniques in 62 children and adults. *Plast Reconstr Surg*. 2010;126(6):2115-2124.

30. Songu M, Kutlu A. Health-related quality of life outcome of children with prominent ears after otoplasty. *Eur Arch Otorhinolaryngol*. 2014;271(6):1829-1832.

31. Hao W, Chorney JM, Bezuhly M, Wilson K, Hong P. Analysis of health-related quality-of-life outcomes and their predictive factors in pediatric patients who undergo otoplasty. *Plast Reconstr Surg*. 2013;132(5):811e-817e.

32. Yau AY, Manuel C, Hussain SF, Protsenko DE, Wong BJ. In vivo needle-based electromechanical reshaping of pinnae: New Zealand White rabbit model. *JAMA Facial Plast Surg*. 2014;16(4):245-252.

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Airway Obstruction during Drug-Induced Sleep Endoscopy Correlates with Apnea-Hypopnea Index and Oxygen Nadir in Children

John P. Dahl, MD, PhD, MBA[1,2], Craig Miller, MD[3,4], Patricia L. Purcell, MD, MPH[3,4], David A. Zopf, MD, MS[5,6], Kaalan Johnson, MD[3,4], David L. Horn, MD, MS[3,4], Maida L. Chen, MD[4,7], Dylan K. Chan, MD, PhD[8,9], and Sanjay R. Parikh, MD[3,4]

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Abstract

Objective. To determine if standardized intraoperative scoring of anatomic obstruction in children with obstructive sleep apnea correlates with the apnea-hypopnea index (AHI) and lowest oxygen saturation on preprocedural polysomnogram (PSG). A secondary objective was to determine if age, presence of a syndrome, or previous adenotonsillectomy affect this correlation.

Study Design. Case series with chart review.

Setting. Two tertiary care children's hospitals.

Subjects. Patients with a preprocedural PSG who underwent drug-induced sleep endoscopy (DISE) over a 4-year period.

Methods. All DISEs were graded in a systematic manner with the Chan-Parikh (C-P) scoring system. AHI and nadir oxygen saturations were extracted from preprocedural PSG. Data were analyzed with a multivariate linear regression model that controlled for age at time of sleep endoscopy, syndrome diagnosis, and previous adenotonsillectomy.

Results. A total of 127 children underwent PSG prior to DISE: 56 were syndromic, and 21 had a previous adenotonsillectomy. Mean AHI was 13.6 $\pm$ 19.6 ($\pm$ SD), and mean oxygen nadir was 85.4% $\pm$ 9.4%. Mean C-P score was 5.9 $\pm$ 2.7. DISE score positively correlated with preoperative AHI (r = 0.36, $P <$ .0001) and negatively correlated with oxygen nadir ($r = -0.26$, P = .004). The multivariate linear regression models estimated that for every 1-point increase in C-P score, there is a 2.6-point increase in AHI (95% confidence interval: 1.4-3.8, $P <$ .001) and a 1.1% decrease in the lowest oxygen saturation (95% confidence interval: –1.7 to -0.6, $P <$ .001).

Conclusion. The C-P scoring system for pediatric DISE correlates with both AHI and lowest oxygen saturation on preprocedural PSG.

Keywords

obstructive sleep apnea, drug-induced sleep endoscopy, polysomnogram, sleep-disordered breathing, pediatrics

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Drug-induced sleep endoscopy (DISE) is a new diagnostic tool in the evaluation of adults and children with obstructive sleep apnea (OSA).[1-3] Typically, it is a flexible fiberoptic observation of the upper airway under general anesthesia while maintaining spontaneous ventilation.[2-4] DISE has been reported to be a useful tool for identifying additional sites of obstruction in children and adults beyond tonsil and adenoid hypertrophy as appreciated on clinical examination.[1-6]

[1]Department of Otolaryngology–Head and Neck Surgery, Indiana University School of Medicine, Indianapolis, Indiana, USA
[2]Riley Hospital for Children, Indianapolis, Indiana, USA
[3]Department of Otolaryngology–Head and Neck Surgery, University of Washington School of Medicine, Seattle, Washington, USA
[4]Seattle Children's Hospital, Seattle, Washington, USA
[5]Department of Otolaryngology–Head and Neck Surgery, University of Michigan School of Medicine, Ann Arbor, Michigan, USA
[6]C.S. Mott Children's Hospital, Ann Arbor, Michigan, USA
[7]Department of Pediatrics, Division of Pulmonary and Sleep Medicine, University of Washington School of Medicine, Seattle, Washington, USA
[8]Department of Otolaryngology–Head and Neck Surgery, University of California–San Francisco, San Francisco, California, USA
[9]Benioff Children's Hospital, San Francisco, California, USA

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Corresponding Author:
Sanjay R. Parikh, MD, Department of Otolaryngology–Head and Neck Surgery, University of Washington School of Medicine, Seattle Children's Hospital, OA.9.220–Otolaryngology, 4800 Sand Point Way NE, Seattle, WA 98105, USA
Email: sanjay.parikh@seattlechildrens.org

DISE scoring systems have not been proven to correlate well with sleep apnea parameters in adults.[7] It is still unknown if DISE accurately identifies sites of obstruction in children with polysomnogram (PSG)–diagnosed OSA. In 2014, we introduced and validated a new scoring system for DISE (Chan-Parikh [C-P] score) in children with OSA to identify the location and severity of obstruction.[8] This study builds on that work by presenting new data on patients undergoing DISE to determine if standardized scoring correlates with PSG parameters. We hypothesized that the C-P DISE score would correlate with PSG findings—specifically, apnea-hypopnea index (AHI) and oxygen nadir, broad indicators of OSA severity. As a secondary objective, we sought to determine if age at the time of DISE, presence of a syndrome, or history of adenotonsillectomy affect this relationship.

Methods

Institutional Review Board approval was obtained from the 2 participating institutions: Seattle Children's Hospital (SCH) and the University of California–San Francisco (UCSF). At both institutions, all patients undergoing DISE are scored prospectively via the C-P score, and the findings are recorded in a database. These databases contain basic patient demographic information (date of birth, date of procedure, comorbidities), limited PSG parameters (AHI, lowest O_2 saturation) if the patient underwent preoperative PSG, and the C-P score. Records of all patients in these databases were screened between January 1, 2011, and December 31, 2014, to obtain past medical and surgical history. All patients who underwent PSG prior to DISE were included in the study; there was no restriction on how far in advance of DISE the PSG was performed. The decision to perform DISE was based on clinical evaluation by the attending surgeon. DISEs were typically performed on children with small or absent tonsils or with clinical suspicion for multilevel airway obstruction. Children who did not have preoperative PSG were excluded from the study; PSG was not always obtained prior to DISE, based on clinical judgment, cost, and family decision making.

Subjects underwent PSG at an accredited sleep laboratory as part of clinically indicated care, with results interpreted by board-certified pediatric sleep medicine physicians. PSGs were scored in accordance with the American Academy of Sleep Medicine parameters.[9] AHI and lowest recorded oxygen saturation were noted from the preprocedural PSG.

At both tertiary care facilities, sleep endoscopy is carried out in standardized fashion, with all reports being categorized per the C-P scoring system, which has been published and validated.[8] The anesthetic technique for all DISE utilized sevoflurane and propofol per institutional protocols. The C-P score is based on 5 anatomic locations, with each site graded on a 4-point scale according to severity of obstruction. Sleep endoscopy scores were noted at the time of surgery by the surgeon responsible for each case.

After all cases had been identified, chart review was performed to acquire the demographic characteristics of the participants, including age at time of sleep endoscopy, surgical history, and presence of concomitant syndromal or genetic disorder (eg, Trisomy 21). Univariate analyses were performed to obtain descriptive statistics. Means were calculated for continuous variables, such as PSG and sleep endoscopy scores, along with average age at time of DISE. Proportions were calculated for binary variables, such as the presence of a syndrome. Mean AHI and lowest oxygen saturation values for PSGs performed at UCSF and SCH were compared with Student's t test to ensure consistency between studies performed at the separate institutions.

Spearman's correlation coefficients (2-tailed) were then calculated to determine the degree of linear correlation between C-P score and each PSG result: AHI and oxygen nadir. To determine if there was significant variability in DISE results among the 8 attending surgeons, Spearman's correlation coefficients were also calculated for AHI and lowest oxygen saturation for patients who underwent DISE by the senior author (S.R.P.; n = 58) and the other 7 surgeons (n = 69). Two separate multivariable linear regression models were then created, controlling for syndrome diagnosis, history of adenotonsillectomy, and age at time of sleep endoscopy. AHI and oxygen nadir were used as the dependent variables in these models, while C-P score was the independent variable. For all tests, $P < .05$ was considered statistically significant. Stata 13.1 (Stata Inc, College Station, Texas) statistical software was used for all analyses.

Results

A total of 127 children met inclusion criteria for the study. The demographic composition of this patient population is outlined in **Table 1**. The mean AHI value for PSGs performed at UCSF was 11.7 ± 12.8 (± SD), while at SCH the mean AHI value was 14.1 ± 20.9. There was no statistically significant difference in the mean AHI values between the centers ($P = .6$). Mean lowest oxygen saturations were also not significantly different between patients at the 2 institutions: mean O_2 nadir at UCSF was 82% ± 9.5%, compared with 86% ± 9.4% at SCH ($P = .1$). The scatterplots represented in **Figure 1** demonstrate AHI and oxygen nadir as a function of C-P score. Correlation analysis

Table 1. Demographic Characteristics of the Study Population.[a]

Subjects	127
Age at time of DISE, y	6.55 ± 5.34
Syndromal or genetic disorder	56 (44)
Previous adenotonsillectomy	21 (16.5)
AHI, events/h	13.6 ± 19.6
O_2 nadir, % (O_2 saturation)	85.4 ± 9.4
Chan-Parikh score	5.9 ± 2.7

Abbreviations: AHI, apnea-hypopnea index; DISE, drug-induced sleep endoscopy.
[a]Values presented as n (%) or mean ± SD.

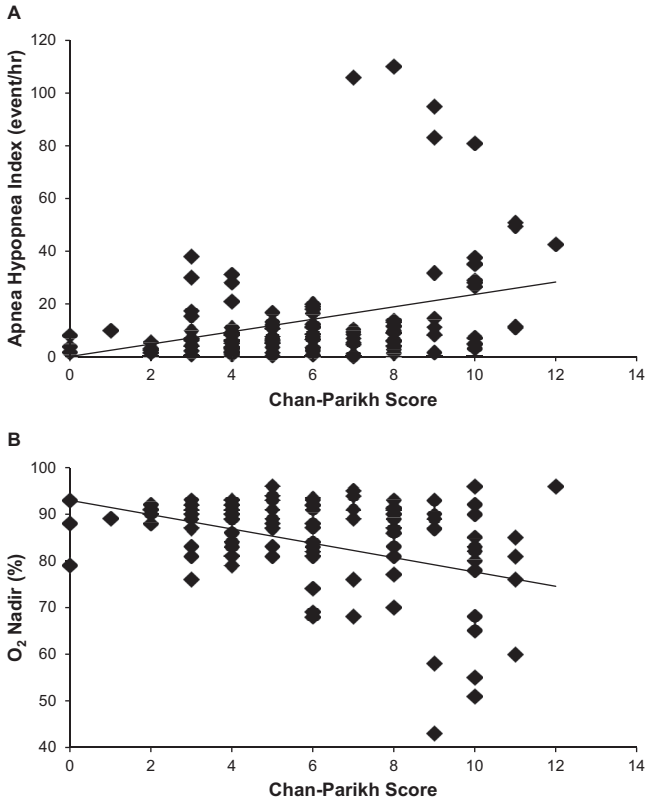

Figure 1. Correlation analysis: (A) apnea-hypopnea index and Chan-Parikh score ($r = 0.36$, $P < .0001$) and (B) O_2 nadir and Chan-Parikh score ($r = -0.26$, $P = .004$).

demonstrated a positive moderate agreement ($r = 0.36$, $P < .0001$) between the AHI and the C-P score (**Figure 1A**). This analysis includes 5 patients with an AHI >70; if these subjects are excluded from the study population, there is still a positive moderate agreement ($r = 0.32$, $P = .0004$). Correlation analysis for AHI for patients who underwent DISE by the senior author demonstrated a positive moderate agreement (n = 58, $r = 0.33$, $P = .01$), as did correlation analysis for the remaining 7 surgeons (n = 69, $r = 0.37$, $P = .002$).

Using the same methodology, we found a negative weak agreement between the lowest oxygen saturation and the C-P score ($r = -0.26$, $P = .004$; **Figure 1B**). Five patients were included in this analysis with a lowest oxygen saturation <65%, and excluding these subjects from the study population failed to demonstrate any agreement between C-P score and lowest oxygen saturation ($r = 0.16$, $P = .08$). Correlation analysis for O_2 nadir for patients who underwent DISE by the senior author demonstrated a similar negative moderate agreement (n = 58, $r = -0.3$, $P = .03$); however, correlation analysis for the remaining 7 surgeons did not identify a significant correlation (n = 64, $r = -0.2$, $P = .1$).

Multivariate linear regression analysis—controlling for age at endoscopy, presence of a syndrome, and history of adenotonsillectomy—demonstrated a statistically significant association between the C-P score and both preprocedural AHI and oxygen nadir. This analysis revealed that a 2.6-point increase in AHI corresponds to a 1-point increase in the C-P score (95% confidence interval: 1.4-3.8, $P < .001$). A similar, 1.1% decrease in oxygen nadir corresponds to a 1-point increase in the C-P score (95% confidence interval: –1.7 to -0.5, $P < .001$). These results indicate that the severity of anatomic obstruction in pediatric OSA, as defined with a systematic scoring system for DISE, correlates with both AHI and the lowest oxygen saturation on preprocedural PSG when known covariates are accounted for.

Discussion

The present data extend the previously published relationship between C-P score and PSG severity to a larger, multi-institutional prospective series of patients who underwent DISE. We hypothesized that the severity of anatomic obstruction would correlate with the severity of OSA as defined by the PSG. For this study, we chose to include all children who presented to our institutions with a PSG and met the criteria for undergoing DISE, regardless of age, severity of OSA, and medical complexity. We found a statistically significant positive correlation between the C-P score and the AHI, as well as a statistically significant negative correlation between the C-P score and the lowest oxygen saturation. Our analysis found a much stronger relationship between C-P score and AHI than between C-P score and lowest oxygen saturation, as evidenced by the fact that a few patients with very low oxygen saturations had a significant influence over this correlation. These data provide initial evidence supporting our hypothesis that the severity of anatomic obstruction in children with OSA, as measured with DISE, correlates with PSG parameters. Such data are important clinically, as DISE is becoming a widely utilized tool for the identification of airway obstruction in children with OSA. The evidence supporting DISE-directed surgery in the management of pediatric OSA is limited, and an organized approach toward studying this procedure, such as the one provided by the C-P scoring system, is critical to determining the proper role of DISE in the treatment of OSA.

To our knowledge, this study represents the first to examine the relationship between anatomic obstruction in OSA, as measured by DISE, and preprocedural PSG parameters in children. A number of studies have examined whether DISE findings are correlated with PSG severity in adult populations. Most recently, Dedhia and Weaver reviewed a case series of 65 adult patients who underwent DISE, and they scored the anatomic obstruction using the VOTE system (velum, oropharynx, tongue, epiglottis).[7] In this study, the authors failed to detect a significant association between the level of anatomic obstruction on DISE and the pre-DISE PSG parameters. Furthermore, this study failed to detect any significant associations between the severity of anatomic obstruction on DISE and Epworth Sleepiness Scale scores or quality of life as measured by the SNORE25 instrument. This study calls into question the external validity and clinical usefulness of DISE scoring systems for adult OSA patients.

A 2014 study by Vroegop et al retrospectively examined a case series of 1249 adult patients who underwent both PSG and DISE.[10] This study found a statistically significant association between AHI and airway obstruction at the level of the epiglottis. DeCorso et al prospectively evaluated the relationship between PSG parameters and airway obstruction on DISE in a cohort of 138 adult patients with OSA.[11] This study utilized the VOTE system to grade the anatomic obstruction on DISE, and the authors found a statistically significant association between AHI and the severity of anatomic obstruction on DISE. While both these studies found a correlation between anatomic obstruction on DISE and pre-DISE PSG parameters, they included only adult patients; the management of pediatric OSA patients is very different from that of adults, and these results may not be applicable to children.

While the above studies represent significant contributions to the DISE literature, data derived from adult OSA patients will not necessarily have a direct correlation with pediatric OSA patients. There are a number of important differences to point out regarding the etiology and management of pediatric and adult OSA: the obvious physiologic differences (eg, airway size and compliance), the presence of medical comorbidities associated with the aging process, the differences in neuromuscular control, the prevalence of morbid obesity, and the potential for growth and continued development that likely differentiate pediatric from adult OSA. In adults, surgical intervention is considered only after an appropriate trial of continuous positive airway pressure (CPAP) treatment. In children, surgery is often the first-line therapy; the clinical expertise necessary to manage CPAP in children is scarce.[12] In addition, CPAP is not Food and Drug Administration approved for outpatient use in patients <40 kg, and industry support in terms of providing appropriate equipment for pediatric CPAP is limited. Such differences highlight the need for continued research into pediatric DISE as well as the development of DISE-directed surgical procedures.

Given the weak to moderate correlation coefficients obtained from our statistical analysis, there are other factors not controlled for in the present study that influenced the relationship between the level of anatomic obstruction observed on DISE and the severity of pediatric OSA in this study. First, the surgeons performing DISE were not blinded to the preendoscopy PSG parameters; this introduces bias that we were not able to control for using the outlined statistical methods. Given the retrospective nature of the present study, it was not feasible to blind the surgeons from the PSG data, as such data were used to determine each patient's candidacy to undergo DISE and DISE-directed surgery for OSA. However, these correlations still provide the needed foundational data to build further prospective investigations performed in a blinded manner similar to the methods described in our initial work.[8] For the present study, we chose to include all children who presented to our institutions with a PSG and met the criteria for undergoing DISE, regardless of age, severity of OSA, and medical complexity. This ''real world'' strategy, when coupled with basic PSG results, provides a broad illustration of these early correlations, again helping to set the stage for further studies that will ideally focus on both typically developing and medically complex populations.

In addition, the present study included data from DISE performed by 8 attending surgeons and PSGs performed at multiple sleep laboratories; the differences in surgical technique and PSG interpretation introduce variability that cannot be controlled for in our statistical model. There was also no documentation of the anesthetic technique used for the DISE procedures included in this study. The specific doses and durations of the anesthesia administered during DISE or variations from the institutional protocols for DISE anesthesia were not collected as part of the study and therefore could not be included in our analysis.

Moving forward, we propose to use the results from the present study as a basis for a multicenter prospective study evaluating the association between PSG parameters and the level of anatomic obstruction on pediatric DISE. Expanding the breadth and depth of investigations via PSG parameters, surgical and anesthetic techniques, and patient-reported outcomes (including quality of life) and focusing on specific patient populations will further guide research studies that will undoubtedly help to shape the clinical practice of treating the many facets of pediatric OSA. To do so, we will need to follow patients undergoing DISE-directed surgery longitudinally and collect data from postintervention PSGs to determine the impact of such procedures on PSG parameters and quality-of-life measures. In addition, with a larger cohort of patients, we will be able to look at specific sites of anatomic obstruction, as defined by the C-P score, to characterize the impact of that site or a procedure directed at that anatomic location in the pathophysiology and treatment of pediatric OSA. Such an approach should also allow us to examine the incidence and treatment of pediatric OSA caused by multiple sites of airway obstruction.

Author Contributions

John P. Dahl, conception and design, data acquisition, analysis, and interpretation, drafting the work, critical revisions, final approval and accountability for entire product; **Craig Miller**, data acquisition and interpretation, critical revisions, final approval and accountability for entire product; **Patricia L. Purcell**, conception and design, data acquisition, analysis, and interpretation, drafting the work, critical revisions, final approval and accountability for entire product; **David A. Zopf**, data acquisition and interpretation, critical revisions, final approval and accountability for entire product; **Kaalan Johnson**, data acquisition and interpretation, critical revisions, final approval and accountability for entire product; **David L. Horn**, data acquisition and interpretation, critical revisions, final approval and accountability for entire product; **Maida L. Chen**, data acquisition and interpretation, critical revisions, final approval and accountability for entire product; **Dylan K. Chan**, data acquisition and interpretation, critical revisions, final approval and accountability for entire product; **Sanjay R. Parikh**, conception and design, data acquisition, analysis, and interpretation, drafting the work, critical revisions, final approval and accountability for entire product.

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References

1. Kezirian EJ, White DP, Malhotra A, et al. Interrater reliability of drug-induced sleep endoscopy. *Arch Otolaryngol Head Neck Surg*. 2010;136:393-397.
2. Lin AC, Koltai PJ. Sleep endoscopy in the evaluation of pediatric obstructive sleep apnea. *Int J Pediatr*. 2012;2012:576719.
3. Ulualp SO, Szmuk P. Drug-induced sleep endoscopy for upper airway evaluation in children with obstructive sleep apnea. *Laryngoscope*. 2013;123:292-297.
4. Digoy GP, Shukry M, Stoner JA. Sleep apnea in children with laryngomalacia: diagnosis via sedated endoscopy and objective outcomes after supraglottoplasty. *Otolaryngol Head Neck Surg*. 2012;147:544-550.
5. Durr ML, Meyer AK, Kezirian EJ, et al. Drug-induced sleep endoscopy in persistent pediatric sleep-disordered breathing after adenotonsillectomy. *Arch Otolaryngol Head Neck Surg*. 2012;138:638-643.
6. Mase CA, Chen ML, Horn DL, et al. Supraglottoplasty for sleep endoscopy diagnosed sleep dependent laryngomalacia. *Int J Pediatr Otorhinolaryngol*. 2015;79:511-515.
7. Dedhia RC, Weaver EM. Association between drug-induced sleep endoscopy and measures of sleep apnea burden. *Otolaryngol Head Neck Surg*. 2015;153:875-880.
8. Chan DK, Liming BJ, Horn DL, et al. A new scoring system for upper airway pediatric sleep endoscopy. *JAMA Otolaryngol Head Neck Surg*. 2014;140:595-602.
9. Iber C, Ancoli-Israel S, Chesson A, Quan SF; for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*. Westchester, IL: American Academy of Sleep Medicine; 2007.
10. Vroegop AV, Vanderveken OM, Boudewyns AN, et al. Drug-induced sleep endoscopy in sleep-disordered breathing: report on 1,249 cases. *Laryngoscope*. 2014;124:797-802.
11. deCorso E, Fiorita A, Rizzotto G, et al. The role of drug-induced sleep endoscopy in the diagnosis and management of obstructive sleep apnoea syndrome: our personal experience. *Acta Otorhinolaryngol Ital*. 2013;33:405-413.
12. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012;130:576-584.

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PANDAS: A systematic review of treatment options☆

Zachary Farhood, Adrian A. Ong, Christopher M. Discolo*

Department of Otolaryngology – Head and Neck Surgery, Medical University of South Carolina, United States

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ABSTRACT

Introduction: Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) is a rare but important condition for pediatric otolaryngologists to recognize. Several treatment options exist including tonsillectomy, antibiotic treatment/prophylaxis, intravenous immunoglobulin (IVIG), and psychiatric medications/therapy.

Methods: A systematic review of the PubMed, EMBASE, and Scopus databases was performed searching for articles that focused exclusively on the aforementioned treatment modalities in the PANDAS population. Review articles, single patient case reports, and studies examining the natural history or diagnostic strategies were excluded.

Results: Five articles regarding tonsillectomy treatments with level of evidence (LOE) 4 were found but no clear benefit could be determined. Three articles were selected involving the use of antibiotic therapy. One prospective study and one double-blind randomized control trial (DB RCT) supported the use of antibiotics but a separate DB RCT showed no benefit. Two selected articles described the use of IVIG: one unblinded RCT and one retrospective study. One prospective study on cognitive-behavioral therapy (CBT) showed benefit in PANDAS.

Conclusion: There is a paucity of high-level studies regarding this rare disorder and no hard treatment recommendations can be made. Tonsillectomy should only be performed in those who are surgical candidates based on current published guidelines. Antibiotics are an option but provide uncertain benefit. CBT remains a low-risk option. Studies support the use of IVIG, however more investigation is needed prior to widespread adoption of this treatment given its potential risks.

1. Introduction

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) is a rare pediatric disorder with otolaryngic ties that was described by Swedo et al., in 1998 with specific criteria (Table 1) [1]. The criteria continue to be refined but the course of the disease involves tics and/or obsessions/compulsions that worsen in relation to acute infection caused by group A β-hemolytic (GABHS) streptococcus. This is a waxing and waning disorder with an incompletely understood pathophysiology. Several treatment options have been proposed including surgery, medical therapy, and cognitive behavioral treatment. The objective of this study was to systematically review the literature for treatment options of PANDAS.

2. Methods

Systematic reviews of published literature are deemed exempt by our institutional review board. A systematic review of the PubMed, EMBASE, and Scopus databases was performed in August 2015, searching for articles focusing exclusively on treatment modalities in the PANDAS population. The primary outcome was improvement in symptoms. There were no date restrictions. The specific search strategy is detailed in Table 2.

Articles in the English or Spanish language were included. Review articles, single patient case reports, and studies examining the natural history or diagnostic strategies were excluded. Two individuals (Z.F. and A.A.O) performed the search and analyzed each article for appropriateness to include in the systematic review. The

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* Corresponding author. 135 Rutledge Ave, MSC 550, Charleston, SC 29425-5500, United States.
E-mail address: discolo@musc.edu (C.M. Discolo).

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Table 1
Swedo criteria for diagnosis of PANDAS.

Swedo criteria
1 Presence of OCD and/or a tic disorder.
2 Symptom onset between 3 years of age and the beginning of puberty.
3 Episodic clinical course: abrupt symptom onset or exacerbations of OCD/tics. Symptoms usually decrease between episodes or may resolve completely.
4 Association of the exacerbation with evidence of group A β-hemolytic (GABHS) streptococcal infection, i.e., a positive throat culture and/or increased levels of anti-GABHS antibody titers.
5 Association with neurologic abnormalities such as adventitious movements and/or motoric hyperactivity.

Table 2
Search methods used in systematic review.

Term
• PANDAS AND ◦ (tonsillectomy OR adenotonsil*) ◦ (antibiotic* OR penicillin OR augmentin OR cephalosporin* OR azithro*) ◦ (intravenous immunoglobulin OR IVIG) ◦ (cognitive behavioral therapy) ◦ (fluoxetine OR fluvoxamine OR sertraline OR paroxetine OR SSRI OR selective serotonin reuptake inhibitor)

references of full-text included articles were scanned for additional sources. Level of evidence was assessed using the Oxford Centre for Evidence Based Medicine criteria [2].

3. Results

The results of our search strategy are shown in Fig. 1. Thirteen articles were ultimately included in this review. The following sections details the search results by treatment modality.

3.1. Adenotonsillectomy

Six articles regarding tonsillectomy treatments were found [3–8]; all PANDAS patients received tonsillectomy for conditions which met the criteria of the American Academy of Otolaryngology-Head & Neck Surgery [9]. Orvidas & Slattery reported two siblings who although responded symptomatically to antibiotic treatment during Group-A Beta-Hemolytic Streptococcus (GABHS) infections, underwent tonsillectomy with resolution of symptoms in one child and improvement in the other 11 months

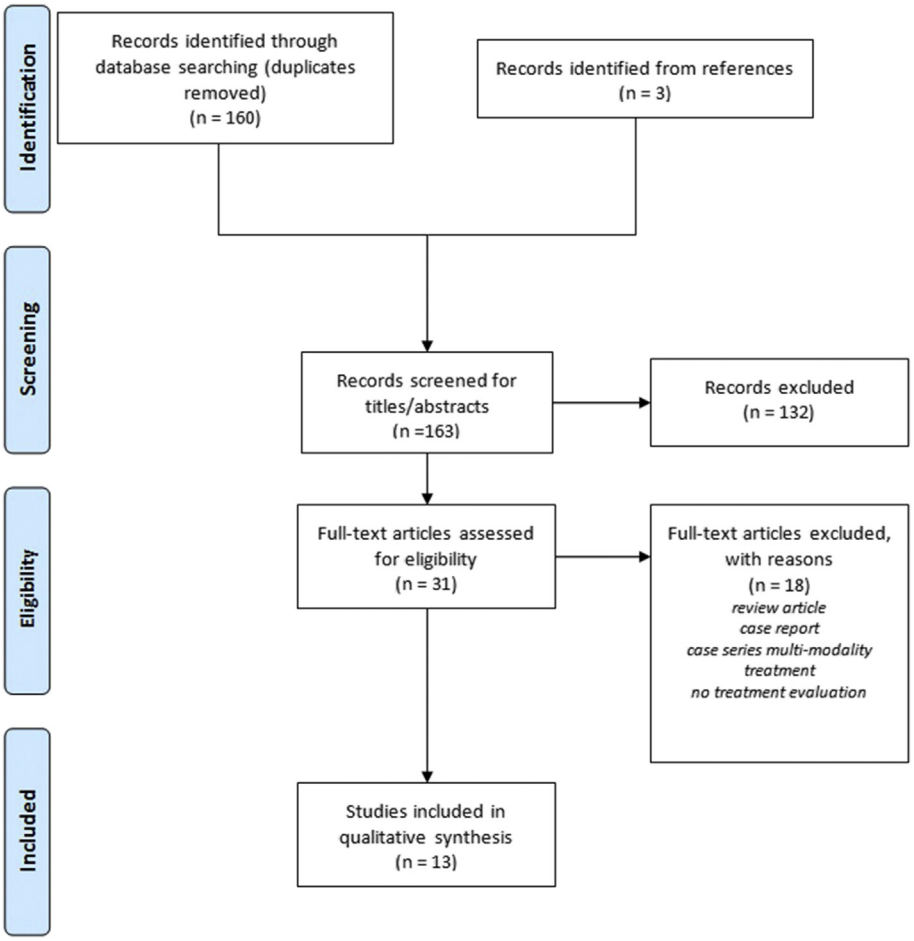

Fig. 1. Literature search results.

postoperatively [3].

Similarly, Heubi & Shott reported a similar experience with two siblings; one with Tourette's syndrome (TS) and one with obsessive-compulsive disorder (OCD) [4]. The child with OCD discontinued sertraline 1 year postoperatively and no longer required follow-up with a psychiatrist. The child with TS was symptom-free 2 months postoperatively and had his clonidine dosage reduced.

Murphy, Storch et al. examined a cohort of children with OCD and found that PANDAS cases had a high association of undergoing surgery compared to those with OCD without PANDAS [5]. Of note, they also observed that PANDAS subjects were more likely to have remission of symptoms when receiving antibiotic therapy. In another study, Murphy, Lewin et al. examined a group of 43 PANDAS patients, 20 of whom had tonsillectomy and/or adenoidectomy [6]. They found no difference in streptococcal titer levels or symptom severity between the surgical and nonsurgical groups. Moreover, a majority of the patients had symptom onset more than 2 years after surgery and so the authors concluded that surgery does not prevent disease onset. This study corroborates the previous study that those with PANDAS were more likely to have surgery compared to non-PANDAS subjects with OCD.

In a prospective study of 120 PANDAS patients, 56 underwent adenotonsillectomy [7]. There were no differences in symptom severity or titer elevation (i.e. antistreptolysin O, antideoxyribonuclease B, and antineural antibodies) following surgery compared to the nonsurgical group. Timing of surgery did not affect time to first relapse (mean = 45.1 ± 17.8 days). The authors concluded that PANDAS is not an indication for adenotonsillectomy.

Finally, Demesh et al. recently conducted a retrospective review of 10 PANDAS patients who received antibiotic therapy followed by tonsillectomy in 9 patients [8]. The parents of the subjects were also contacted and administered a questionnaire regarding the severity of their child's symptoms. Half of the children responded to antibiotic treatment per the parents but symptom resolution was not noted. All nine children who underwent tonsillectomy were noted to have symptom improvement with 3 experiencing complete resolution of OCD symptoms. However, the retrospective nature of the study and post-treatment screening limit the conclusions, as the interpreted results are susceptible to recall bias.

3.2. Antibiotic therapy

Three articles were selected involving the use of antibiotic therapy (ABX) [10–12]. In a double-blind randomized control trial (DB RCT), 37 patients were given oral penicillin V or placebo followed by crossover after 4 months [10]. The authors found no difference in infection rate or symptom severity by treatment phase. Sixteen of the children were also on neuropsychiatric medications at various points during the study.

One prospective study evaluated antibiotic therapy for acute infections and exacerbations in 12 patients over a 3-year period [11]. Antibiotics (either penicillins or cephalosporins) for treatment of GABHS infection alleviated neuropsychiatric symptoms, although half of the patients experienced a recurrence in symptoms. Again, when the recurrence was treated with antibiotics there was improvement in symptoms.

One DB RCT examined the utility of azithromycin or penicillin prophylaxis in a PANDAS cohort of 23 patients [12]. The patients served as their own controls and decreased rates of infection and neuropsychiatric exacerbations were noted in both groups compared to pretreatment. A limitation of this study was retrospective collection of medical history.

Finally, a case report of 2 patients that received benzathine penicillin showed potential benefit of antibiotics [13]. One 9 year old patient who had a favorable response received monthly injections. The dosing frequency was tapered over time, and the patient was symptom-free at 16 years of age. Another showed improvement but was eventually lost to follow up after 6 months.

3.3. Intravenous immunoglobulin therapy

Two selected articles described the use of IVIG: one RCT and one retrospective study [14,15]. Perlmutter et al. in a partially DB RCT, examined the efficacy of IVIG or plasma exchange [14]. Investigators and participants were blinded if IVIG or placebo was administered, but not plasma exchange. Both treatment groups showed significant improvement compared to the placebo group at 1 month and 1 year follow up. Adverse events reported included headache, fever, pallor, dizziness, nausea, and vomiting.

Later, Kovacevic et al. retrospectively presented 12 patients that received IVIG [15]. Follow up ranged from 4 months to 7 years and patients reported significant improvement or complete recovery in all instances. Several patients were also on antibiotic prophylaxis. Additionally, seven patients were retreated with a second course of IVIG due to recurrence or no response to initial treatment with a noted improvement in symptoms.

3.4. Cognitive behavioral therapy

One prospective study examined cognitive-behavioral therapy (CBT) in seven patients, with 6 concurrently taking selective serotonin reuptake inhibitors (SSRIs) [16]. Subjects underwent 3 weeks of intensive CBT and were evaluated at 4 weeks prior to treatment, before the first session, before the final session, and 3 months after the final session. There was significant and sustained reduction in symptom severity, however 2 patients experienced complete relapse and one partial relapse.

4. Discussion

This systematic review examined treatment modalities for a rare pediatric disease occasionally evaluated by an Otolaryngologist. The pathophysiology of this disease is still poorly understood, though it has been likened to Sydenham's chorea given the common link with GABHS. Autoimmune theories propose molecular mimicry in which an acute infection triggers the generation of antineuronal antibodies that cross-react with the basal ganglia [17]. However, such antibodies have not been demonstrated and used to identify patients with PANDAS [18,19]. Other alterations in the immune system are also debatable as one study recently demonstrated distinct differences in cytokine levels among these patients [20]. Another found no differences in B-Cell expression between the tonsils of PANDAS and non-PANDAS patients [21]. In light of these findings, it is still difficult to establish a true immunologic link.

Most of the included studies graded symptom severity using a variety of scales, including the Yale Global Tic Severity Scale (YGTSS) and the Yale-Brown Obsessive Compulsive Scale (YBOCS). Some studies used questionnaires that were more arbitrary and asked the parents their overall perception of their child's well-being. Others simply reported whether the child continued to experience symptoms. The YGTSS or YBOCS would be the most appropriate tools to use in symptom evaluation, as they are quite reliable and valid, although they may not be readily familiar to Otolaryngologists [22,23].

The benefit of tonsillectomy is uncertain due to conflicting results. In theory, removing the tonsils would serve to reduce the rate of infection and therefore exacerbation frequency. Overall,

tonsillectomy was not shown to be an effective treatment modality for PANDAS except in small anecdotal settings, and those who did improve were also subject to other treatments including neuropsychiatric medications and/or antibiotics, confounding the true results of tonsillectomy. Therefore, it is suggested that practitioners continue to offer tonsillectomy per the current American Academy of Otolaryngology-Head & Neck Surgery guidelines [9].

Antibiotic therapy has two strategies: prophylaxis and treatment. By preventing infection or rapidly treating with antibiotics, one would expect a reduction in symptom severity. In this systematic review, prophylaxis did not appear beneficial but acute episodes did seem to resolve when treated with antibiotics. Based on this we can conclude that antibiotic therapy remains an option in the management of PANDAS, but efficacy is uncertain.

Due to the proposed autoimmune component of PANDAS, IVIG has been considered as a possible treatment option. It has previously been studied in patients with rheumatic fever and was suggested to improve symptoms associated with Sydenham's chorea [24,25]. Although there may be benefit from IVIG for exacerbations and recurrences, it is not a benign treatment and the potential risks and complications should be weighed when deciding to employ it. It is worth noting that while adverse events were frequent in these studies, all were considered mild. Steroids are unlikely to be used in this population as they may worsen the neuropsychiatric symptoms [14,26].

CBT confronts PANDAS from a psychiatric standpoint and due to the minimal risk involved in receiving therapy, it can be recommended for management of symptoms. Unlike traditional OCD, the symptoms of PANDAS have an abrupt onset and resolution which manifest at an earlier age [27]. Only one case report utilizing SSRIs was identified, but not included in this systematic review [28]. This treatment caused behavioral activation in the patient consisting of mood instability and suicidality.

A substantial obstacle in evaluating treatment modalities is that most have received multiple treatments, leaving interpretation susceptible to confounding factors. Furthermore, the pathophysiology is still poorly defined/understood. Finally, this is a rare disease with an uncertain prevalence [29]. Antibiotics, SSRIs, and IVIG may continue to be studied as there is currently a Phase 2 clinical trial registered on clinicaltrials.gov [30]. In spite of these limitations, the current study summarizes the evidence for treatment strategies in the PANDAS population and can serve as a reference for otolaryngologists who may be less familiar with the disease.

5. Conclusion

Assessing treatment strategies for PANDAS remains difficult, as it is a rare disease with few published high quality studies. Many of these studies are retrospective in nature and consist of small populations. Furthermore, patients often undergo multiple treatment modalities, leaving room for confounding. Adenotonsillectomy does not seem to clearly benefit this patient population. Antibiotics may prove to be useful in preventing or treating infections and therefore neuropsychiatric exacerbation, but there is limited evidence to recommend it. Though IVIG proved to be effective in certain patient populations, it is not without serious risk and should be reserved for the immunocompromised or most severe cases. Finally, traditional psychiatric therapy for PANDAS may be effective and is of minimal risk to the patient.

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Conflicts of interest

None.

References

[1] S.E. Swedo, H.L. Leonard, M. Garvey, et al., Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases, Am. J. Psychiatry 155 (2) (1998) 264–271.
[2] J. Howick, I. Chalmers, P. Glasziou, et al., The 2011 Oxford CEBM Levels of Evidence, CEBM, Oxford, UK, 2011.
[3] L.J. Orvidas, M.J. Slattery, Pediatric autoimmune neuropsychiatric disorders and streptococcal infections: role of otolaryngologist, Laryngoscope 111 (9) (2001) 1515–1519.
[4] C. Heubi, S.R. Shott, PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections—an uncommon, but important indication for tonsillectomy, Int. J. Pediatr. Otorhinolaryngol. 67 (8) (2003) 837–840.
[5] T.K. Murphy, E.A. Storch, A.B. Lewin, P.J. Edge, W.K. Goodman, Clinical factors associated with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, J. Pediatr. 160 (2) (2012) 314–319.
[6] T.K. Murphy, A.B. Lewin, E.C. Parker-Athill, E.A. Storch, P.J. Mutch, Tonsillectomies and adenoidectomies do not prevent the onset of pediatric autoimmune neuropsychiatric disorder associated with group A streptococcus, Pediatr. Infect. Dis. J. 32 (8) (2013) 834–838.
[7] P. Pavone, V. Rapisarda, A. Serra, et al., Pediatric autoimmune neuropsychiatric disorder associated with group a streptococcal infection: the role of surgical treatment, Int. J. Immunopathol. Pharmacol. 27 (3) (2014) 371–378.
[8] D. Demesh, J.M. Virbalas, J.P. Bent, The role of tonsillectomy in the treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), JAMA Otolaryngol. Head Neck Surg. 141 (3) (2015) 272–275.
[9] R.F. Baugh, S.M. Archer, R.B. Mitchell, et al., Clinical practice guideline: tonsillectomy in children, Otolaryngol. Head Neck Surg. 144 (1 Suppl) (2011) S1–S30.
[10] M.A. Garvey, S.J. Perlmutter, A.J. Allen, et al., A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections, Biol. Psychiatry 45 (12) (1999) 1564–1571.
[11] M.L. Murphy, M.E. Pichichero, Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS), Arch. Pediatr. Adolesc. Med. 156 (4) (2002) 356–361.
[12] L.A. Snider, L. Lougee, M. Slattery, P. Grant, S.E. Swedo, Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders, Biol. Psychiatry 57 (7) (2005) 788–792.
[13] M.J. Redondo-Granado, P. Garcia-Saseta, I. Vizcaino-Lopez, R. Palencia-Luaces, Successful treatment with benzathine penicillin of two patients suspected of suffering from PANDAS, Rev. Neurol. 54 (2) (2012) 125–127.
[14] S.J. Perlmutter, S.F. Leitman, M.A. Garvey, et al., Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood, Lancet 354 (9185) (1999) 1153–1158.
[15] M. Kovacevic, P. Grant, S.E. Swedo, Use of intravenous immunoglobulin in the treatment of twelve youths with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, J. Child. Adolesc. Psychopharmacol. 25 (1) (2015) 65–69.
[16] E.A. Storch, T.K. Murphy, G.R. Geffken, et al., Cognitive-behavioral therapy for PANDAS-related obsessive-compulsive disorder: findings from a preliminary waitlist controlled open trial, J. Am. Acad. Child. Adolesc. Psychiatry 45 (10) (2006) 1171–1178.
[17] M.W. Cunningham, Pathogenesis of group A streptococcal infections and their sequelae, Adv. Exp. Med. Biol. 609 (2008) 29–42.
[18] H.S. Singer, J.J. Hong, D.Y. Yoon, P.N. Williams, Serum autoantibodies do not differentiate PANDAS and Tourette syndrome from controls, Neurology 65 (11) (2005) 1701–1707.
[19] H.S. Singer, C. Gause, C. Morris, P. Lopez, Serial immune markers do not correlate with clinical exacerbations in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, Pediatrics 121 (6) (2008) 1198–1205.
[20] A. Walls, M. Cubangbang, H. Wang, et al., Pediatric autoimmune neuropsychiatric disorder associated with Streptococcus immunology: a pilot study, Otolaryngol. Head Neck Surg. 153 (1) (2015) 130–136.
[21] A. Walls, S. Dermody, R. Kumaran, N. Krishnan, E.H. Harley, Characterization of B-Cells in tonsils of patients diagnosed with pediatric autoimmune neuropsychiatric disorder associated streptococcus, Int. J. Pediatr. Otorhinolaryngol. 80 (2016) 49–52.
[22] E.A. Storch, T.K. Murphy, G.R. Geffken, et al., Reliability and validity of the Yale global tic severity scale, Psychol. Assess. 17 (4) (2005) 486–491.
[23] J.A. Lopez-Pina, J. Sanchez-Meca, J.A. Lopez-Lopez, et al., The yale-brown obsessive compulsive scale: a reliability generalization meta-analysis, Assessment 22 (5) (2015) 619–628.
[24] T.D. van Immerzeel, R.M. van Gilst, N.G. Hartwig, Beneficial use of immunoglobulins in the treatment of Sydenham chorea, Eur. J. Pediatr. 169 (9) (2010) 1151–1154.

[25] C. Gregorowski, C. Lochner, L. Martin, et al., Neuropsychological manifestations in children with Sydenham's chorea after adjunct intravenous immunoglobulin and standard treatment, Metab. Brain Dis. 31 (1) (2016) 205–212.
[26] G. Jonasson, S.R. Wilkinson, Prednisolone-induced obsessive-compulsive behavior in a child, Tidsskr. Nor. Laegeforen. 113 (25) (1993) 3162–3163.
[27] A.H. Zohar, The epidemiology of obsessive-compulsive disorder in children and adolescents, Child. Adolesc. Psychiatr. Clin. N. Am. 8 (3) (1999) 445–460.
[28] T.K. Murphy, E.A. Storch, M.S. Strawser, Selective serotonin reuptake inhibitor-induced behavioral activation in the PANDAS subtype, Prim. Psychiatry 13 (8) (2006) 87–89.
[29] J.S. March, Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS): implications for clinical practice, Arch. Pediatr. Adolesc. Med. 158 (9) (2004) 927–929.
[30] ClinicalTrials.gov. Antibiotic Treatment and Intravenous Immunoglobulin Trial for PANDAS (ATIVPANDAS). https://clinicaltrials.gov/ct2/show/NCT01769027?term=PANDAS&rank=4. accessed 24.03.16.

The Laryngoscope

Transcervical Ultrasonography in the Diagnosis of Pediatric Peritonsillar Abscess

M. Taylor Fordham, MD; Alex N. Rock, BA; Anjum Bandarkar, MD; Diego Preciado, MD, PhD; Michelle Levy, PA-C; Joanna Cohen, MD; Nabile Safdar, MD; Brian K. Reilly, MD

Objectives/Hypothesis: Pediatric peritonsillar abscess (PTA) is a common infection, particularly in the adolescent population. Physical examination alone is not always sufficient to diagnose this pathology, and thus, computed tomography is often utilized as a diagnostic adjunct. With growing concern over radiation exposure in the pediatric population, we conducted a prospective study to investigate the use of ultrasonography in the detection of pediatric PTA.

Study Design: Prospective single arm cohort study.

Methods: Pediatric patients examined in consultation for concern for PTA were prospectively enrolled in the study. Patients were managed based on clinical symptoms and presentation. Transcervical ultrasonography of the peritonsillar region was performed on all patients. Clinical outcomes were reviewed retrospectively and compared to ultrasound findings.

Results: Forty-three patients (age range, 2–20 years) were enrolled in the study. The sensitivity and specificity of transcervical ultrasound when compared to clinical outcomes were 100% and 76.5%, respectively. The positive and negative predictive values were 52.9% and 100%, respectively. Fisher exact test showed a statistically significant association ($P < .01$) between negative ultrasonography and successful medical management, and multivariate regression analysis showed a strong correlation between ultrasound findings and presence/absence of purulence during surgical intervention ($P = .01$).

Conclusions: Transcervical ultrasonography is a useful tool in diagnosing pediatric PTA. This imaging modality not only avoids undue radiation exposure, but it also proves to be an excellent tool at identifying patients who will not need surgical intervention. To our knowledge, this is the first study to explore this technique for the diagnosis of pediatric PTA.

Key Words: Pediatric peritonsillar abscess, ultrasound, transcervical, pediatric head and neck infection.

Level of Evidence: 2b

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INTRODUCTION

Peritonsillar abscess (PTA) is a commonly occurring and potentially life-threatening suppurative infection located between the palatine tonsil capsule and the more lateral pharyngeal constrictor muscle. PTA affects children and adults but is more common in adolescents, with an estimated incidence of between 14 and 40 per 100,000 in patients younger than 18 years old.[1] Both medical and surgical management are frequently curative. Inadequate treatment of PTA can result in rare but serious consequences, such as sudden rupture with aspiration of purulent exudate, extension of the infection into the mediastinum, acute airway obstruction, and/or sepsis. Therefore, appropriate diagnosis and management are crucial.[2,3]

Treatment is based on differentiating among PTA, peritonsillar cellulitis (PTC), and tonsillitis (viral or bacterial); however, distinguishing these entities may be challenging based on history and physical exam alone. A prior small study found the sensitivity and specificity of using clinical impression to diagnose PTA to be only 78% and 50%, respectively.[4] Computed tomography (CT) has been shown to be the most sensitive imaging modality for diagnosis (100% sensitivity) and provides the additional benefit of identifying spread of infection beyond the peritonsillar tissues.[5] Although CT is an attractive option to assist in the diagnosis of a PTA, cost and increased awareness of radiation exposure prohibit this modality from being considered standard of care, especially in the pediatric population.[6–9] Procedural intervention, such as incision and drainage, provides clarity of diagnosis as well as potential therapeutic benefit, but this management is obviously invasive and not without risk to the child.

Ultrasound (US) has been shown to reliably distinguish PTA from PTC in a number of small-scale studies with adult patients.[4,10–14] There is currently no literature addressing the use of US for peritonsillar infection in an exclusively pediatric population. Thus, the primary objective of this study was to evaluate the efficacy of US in the diagnosis of pediatric PTA. We hypothesized that

From the Department of Pediatric Otolaryngology (M.T.F., D.P., M.L., B.R.K.), Department of Radiology (A.B., N.S.), and Department of Emergency Medicine (J.C.), Children's National Health System, Washington, DC; and George Washington University School of Medicine (A.N.R.), Washington, DC, U.S.A.

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Send correspondence to M. Taylor Fordham, MD, Department of Pediatric Otolaryngology, Children's National Health System, 111 Michigan Ave., Washington, DC 20010. E-mail: fordham@bcm.edu

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TABLE I.
Patient Demographics.

	No. of Patients	Mean Age (SD), yr	Median Age (IQR), yr	Age Range, yr	Gender	Race
Ultrasound cohort	43	12.0 (5.3)	13 (7–17)	2–20	M: 23, F: 20	W: 7, A: 35, H: 1

A = African American; H = Hispanic; IQR = interquartile range; SD = standard deviation; W = white.

US would accurately predict the presence of purulence in children being evaluated for possible PTA.

MATERIALS AND METHODS

After obtaining institutional review board approval, a convenience sample of children and adolescents with suspected PTA per the evaluating provider were prospectively enrolled in the study. The diagnosis of PTA was based on a history of sore throat and/or fever, neck pain, trouble swallowing, and voice changes in conjunction with physical exam findings such as asymmetric tonsils, palatal edema, uvular deviation, trismus, and peritonsillar fullness or erythema. Children <2 years old, those with significant airway compromise, and those being evaluated for retropharyngeal processes were excluded from the study. A physician board certified in pediatrics or pediatric emergency medicine evaluated each patient and then obtained consultation from the otolaryngology service. Patients were managed based on clinical impression alone, but all enrolled patients underwent a transcervical US to evaluate for PTA. The transcervical technique utilizes a high-frequency probe placed below the inferior border of the mandible to visualize the submandibular gland, deep to which the tonsil and peritonsillar space can be assessed. A blinded radiologist (A.B.) viewed and analyzed all final US images.

The results of the US were compared to the results of procedural interventions and clinical patient outcomes. A positive US was defined as an anechoic or hypoechoic pocket in the peritonsillar plane suggestive of abscess. A true-positive PTA was defined as purulence discovered during surgical intervention in the setting of a positive US. A false-positive PTA was defined as the absence of purulence during surgical intervention or successful medical management in the setting of a positive US. A true-negative PTA was defined as no purulence noted during procedural intervention or clinical improvement with medical management alone in the setting of a negative US. Last, a false-negative PTA was defined as purulence discovered during surgery in the setting of a negative US.

Following discharge, patients' medical records were retrospectively reviewed for treatment failures, defined as those patients managed initially medically who ultimately underwent drainage of a PTA. Statistical analysis with Fisher exact test was performed using GraphPad Prism software GraphPad Software, Inc., La Jolla, CA), and sensitivity, specificity, and positive and negative predictive values were calculated based on our results. Multivariate regression analysis was conducted analyzing any correlations between age, sex, otolaryngologist clinical diagnosis, and US findings with the presence/absence of PTA.

RESULTS

Forty-three patients were enrolled in this study from May 2013 to April 2014. The demographic and age distribution of these patients can be seen in Table I. Using the definitions described earlier, we compared the US findings to procedural findings and/or clinical management outcomes (Table II). The US was positive for PTA in 17 (39.5%) patients. Of these patients, nine were found to have had true-positive PTA by our definition. The greatest measurable dimension of these abscesses ranged from 7 mm to 32 mm, with a mean of 25 mm. Of the eight false-positive ultrasounds, the diameter of the abscesses ranged from 11 mm to 28 mm with a mean of 18 mm. The size differences between these two groups, which was statistically significant, can be viewed in Table III. Of the eight false positives, three patients had drainage procedures without procurement of pus, and five were medically managed successfully. The diameter of the abscess cavity on US in these five patients ranged from 11 mm to 21 mm, with a mean of 15 mm. Of the three patients undergoing negative procedures, two had bedside needle aspiration without evidence of purulence, and one underwent a negative incision and drainage in the operating room based on clinical exam. Three patients diagnosed with PTA clinically but managed medically also had US findings consistent with abscess. Either these patients responded promptly to initiation of medical management, or the parent opted to forego elective surgical intervention as initial therapy.

US did not reveal a PTA in 26 (60.5%) of the children enrolled. The breakdown of the US diagnoses for these patients can be seen in Table IV. Two of these children underwent drainage procedures following clinical diagnosis of PTA but with no purulence identified in

TABLE II.
Ultrasound Results and Surgical Findings.

	Ultrasound Results		
Surgical Intervention	Positive	Negative	Total
None or negative I&D	8	26	34
Positive I&D	9	0	9
Total	17	26	43

I&D = Incision and drainage.

TABLE III.
Comparison of True Positive and False Positive Abscess Cavity Dimensions.

	True Positive	False Positive
No.	9	8
Range, mm	7–32	11–28
Mean, mm	25	18
P value	<.05	

P value calculated using two-tailed Mann-Whitney test.

TABLE IV.
Radiographic Diagnoses of Patients Without Evidence of Peritonsillar Abscesses.

Diagnosis	No.
Unilateral tonsillitis	11
Bilateral tonsillitis	9
Normal tonsils	2
Parapharyngeal phlegmon	1
Reactive lymphadenopathy	1
Lymphadenitis	2

either case. Interestingly, one of these patients had a CT scan from an outside facility suggestive of PTA. The remaining 24 patients were exclusively managed medically without any treatment failures. After a negative needle aspiration on initial visit 2 days prior, one patient returned to the emergency room. This patient was not determined to have a PTA at the time of representation and was again managed medically without failure. Another patient was readmitted following operative incision and drainage of a clinical PTA due to reaccumulation of infection.

We compared the ages of patients undergoing drainage and those not undergoing procedures. After performing a Mann-Whitney test on these data, we discovered the *P* value comparing the ages was not statistically significant. The box plot in Figure 1 represents these data. Furthermore, we elected to perform a multivariate analysis using age, sex, otolaryngologist clinical diagnosis, and US findings as independent variables to see if any correlated statistically with the presence or absence of purulence. These data can be viewed in Table V. US finding was the only independent variable found to be correlative with the presence or absence of PTA ($P < .05$).

The sensitivity and specificity (with 95% confidence intervals) of transcervical ultrasonography in the diagnosis of pediatric PTA are 100% (86.8%-100%) and 76.5% (58.9%-89.2%), respectively. The positive and negative

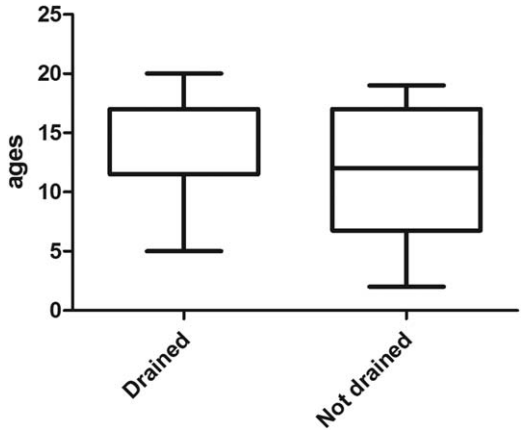

Fig. 1. Box plot comparing the age of patients undergoing drainage procedures and those not undergoing drainage procedures. There was no statistical difference in age of patients in the two groups.

TABLE V.
Multivariate Analysis Assessing Correlation Between Age, Sex, Otolaryngologist Clinical Diagnosis and US Finding With Presence/Absence of Peritonsillar Abscess.

	Coefficients	Standard Error	*t* Statistic	*P* Value	Lower 95%	Upper 95%
Age	0.009	0.009	0.884	.382	−0.011	0.028
Sex	−0.030	0.101	−0.300	.765	−0.235	0.174
US finding	0.399	0.151	2.637	.012	0.092	0.705
ENT dx	0.229	0.144	1.589	.120	−0.062	0.520

x = diagnosis; ENT = ear, nose, and throat; US = ultrasound.

predictive values (with 95% confidence intervals) are 52.9% (27.9%-77.1%) and 100% (66.4%-100%), respectively. When a Fisher exact test was performed, the *P* value was statistically significant ($P < .01$), indicating an important correlation between a negative US and patients who were able to be managed medically. Examples of US images obtained in these patients are present in Figures 2–4.

DISCUSSION

Peritonsillar abscesses are common in the pediatric population; however, diagnosis in this cohort is challenging due to limitations imposed by smaller oropharyngeal anatomy and the potential for uncooperative patients. As a result of these clinical hurdles, CT is frequently utilized as a diagnostic tool. One study of pediatric emergency room visits reported that CT was ordered in 65% of patients in whom a PTA was suspected.[15] Other groups have reported algorithms that include exams of the oropharynx under anesthesia or trials of intravenous antibiotics followed by operative intervention.[16,17] This study aimed to investigate the role of transcervical US in diagnosing pediatric PTA.

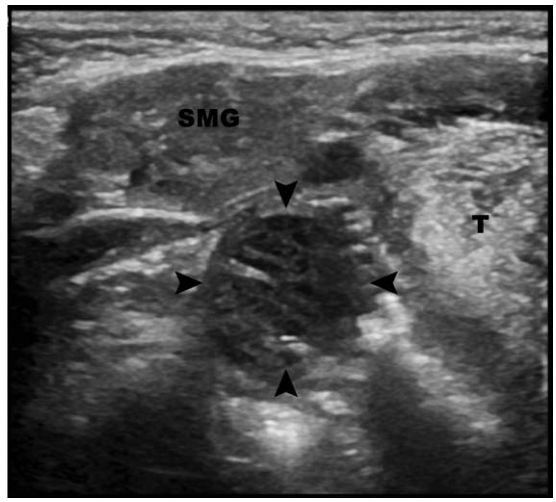

Fig. 2. Example of a normal transcervical ultrasound of the tonsil and peritonsillar region. The tonsil has a striated appearance and is outlined by the black arrow heads. SMG = submandibular gland; T = tongue.

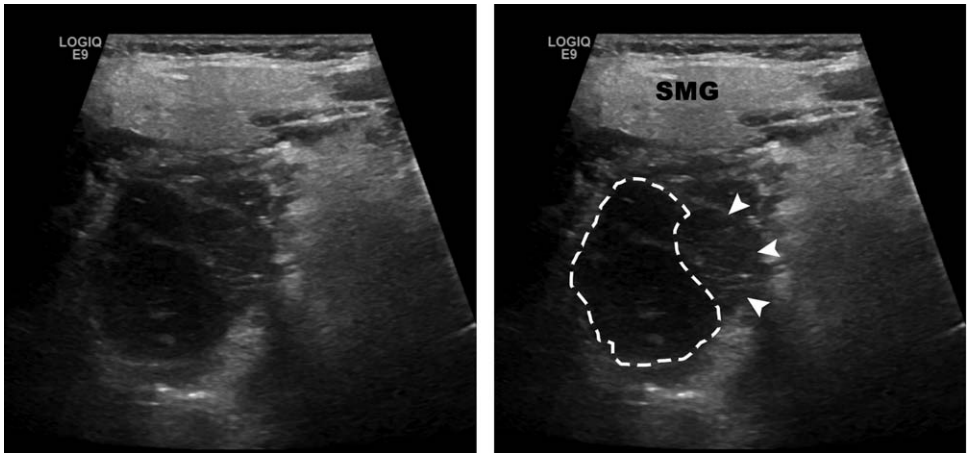

Fig. 3. Identical images of a right peritonsillar abscess (PTA) with the image on the right labeled. The PTA is outlined by a dashed white line. The tonsil (white arrow heads) and submandibular gland (SMG) are once again identified.

The sensitivity and specificity of US in this study were 100% and 76.5%, respectively. Our data are similar to that of other studies. Araujo Filho et al. reported sensitivity and specificity as 80% and 92.8%, respectively, for transcervical US, primarily in adult patients.[13] The differences in anatomy and amount of subcutaneous tissue between the adult and pediatric populations may account for some of the variation between these statistics; however, both studies highlight the utility of this modality in evaluating this infectious process. In this study, it is important to note that of the patients who had a negative US, none failed medical management.

US is a very sensitive tool for identifying fluid collections within tissue planes; therefore, we were not surprised to have a number of false positives, as oftentimes small fluid collections on CT or US are reported. Several patients who were successfully managed medically were diagnosed with PTA both on physical exam and US. These patients, who responded promptly to initial medical therapy prior to procedural intervention, or whose parents opted for a more conservative medical treatment in lieu of surgical drainage, were followed clinically. Given that the peritonsillar regions of all exclusively medically managed children were never opened, it is possible that small collections of purulence may have been found on some of these patients. With this is mind, we may have overcalled the number of false positives. Our study design did not mandate exploration of every peritonsillar space or require CT on every patient. For statistical integrity, however, children with positive ultrasounds managed medically successfully were not discarded, but rather counted as false positives. Based on these data, we believe that smaller PTAs may resolve with medical therapy alone; therefore, our study results likely represent an underestimation of ultrasound's specificity for PTA.

When comparing the sizes of the measured abscesses in the true- and false-positive groups, a statistically significant difference was found, with the false positives measuring smaller. Although US is capable of visualizing small PTAs in pediatric patients, the spectrum of peritonsillar and intratonsillar findings may lead a radiologist to overcall an abscess. This conclusion assumes that all of the false positives indeed did not have purulence. If purulent cavities were in fact present on some of these patients, then smaller abscesses either respond to medical management alone and/or are difficult to locate during procedural interventions.

Based on these findings, we developed an algorithm for PTA management (Fig. 5), which is now utilized at

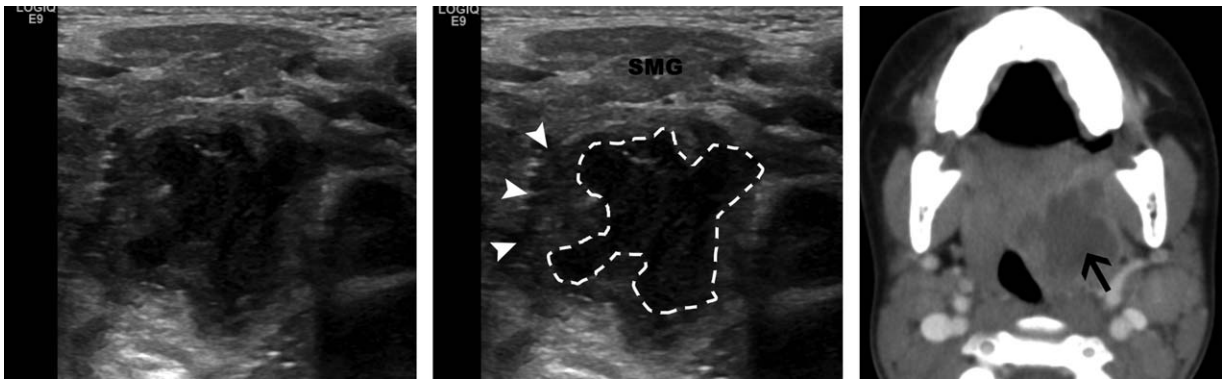

Fig. 4. Ultrasound and computed tomography (CT) images from the same patient. The far left and center images are identical, the center image being marked to identify the structures. The irregularly marginated hypoechoic region (outlined by white dashed line) is consistent with a left peritonsillar abscess. Again the tonsil (white arrow heads) and submandibular gland (SMG) are labeled for reference. The CT image (far right) shows the corresponding abscess (black arrow).

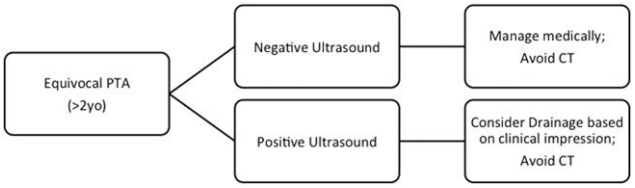

Fig. 5. This generalized basic management algorithm has been adopted by our institution. CT = computed tomography; PTA = peritonsillar abscess.

our institution. For evaluation of equivocal PTA, we have eliminated CT scans from our workup protocol altogether. Patients are managed medically if they have a negative US. Whether or not they are admitted for initiation of treatment is contingent on severity of symptoms and overall clinical picture. If the US is positive, history and physical exam dictate treatment. If the physical exam also suggests PTA, then drainage is attempted pending consent. If the physical exam is equivocal, then medical therapy is attempted first. In cases of a difficult or limited exam, one may elect to attempt drainage of larger abscesses (>15 mm) seen on US while attempting medical management of ones that are smaller and/or less symptomatic. As has been described in previous studies on pediatric deep neck space infections as well as pediatric PTA, some fluid collections are likely to respond to antibiotic therapy alone.[16,18–20]

In our study, six children were transferred to our institution with prior CT scans. All of these patients were enrolled and received a transcervical US per study protocol. Although the aim of the study was not to compare these two modalities, it is worth noting that the final US read was identical to the CT findings in five of six cases. In the one case where the two modalities differed, the physical exam and CT were suggestive of PTA, whereas the US was negative. When that child was taken to the operating room for drainage, no purulence was found.

In summary, we believe that there are several significant advantages to using ultrasound as the primary diagnostic tool for equivocal pediatric PTA. In addition to cost reduction compared to CT, the other obvious advantage is the avoidance of undue radiation exposure in children. Given how well US is tolerated and how quickly it can be performed, one may also argue that sedation requirements will be lower than when using other imaging modalities that may require intravenous injections and/or sedation simply to complete the exam. Moreover, US provides real-time imaging with excellent assessment of the tonsils and peritonsillar space. Interestingly, the images from this study may even begin to help differentiate intratonsillar from peritonsillar processes, both of which may present with a largely swollen and asymmetric oropharynx.

Perhaps the largest impediment to the use of US is the interuser variability. Although the technique itself is rather simple, interpreting the images accurately involves appreciating the nuances of this modality. Despite these limitations, the authors still find the exam and its interpretation to be well within the skill set of radiologists, otolaryngologists, and emergency physicians alike.

Our study was limited by our small sample size and our inability to enroll a random or continuous sample of patients. Missing follow-up may have biased our results, as it is certainly possible that patients presented to other hospitals with recurrent or persistent symptoms after having been evaluated and treated initially at ours. Last, it was impossible to ensure that clinicians were universally blinded to all radiographic results, ultrasound, or outside CT impressions. This lack of blinding may have biased clinical decision making in some circumstances.

Overall, our study results support the use of transcervical US in the workup of pediatric PTA. Although not all children who present with signs and symptoms consistent with a PTA warrant imaging, the authors believe that US will prove to be the optimal modality in evaluating these patients when imaging is indicated. In addition to being safe and well-tolerated, statistically significant data show that US is highly predictive in identifying those patients with equivocal PTA who are likely to improve without the need for surgical intervention. Furthermore, US findings (more so than clinical diagnosis or age) are highly correlative with the presence or absence of PTA. Even so, additional prospective studies are needed to better elucidate the role this technology will play in these patients and to better define which PTAs can be best managed medically versus surgically.

CONCLUSION

This study is the first to investigate the efficacy of transcervical ultrasound in the diagnosis of pediatric PTA. Our results show that ultrasound is a reliable and useful tool in the evaluation of these children and is highly correlative with surgical findings and clinical outcomes. The authors believe that this study should bolster a transition away from CT as the imaging modality of choice. Although the authors still maintain that there is a role for CT in the evaluation of complex head and neck infections, we also emphasize the physician's role in the thoughtful use of this modality in light of documented concerns over radiation exposure in children.

BIBLIOGRAPHY

1. Millar KR, Johnson DW, Drummond D, Kellner JD. Suspected peritonsillar abscess in children. *Pediatr Emerg Care* 2007;23:431–438.
2. Dalton RE, Abedi E, Sismanis A. Bilateral peritonsillar abscesses and quinsy tonsillectomy. *J Natl Med Assoc* 1985;77:807–812.
3. Brook I. Microbiology and management of peritonsillar, retropharyngeal, and parapharyngeal abscesses. *J Oral Maxillofac Surg* 2004;62:1545–1550.
4. Scott PMJ, Loftus WK, Kew J, Ahuja A, Yue V, Van Hasselt CA. Diagnosis of peritonsillar infections: a prospective study of ultrasound, computerized tomography and clinical diagnosis. *J Laryngol Otol* 1999;113:229–232.
5. Powell J, Wilson JA. An evidence-based review of peritonsillar abscess. *Clin Otolaryngol* 2012;37:136–145.
6. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med* 2009;169:2078–2086.

7. Brenner DJ, Elliston CD, Hall EJ, Berdon WE. Estimated risks of radiation-induced fatal cancer from pediatric CT. *Am J Roentgenol* 2001; 176:289–296.
8. Brenner DJ, Hall EJ, Phil D. Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007;357:2277–2284.
9. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 2012;380:499–505.
10. Ahmed K, Jones AS, Shah K, Smethurst A. The role of ultrasound in the management of peritonsillar abscess. *J Laryngol Otol* 1994;108:610–612.
11. Buckley AR, Moss EH, Blokmanis A. Diagnosis of peritonsillar abscess: value of intraoral sonography. *Am J Roentgenol* 1994;162:961–964.
12. Strong EB, Woodward PJ, Johnson LP. Intraoral ultrasound evaluation of peritonsillar abscess. *Laryngoscope* 1995;105:779–782.
13. Araujo Filho BC, Sakae FA, Sennes LU, Imamura R, de Menezes MR. Intraoral and transcutaneous cervical ultrasound in the differential diagnosis of peritonsillar cellulitis and abscesses. *Rev Bras Otorhinolaringol* 2006;72:377–381.
14. Costantino TG, Satz WA, Dehnkamp W, Goett H. Randomized trial comparing intraoral ultrasound to landmark-based needle aspiration in patients with suspected peritonsillar abscess. *Acad Emerg Med* 2012;19:626–631.
15. Baker KA, Stuart J, Sykes KJ, et al. Use of computer tomography in the emergency department for the diagnosis of pediatric peritonsillar abscess. *Pediatr Emer Care* 2012;28:962–965.
16. Blotter JW, Yin L, Glynn M, Wiet GJ. Otolaryngology consultation for peritonsillar abscess in the pediatric population. *Laryngoscope* 2000;110: 1698–1701.
17. Schraff S, McGinn JD, Derkay CS. Peritonsillar abscess in children: a 10-year review of diagnosis and management. *Int J Pediatr Otorhinolaryngol* 2001;57:213–218.
18. Cheng J, Elden L. Children with deep space neck infections: our experience with 178 children. *Otolaryngol Head Neck Surg* 2013;148:1037–1042.
19. Saluja S, Brietzke SE, Egan KK, et al. A prospective study of 113 deep neck infections managed using a clinical practice guideline. *Laryngoscope* 2013;123:3211–3218.
20. Bolton M, Wang W, Hahn A, Ramilo O, Mejias A, Jaggi P. Predictors for successful treatment of pediatric deep neck infections using antimicrobials alone. *Pediatr Infect Dis J* 2013;32:1034–1036.

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Quality of Life and Obstructive Sleep Apnea Symptoms After Pediatric Adenotonsillectomy

Susan L. Garetz, MD[a], Ron B. Mitchell, MD[b], Portia D. Parker, MS[c], Reneé H. Moore, PhD[d], Carol L. Rosen, MD[e], Bruno Giordani, PhD[f], Hiren Muzumdar, MD[g], Shalini Paruthi, MD[h], Lisa Elden, MD[i], Paul Willging, MD[j], Dean W. Beebe, PhD[k], Carole L. Marcus, MBBCh[l], Ronald D. Chervin, MD, MS[m], Susan Redline, MD, MPH[n]

abstract

BACKGROUND AND OBJECTIVES: Data from a randomized, controlled study of adenotonsillectomy for obstructive sleep apnea syndrome (OSAS) were used to test the hypothesis that children undergoing surgery had greater quality of life (QoL) and symptom improvement than control subjects. The objectives were to compare changes in validated QoL and symptom measurements among children randomized to undergo adenotonsillectomy or watchful waiting; to determine whether race, weight, or baseline OSAS severity influenced changes in QoL and symptoms; and to evaluate associations between changes in QoL or symptoms and OSAS severity.

METHODS: Children aged 5 to 9.9 years with OSAS (N = 453) were randomly assigned to undergo adenotonsillectomy or watchful waiting with supportive care. Polysomnography, the Pediatric Quality of Life inventory, the Sleep-Related Breathing Scale of the Pediatric Sleep Questionnaire, the 18-item Obstructive Sleep Apnea QoL instrument, and the modified Epworth Sleepiness Scale were completed at baseline and 7 months. Changes in the QoL and symptom surveys were compared between arms. Effect modification according to race and obesity and associations between changes in polysomnographic measures and QoL or symptoms were examined.

RESULTS: Greater improvements in most QoL and symptom severity measurements were observed in children randomized to undergo adenotonsillectomy, including the parent-completed Pediatric Quality of Life inventory (effect size [ES]: 0.37), the 18-item Obstructive Sleep Apnea QoL instrument (ES: –0.93), the modified Epworth Sleepiness Scale score (ES: –0.42), and the Sleep-Related Breathing Scale of the Pediatric Sleep Questionnaire (ES: –1.35). Effect modification was not observed by obesity or baseline severity but was noted for race in some symptom measures. Improvements in OSAS severity explained only a small portion of the observed changes.

CONCLUSIONS: Adenotonsillectomy compared with watchful waiting resulted in significantly more improvements in parent-rated generic and OSAS-specific QoL measures and OSAS symptoms.

[a]*Department of Otolaryngology–Head and Neck Surgery and Sleep Disorders Center,* [f]*Departments of Psychiatry and Psychology and Sleep Disorders Center, and* [m]*Department of Neurology and Sleep Disorders Center, University of Michigan Health Center, Ann Arbor, Michigan;* [b]*Departments of Otolaryngology and Pediatrics, Utah Southwestern and Children's Medical Center, Dallas, Texas;* [c]*SAS Institute Inc, Cary, North Carolina;* [d]*Department of Statistics, North Carolina State University, Raleigh, North Carolina;* [e]*Department of Pediatrics, Rainbow Babies & Children's Hospital, University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio;* [g]*Division of Pulmonary Medicine, Allergy, & Immunology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, Pennsylvania;* [h]*Department of Pediatrics, Cardinal Glennon Children's Medical Center, Saint Louis University, St Louis, Missouri; Departments of* [i]*Otolaryngology and* [j]*Pediatrics, Sleep Center, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania;* [l]*Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati College of Medicine, and* [k]*Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; and* [n]*Departments of Medicine and Neurology, Brigham and Women's Hospital, and Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts*

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WHAT'S KNOWN ON THIS SUBJECT: Pediatric obstructive sleep apnea syndrome (OSAS) has been associated with decreased health-related quality of life (QoL). Observational studies suggest that adenotonsillectomy for pediatric OSAS improves QoL, but these studies did not use a randomized study design or a control group of children with OSAS managed nonsurgically.

WHAT THIS STUDY ADDS: A prospective, randomized controlled study of adenotonsillectomy for pediatric OSAS showed significantly greater QoL and symptom improvements in children undergoing adenotonsillectomy than in the nonsurgical control arm. The extent of improvement was not appreciably influenced by baseline OSAS severity or obesity.

Obstructive sleep apnea syndrome (OSAS) affects ~1% to 3% of children[1,2] and has been associated with an increased risk for developing cardiovascular and other systemic morbidities.[3,4] Even milder forms of sleep-disordered breathing have been associated with behavioral disturbances in children.[5–9] Pediatric OSAS has also been associated with decreased health-related quality of life (QoL). Studies (including a recent meta-analysis) demonstrated that children with OSAS had generic health-related QoL scores lower than healthy children and similar to children with juvenile rheumatoid arthritis.[10–13] Validated QoL instruments have shown moderate to large impairment of disease-specific QoL in more than one-half of surveyed children.[14]

The first-line surgical treatment of pediatric OSAS is adenotonsillectomy (AT). Rising health care costs and emphasis on evidence-based medicine have resulted in scrutiny of common surgical procedures, including measurement of outcomes meaningful to patients. Observational studies have suggested that in pediatric OSAS, AT improves both short-term and longer term QoL.[15–18] However, none of these studies used a randomized study design or a control group of children with OSAS who were not treated surgically.

The recently completed CHAT (Childhood Adenotonsillectomy Trial) was the first multisite, prospective, randomized controlled study on the effects of AT for the treatment of pediatric OSAS. Although the primary cognitive test outcome did not differ significantly between the surgical and observational treatment arms, children randomized to early AT (eAT) rather than watchful waiting had improved behavior and QoL as well as higher rates of OSAS resolution on polysomnography (PSG).[19] For the present report, the impact of AT on QoL was quantified (including specific domains of function) and on OSAS symptoms. The extent to which race, baseline OSAS severity, or obesity affected treatment responses was also explored. Finally, we characterized relationships between changes in PSG indices of OSAS severity and changes in symptom and QoL measures.

METHODS

As part of the CHAT study, 453 children 5 to 9.9 years of age with OSAS were randomly assigned to either AT within 1 month (eAT) or watchful waiting with supportive care (WWSC). A detailed description of the methods of the CHAT study has been published.[20] In brief, children with OSAS were recruited from pediatric sleep centers, otolaryngology and pediatric clinics, and the general community from 6 clinical sites from 2007 to 2011. Institutional review board approval was obtained from participating clinical centers, children provided assent if old enough, and caregivers provided written informed consent.

All children underwent standardized PSG; studies were scored at a central reading center to ensure uniformity.[19] PSG inclusion criteria included OSAS, defined as an obstructive apnea index (OAI) $\geq$1 or obstructive apnea hypopnea index (AHI) $\geq$2. OAI is the number of obstructive apneic events per hours of total sleep time and AHI is the number of mixed or obstructive apneic events and hypopneic events associated with a $\geq$50% reduction in airflow and either $\geq$3% oxygen desaturation or electroencephalographic arousal per hours of total sleep time. Children with severe OSAS as defined by an OAI $>$20, an AHI $>$30, or oxygen saturation $\leq$90% for $>$2% of total sleep time were excluded. All children were deemed appropriate surgical candidates by otolaryngologists.

In addition to PSG data, physical examination and validated survey information were collected at baseline and 7 months later.

Demographic information included age, gender, race, height, weight, ethnicity, maternal education, and family income. BMI and *z* scores were calculated by using standardized formulas.[21]

Generic and disease-specific health-related QoL and severity of OSAS symptoms were assessed with survey instruments validated for these ages. Generic health-related QoL was measured by using the parent and child versions of the Pediatric Quality of Life (PedsQL) inventory that assess physical, emotional, social, and school functioning.[22] The parallel child and parent-proxy forms differ only in use of age-appropriate language. For children ages 5 to 7 years, the survey was administered by an interviewer. Scoring is performed by linear transformation of the 23 item scores to a scale of 0 to 100. Higher values indicate better QoL.

Disease-specific health-related QoL was assessed by caregivers by using the 18-item Obstructive Sleep Apnea (OSA-18) tool. This instrument focuses on perceived impact of OSAS on 5 domains: sleep disturbance, physical suffering, emotional distress, daytime problems, and caregiver concerns.[23] Items are scored on a 7-point scale and totaled, providing a severity score of 18 to 126, with lower scores representing higher QoL. Mean scores for healthy children with no OSAS symptoms are in the range of 31.2 $\pm$ 10.4.[24] Scores $>$60 suggest a moderate impact.

To assess OSAS symptom severity, caregivers completed the Sleep-Related Breathing Disorder (SRBD) scale of the Pediatric Sleep Questionnaire (PSQ) and the Epworth Sleepiness Scale modified for children (mESS). The PSQ SRBD scale contains 22 yes/no questions and provides both a total score, as the proportion of all symptoms endorsed by the caregiver, and subscale scores for snoring, daytime sleepiness, and behavior. The mean of yes (1) and no (0) responses generates a score

between 0 and 1, with higher scores indicating greater symptom severity. Values ≥0.33 have been proposed as identifying higher risk for pediatric OSAS.[25] The sleepiness subscale has been validated against objective sleepiness in children.[26] On the mESS, caregivers rate the likelihood of their child falling asleep from 0 (never) to 3 (almost always) in 8 situations. Scores range from 0 to 24, with higher scores indicating more sleepiness.[27]

PSG parameters used to assess OSAS severity were the AHI and oxygen desaturation index (ODI [ie, number of episodes of oxygen desaturation ≥3% per hour of sleep]). The AHI reflects both sleep fragmentation and hypoxemia, whereas the ODI more specifically assesses intermittent hypoxemia.

Baseline demographic variables are summarized according to treatment arm (ie, eAT, WWSC) as mean ± SD values for continuous variables or frequency (%) for categorical variables. Baseline comparisons of QoL and symptom measurements according to study arm were examined by using 2-sample independent *t* tests (unadjusted *P* value) or analysis of covariance (ANCOVA). These and all other ANCOVA models were adjusted for site, race (African American versus non–African American), age (5–7 vs 8–10 years), and overweight status (≥85th vs <85th BMI percentile) as the primary analysis and site. Race (African American versus non–African American), gender, age (continuous), obesity (≥95th vs <95th BMI percentile), maternal education (less than high school, high school or higher, or missing), income (<$30 000, ≥$30 000, or missing), and baseline log AHI were included in the secondary analysis.[19] To assess whether the WWSC and eAT arms experienced a differential change in QoL and symptom measurements, unadjusted analysis of variance and adjusted ANCOVA models were fit with the QoL and symptom outcomes expressed as change from baseline to follow-up. Additional ANCOVA models included interaction terms to assess effect modification for treatment response according to baseline OSAS severity, race, and weight. Furthermore, linear regression models were used to assess associations between change in QoL or symptoms and change in PSG measures (log transformed to approximate normal distribution). In this last regression model, data from the 2 treatment arms were combined. This technique was used because OSAS resolution, defined as AHI <2 and OAI <1 at follow-up, was observed in a large proportion of subjects in both treatment arms (46% of WWSC subjects and 79% of eAT subjects). Sensitivity analyses were conducted, however, stratified by treatment arm. A total of 24 children (16 in the WWSC arm and 8 in the eAT arm) were not treated per protocol. Exploratory analyses performed for the original CHAT publication did not yield appreciable changes in results when those subjects were excluded from the analyses. Cohen's d effect size was calculated as (mean change difference)/(pooled SD). Statistical analyses were performed by using SAS version 9.3 (SAS Institute, Inc, Cary, NC) with α cutoff of ≤0.01.

RESULTS

No significant baseline differences in demographic characteristics, QoL, or symptom survey total scores were seen between treatment arms. There was a significant difference in the emotional function domain of the parent PedsQL with a higher score seen in the eAT arm (Tables 1 and 2).

Generic Health-Related QoL (PedsQL)

The PedsQL parent-reported total score improved significantly more in

TABLE 1 Demographic Characteristics of the Study Population at Baseline

Characteristic	eAT Arm (*n* = 227)	WWSC Arm (*n* = 226)
Age, mean ± SD, y	6.5 ± 1.4	6.6 ± 1.4
Male sex	118 (52.0)	101 (44.7)
Race		
African American	123 (54.2)	126 (55.8)
White	81 (35.7)	74 (32.7)
Other	23 (10.1)	26 (11.5)
Hispanic ethnicity	21 (9.3)	16 (7.2)
Maternal education		
Less than high school	22 (9.7)	20 (8.8)
High school diploma/GED or higher	200 (88.5)	205 (90.3)
Not sure/missing	4 (1.77)	2 (0.88)
Income		
<$30 000	91 (40.3)	92 (40.5)
≥$30 000	100 (44.3)	107 (47.1)
Missing	35 (15.5)	28 (12.3)
Height *z* score	0.6 ± 1.0	0.7 ± 1.0
Weight *z* score	1.0 ± 1.2	1.0 ± 1.3
Weight class		
Overweight or obese (BMI >85th percentile)	106 (46.7)	107 (47.4)
Obese (BMI >95th percentile)	76 (33.5)	74 (32.7)
Site		
Philadelphia	72 (31.7)	75 (33.2)
Cincinnati	40 (17.6)	39 (17.3)
Cleveland	60 (26.4)	64 (28.3)
St Louis	30 (13.2)	30 (13.3)
New York	9 (4.0)	7 (3.1)
Boston	16 (7.0)	11 (4.9)
AHI	6.9 ± 0.4	6.7 ± 0.4
ODI	7.3 ± 0.5	7.0 ± 0.5

No differences between arms were detected (all $P > .05$). Data are presented as mean ± SD or *n* (%). GED, General Educational Development.

TABLE 2 QoL and Symptom Measures According to Treatment Arm at Baseline

Outcome	eAT Baseline	WWSC Baseline	P^a	P^b
PedsQL (parent) total	77.9 ± 15.4	76.7 ± 15.5	.33	.30
PedsQL (parent) emotional function	78.2 ± 18.6	73.3 ± 19.6	<.01	<.01
PedsQL (parent) physical function	80.3 ± 20.3	83.1 ± 18.3	.12	.19
PedsQL (parent) school function	74.4 ± 19.6	73.2 ± 20.1	.44	.49
PedsQL (parent) social function	84.2 ± 19.0	81.9 ± 19.3	.17	.17
PedsQL (child) total	68.3 ± 16.1	67.6 ± 14.8	.59	.49
PedsQL (child) emotional function	66.0 ± 23.2	64.5 ± 23.5	.46	.36
PedsQL (child) physical function	73.3 ± 18.2	73.5 ± 17.0	.91	.90
PedsQL (child) school function	63.1 ± 21.7	65.4 ± 19.4	.23	.26
PedsQL (child) social function	68.3 ± 24.8	64.0 ± 24.2	.05	.06
OSA-18 total	53.1 ± 18.3	54.1 ± 18.8	.55	.36
OSA-18 sleep disturbance	3.8 ± 1.4	3.8 ± 1.5	.76	.96
OSA-18 emotional distress	2.4 ± 1.5	2.6 ± 1.8	.20	.18
OSA-18 physical suffering	2.7 ± 1.4	2.7 ± 1.3	.61	.91
OSA-18 daytime problems	2.8 ± 1.4	2.9 ± 1.5	.42	.37
OSA-18 caregiver concerns	2.8 ± 1.5	3.0 ± 1.5	.22	.18
PSQ-SRBD total	0.5 ± 0.2	0.5 ± 0.2	.47	.49
PSQL snoring subscale	0.8 ± 0.3	0.8 ± 0.3	.85	.66
PSQL sleepiness subscale	0.4 ± 0.3	0.5 ± 0.3	.49	.52
PSQL behavior subscale	0.4 ± 0.3	0.5 ± 0.3	.34	.43
SLSC total (mESS)	7.1 ± 4.7	7.5 ± 5.2	.23	.25

Data are presented as mean ± SD.

[a] Adjusting for stratified variables only: site, race (African American versus non–African American), age (5–7 vs 8–10 years old), and overweight (≥85th vs <85th BMI percentile).

[b] Adjusting for site, race (African American versus non–African American), age (continuous), obese, gender, maternal education (less than high school, high school or higher, or missing/not sure), income (>$30 000, ≤$30 000, or missing), and baseline log AHI.

the eAT group compared with the WWSC group (5.9 ± 13.6 points vs 0.95 ± 13.3 points [$P < .01$], yielding an effect size of 0.37) (Table 3). Significance did not alter with adjustment for site, continuous age, race, socioeconomic status, or obesity status. This difference was driven by highly significant differences for the school (academic performance) and physical function domains. The change scores for the emotional function domain also differed between arms after adjusting for baseline differences ($P < .01$). Changes in the social function (peer interaction) domain were not significantly different between the arms. No significant differences in change scores between treatment groups in the PedsQL total score or the 4 domains were noted in the surveys answered directly by the children.

Disease-Specific Health-Related QoL (OSA-18)

Total OSA-18 scores in the eAT group improved more than in the WWSC group by –21.4 ± 16.5 vs –4.5 ± 19.3, producing a large effect size of –0.93 ($P < .01$) (Table 3). Significant differences in the change scores between the 2 arms were seen in all of the individual domains of the OSA-18, including sleep disturbance, daytime problems, physical suffering, caregiver concerns, and emotional distress (all $P \leq .01$).

TABLE 3 Change Scores in QoL and Symptom Measures by Treatment Arm

Outcome	eAT		WWSC		Effect Size[a]	P^b	P^c
	Baseline	Change	Baseline	Change			
PedsQL (parent) total	77.9 ± 15.4	5.9 ± 13.6	76.7 ± 15.5	0.9 ± 13.3	0.37	<.01	<.01
PedsQL (parent) emotional function	78.2 ± 18.6	4.9 ± 16.7	73.3 ± 19.6	2.1 ± 18.1	0.16	.12	<.01
PedsQL (parent) physical function	80.3 ± 20.3	7.4 ± 19.9	83.1 ± 18.3	−0.7 ± 18.2	0.42	<.01	<.01
PedsQL (parent) school function	74.4 ± 19.6	7.4 ± 18.1	73.2 ± 20.1	0.2 ± 19.7	0.38	<.01	<.01
PedsQL (parent) social function	84.2 ± 19.0	3.2 ± 19.6	81.9 ± 19.3	2.9 ± 17.2	0.02	>.99	.56
PedsQL (child) total	68.3 ± 16.1	3.4 ± 17.3	67.6 ± 14.8	3.3 ± 16.9	0.01	.92	.43
PedsQL (child) emotional function	66.0 ± 23.2	3.9 ± 28.9	64.5 ± 23.5	2.2 ± 29.5	0.06	.55	.07
PedsQL (child) physical function	73.3 ± 18.2	3.0 ± 20.3	73.5 ± 17.0	2.0 ± 22.3	0.05	.63	.38
PedsQL (child) school function	63.1 ± 21.7	4.3 ± 23.9	65.4 ± 19.4	3.5 ± 22.5	0.03	.70	.89
PedsQL (child) social function	68.3 ± 24.8	2.8 ± 26.1	64.0 ± 24.2	7.0 ± 26.2	−0.16	.12	.63
OSA-18 total	53.1 ± 18.3	−21 ± 16.5	54.1 ± 18.8	−4.5 ± 19.3	−0.93	<.01	<.01
OSA-18 sleep disturbance	3.8 ± 1.4	−2.2 ± 1.3	3.8 ± 1.5	−0.5 ± 1.6	−1.14	<.01	<.01
OSA-18 emotional distress	2.4 ± 1.5	2.1 ± 1.5	2.6 ± 1.8	2.6 ± 1.6	−0.30	<.01	.01
OSA-18 physical suffering	2.7 ± 1.4	−0.9 ± 1.3	2.7 ± 1.3	−0.1± 1.5	−0.60	<.01	<.01
OSA-18 daytime problems	2.8 ± 1.4	−1.0 ± 1.3	2.9 ± 1.5	−0.1 ± 1.5	−0.68	<.01	<.01
OSA-18 caregiver concerns	2.8 ± 1.5	−1.2 ± 1.4	3.0 ± 1.5	−0.4 ± 1.6	−0.51	<.01	<.01
PSQ-SRBD total	0.5 ± 0.2	−0.3 ± 0.2	0.5 ± 0.2	−0.0 ± 0.2	−1.35	<.01	<.01
PSQL snoring subscale	0.8 ± 0.3	−0.7 ± 0.3	0.8 ± 0.3	−0.1 ± 0.4	−1.55	<.01	<.01
PSQL sleepiness subscale	0.4 ± 0.3	−0.3 ± 0.4	0.5 ± 0.3	−0.0 ± 0.4	−0.65	<.01	<.01
PSQL behavior subscale	0.4 ± 0.3	−0.1 ± 0.3	0.5 ± 0.3	−0.0 ± 0.3	−0.34	<.01	<.01
SLSC total (mESS)	7.1 ± 4.7	−2.0 ± 4.2	7.5 ± 5.2	−0.3 ± 4.1	−0.42	<.01	<.01

[a] Cohen's d.

[b] Adjusting stratified variables only: site, race (African American versus non–African American), age (5–7 vs 8–10 years old), and overweight (≥85th vs <85th BMI percentile).

[c] Adjusting for site, race (African American versus non–African American), age (continuous), obese, gender, maternal education (less than high school, high school or higher, or missing/not sure), income (>$30 000, ≤$30 000, or missing), baseline AHI quartile, and baseline outcome variable.

Symptom Questionnaires (PSQ SRBD and mESS Scores)

For the Sleep-Related Breathing Scale of the Pediatric Sleep Questionnaire (PSQ-SRBD), a –0.28 ± 0.2 point change in the eAT group and –0.03 ± 0.2 change in the WWSC group produced a large effect size of –1.35 ($P < .01$) for the differences between arms (Table 3). Moreover, significant differences in the change scores between treatment arms were seen for the behavior, sleepiness, and snoring subscales (all $P < .01$). Improved sleepiness was corroborated by significant improvement in the mESS score in the eAT group of –2.01 ± 4.7 compared with 0.28 ± 4.1 in the WWSC arm, with a moderate effect size of –0.42 ($P < .01$).

Change score differences between the treatment arms for the QoL and symptom survey total scores are summarized in Fig 1.

Assessment of Effect Modification by Race and Baseline Weight and OSAS Severity

Weight did not influence the associations between treatment arm and QoL or symptoms (Table 4, all $P > .05$). Interaction terms for race were not significant for models for the majority of QoL and symptom outcomes. In contrast, effect modification by race was observed for the association between intervention group and both the PSQ-SRBD total score and behavior subscale, even after adjustment for measures of socioeconomic status (Table 5). Specifically, smaller relative improvements associated with AT were reported by caregivers of African-American children compared with non–African-American children for those 2 symptom measures ($P = .01$ and $<.01$, respectively, for the relevant interaction terms). These differences persisted in analyses restricted to the 76 African-American children and 81 non–African-American children in the eAT arm whose OSAS resolved by PSG (P values for the fully adjusted models all $<.01$, data not shown).

Baseline OSAS severity (AHI or ODI quartiles) also did not influence the association between treatment arm and QoL or symptoms (all $P > .01$, data not shown).

Association of QoL and OSAS Symptoms With PSG Measures

In general, improvements in OSAS severity measured by using PSG explained only a small portion of the variance in the QoL and symptom change scores. Change in AHI correlated, albeit weakly, with change in mESS (partial $r^2 = 0.03$, $P < .01$), OSA-18 (partial $r^2 = 0.07$, $P < .01$), PSQ SRBD scale (partial $r^2 = 0.14$, $P < .01$), PSQ snoring subscale (partial $r^2 = 0.17$, $P < .01$), and PSQ sleepiness subscale (partial $r^2 = 0.03$, $P < .01$) (Table 6). Small but significant associations were also seen between change in ODI and OSA-18 total score (partial $r^2 = 0.05$, $P < .01$), PSQ SRBD scale (partial $r^2 = 0.09$, $P < .01$), PSQ snoring subscale (partial $r^2 = 0.09$, $P < .01$), and PSQ sleepiness subscale (partial $r^2 = 0.02$, $P < .01$) (Table 7). In contrast, changes in AHI and ODI were not significantly associated with changes in generic health-related QoL.

DISCUSSION

This large, randomized controlled trial of children with OSAS found that key symptoms and QoL improved

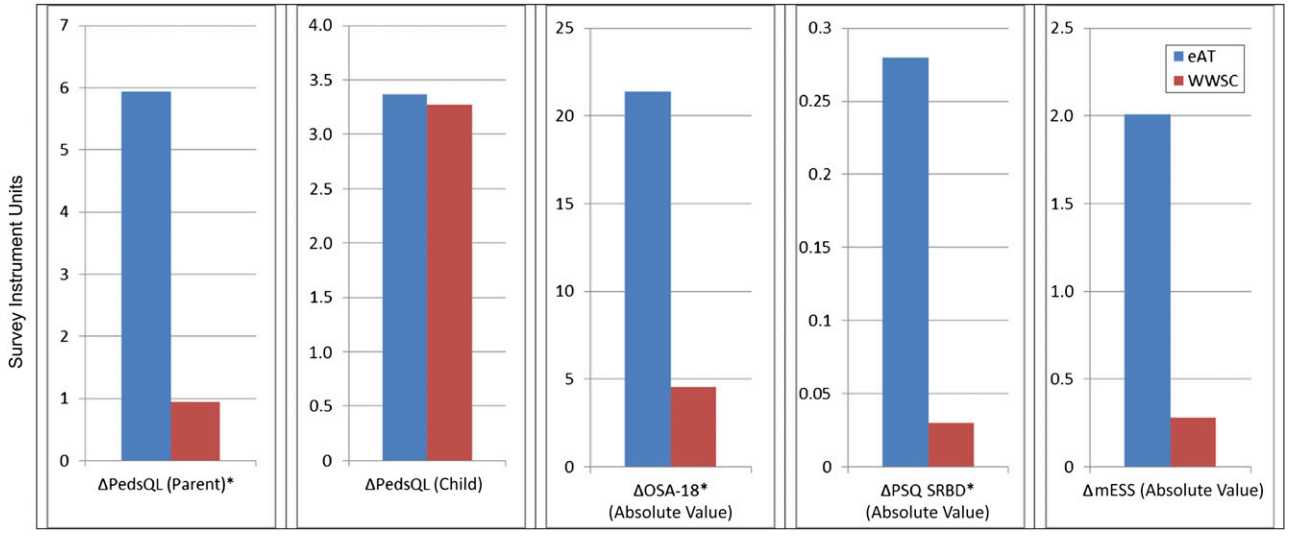

FIGURE 1

Summary of differences in QoL and OSAS symptom score changes in the eAT and WWSC arms. Absolute values were used when change scores were negative to facilitate comparisons of effect magnitude. *$P < .01$ for difference between arms, adjusted for site, race, age, obese (<95 or >95 BMI percentile), gender, maternal education (less than high school, high school or higher, or missing), income (>$30 000, ≤$30 000, or missing), log baseline AHI, and baseline outcome variable.

TABLE 4 Effect Modification on Change: Weight Category (Normal Versus Overweight Versus Obese)

Outcome	eAT			WWSC			P^a	P^b
	Normal	Overweight	Obese	Normal	Overweight	Obese		
Peds QL (parent) total	5.54 ± 1.33	1.91 ± 1.61	4.09 ± 2.31	−0.00 ± 1.24	−2.58 ± 1.56	−0.63 ± 2.33	.99	.91
Peds QL (child) total	5.11 ± 1.73	0.86 ± 2.06	5.22 ± 2.94	4.64 ± 1.65	−0.14 ± 2.06	1.27 ± 3.03	.89	.74
OSA-18 total	−21.23 ± 1.77	−18.57 ± 2.14	−18.70 ± 3.19	−4.19 ± 1.68	−2.33 ± 2.08	−1.14 ± 3.11	.79	.96
PSQ-SRBD total	−0.28 ± 0.02	−0.24 ± 0.02	−0.24 ± 0.03	−0.03 ± 0.02	−0.00 ± 0.02	−0.01 ± 0.03	.92	.76
PSQL snoring subscale	−0.65 ± 0.03	−0.59 ± 0.04	−0.59 ± 0.06	−0.11 ± 0.03	−0.05 ± 0.04	−0.08 ± 0.06	.89	.92
PSQL sleepiness subscale	−0.28 ± 0.03	−0.26 ± 0.04	−0.28 ± 0.06	−0.04 ± 0.03	−0.02 ± 0.04	0.08 ± 0.06	.32	.36
PSQL behavior subscale	−0.12 ± 0.03	−0.12 ± 0.04	−0.04 ± 0.05	0.02 ± 0.03	−0.03 ± 0.04	−0.06 ± 0.05	.10	.13
SLSC total (mESS)	−2.37 ± 0.41	−1.14 ± 0.50	−2.77 ± 0.72	−0.20 ± 0.39	−0.41 ± 0.48	0.13 ± 0.72	.12	.09

Data are presented as mean ± SD; marginal means adjusting for variables included in *P* value 1.

[a] *P* value for interaction term adjusting stratified variables only: site, race (African American versus non–African American), and age (5–7 vs 8–10 years old).

[b] *P* value for interaction term adjusting for site, race (African American versus non–African American), age (continuous), gender, maternal education (less than high school, high school or higher, or missing/not sure), income (>$30 000, ≤$30 000, and missing), baseline log AHI, and baseline outcome variable.

substantially more after eAT than WWSC. Benefits from eAT were evident in generic and disease-specific health-related QoL (as measured by using the PedsQL and OSA-18) and in OSAS symptoms (as reflected by using the PSQ SRBD scale and the mESS). Moderate to large improvements were observed for most QoL and symptom measurements, including the parent-completed PedsQL (total score, school, emotional, and physical function domains), OSA-18 (total and all 5 domains), mESS, and the PSQ SRBD (total score and snoring, sleepiness, and inattentive/behavioral subscales). Improvement in OSAS severity measured by using PSG variables explained only a small proportion of the improvements seen in OSAS symptoms and QoL. These observations have important clinical implications for the many children with OSAS who are evaluated for AT. The findings are of particular relevance, given the growing interest from patients, payers, and providers that QoL and symptom outcomes be highlighted in the management of chronic health conditions.

Clinically, many factors are considered when making a decision to perform surgery or to judge the success of surgical interventions. Previous studies measuring success rates for AT in children with OSAS have often focused somewhat narrowly on normalization of PSG parameters, with reports of surgical success rates ranging from 27% to 83%; lower cure rates are typically reported in obese children.[19,28–31] This emphasis on PSG measures of disease resolution may be partially due to assumptions that PSG severity parallels severity of the symptoms seen with OSAS. This concept is not well supported by the current literature for either neurobehavioral morbidity or QoL.[19,26] Previous studies of children with OSAS have shown no association between baseline OSA-18 scores and severity of OSAS on PSG.[32] Moreover, studies have failed to demonstrate clear correlation between extent of PSG improvements after AT and improvement in QoL.[33,34] In CHAT, we observed correlations between changes in AHI or ODI and changes in QoL and symptom severity measures. However, PSG improvements explained only a small portion of the variance for the change scores (partial r^2 ranging from <0.01 to 0.17). Thus, both previous literature and current data indicate that using PSG results as the sole metric for effectiveness of AT in pediatric OSAS may neglect other benefits that are important to children and their families.

TABLE 5 Effect Modification on Change: Race (African American Versus Non–African American)

Outcome	eAT		WWSC		P^a	P^b
	African American	Non–African American	African American	Non–African American		
Peds QL (parent) total	3.18 ± 2.07	7.44 ± 1.82	−0.12 ± 2.47	2.12 ± 2.22	.57	.77
Peds QL (child) total	4.55 ± 2.50	0.85 ± 2.17	3.09 ± 3.03	2.44 ± 2.65	.48	.26
OSA-18 total	−17.85 ± 2.84	−22.51 ± 2.51	−10.71 ± 3.36	−5.07 ± 3.03	.04	.09
PSQ-SRBD total	−0.23 ± 0.03	−0.32 ± 0.02	−0.10 ± 0.03	−0.07 ± 0.03	.01	.01
PSQL Snoring sub-scale	−0.67 ± 0.05	−0.68 ± 0.05	−0.23 ± 0.06	−0.25 ± 0.06	.91	.79
PSQL Sleepiness sub-scale	−0.13 ± 0.06	−0.29 ± 0.05	−0.07 ± 0.07	−0.02 ± 0.06	.03	.26
PSQL Behavior sub-scale	−0.01 ± 0.04	−0.18 ± 0.04	−0.06 ± 0.05	−0.03 ± 0.05	<.01	<.01
SLSC total (mESS)	−1.67 ± 0.60	−2.57 ± 0.53	−0.90 ± 0.72	−0.91 ± 0.65	.40	.32

Data are presented as mean ± SD; marginal means adjusting for variables included in *P* value 1.

[a] *P* value for the effect modification adjusting for stratified variables only: site, age (5–7 vs 8–10 years old), and overweight (≥85th vs <85th BMI percentile).

[b] *P* value for the effect modification adjusting for site, age (continuous), obese (<95 vs ≥95 BMI percentile), gender, maternal education (less than high school, high school or higher, or missing/not sure), income (>$30 000, ≤$30 000, or missing), baseline log AHI, and baseline outcome variable.

TABLE 6 Association Between QoL and Symptom Change Scores and PSG Change Scores (Log AHI)

Outcome	P^a			P^b		
	Log AHI Change β(SE)	Partial R^2	Log AHI Change *P*	Log AHI Change β(SE)	Partial R^2	Log AHI Change *P*
Peds QL (parent) total	−0.66 (0.42)	<0.01	0.12	−0.75 (0.38)	<0.01	0.05
Peds QL (child) total	0.60 (0.54)	<0.01	0.27	−0.07 (0.48)	<0.01	0.88
OSA-18 total	3.32 (0.60)	0.07	<0.01	3.49 (0.55)	0.07	<0.01
PSQ-SRBD total	0.05 (0.01)	0.14	<0.01	0.05 (0.01)	0.13	<0.01
PSQL Snoring subscale	0.12 (0.01)	0.17	<0.01	0.12 (0.01)	0.17	<0.01
PSQL Sleepiness subscale	0.04 (0.01)	0.03	<0.01	0.05 (0.01)	0.04	<0.01
PSQL Behavior subscale	0.01 (0.01)	<0.01	0.34	0.02 (0.01)	<0.01	0.04
SLSC total (mESS)	0.47 (0.13)	0.03	<0.01	0.51 (0.12)	0.04	<0.01

[a] *P* value for change in log AHI adjusting stratified variables only: site, race (African American versus non–African American), age (5–7 vs 8–10 years old), and overweight (≥85th vs < 85th BMI percentile).

[b] *P* value for change in log AHI adjusting for site, race (African American versus non–African American), age (continuous), obese (<95 vs ≥95 BMI percentile), gender, maternal education (less than high school, high school or higher, or missing/not sure), income (>$30 000, ≤$30 000, or missing), baseline log AHI, and baseline outcome variable.

The large proportion of our subjects who were overweight or obese allowed for subgroup analysis of QoL and symptoms. Increased likelihood of persistent OSAS after AT in obese children has been well documented, including a meta-analysis of 23 studies.[28,30] Obesity has also been associated with decreased QoL in children.[35] Improvement in QoL after AT for OSAS in the obese population has, however, been reported. A study of children with OSAS and BMI >95% showed improvement in OSA-18 general and domain scores despite lack of resolution of OSAS in the majority of subjects.[31] In the present analysis, although only obese children considered to be candidates for AT were included, obesity did not influence the relative changes in QoL or OSAS symptom severity with each intervention. These findings are supported by a study of QoL in children with severe obesity which showed that of 7 obesity-related comorbidities, only OSAS was associated with significant decreases in QoL.[35] The improved QoL and symptom outcomes seen in obese children support a clinically beneficial effect of surgery relative to watchful waiting for children in this group for whom treatment controversies exist.

OSAS has also been shown to be more common in African-American children.[36] More than one-half (55%) of the CHAT study participants were African American, which enabled evaluation for effect modification of race on the changes in QoL and symptoms between treatment arms. A significant effect modification of treatment by race was seen when comparing African-American versus non−African-American study participants for the PSQ SRBD total score and behavior subscale. Specifically, caregivers of American-African children in the eAT arm reported less improvement in children's behavior than did caregivers of non−African-American children. These differences persisted after adjustment for socioeconomic status and in an analysis restricted to children in whom OSAS resolved by PSG. In conjunction with the lack of improvement noted by the child-completed PedsQL survey, however, it must be considered that differing caregiver expectations about the beneficial effects of surgery or what constitutes problematic behavior may have influenced responses.

In the present study, none of the child-reported PedsQL measurements differed significantly between the 2 treatment groups. Previous studies have shown an ability of the child PedsQL to detect significant differences in the summary and

TABLE 7 Association Between QoL and Symptom Change Scores and PSG Change Scores (log ODI)

Outcome	P^a			P^b		
	Log ODI Change β(SE)	Partial R^2	Log ODI Change P	Log ODI Change β(SE)	Partial R^2	Log ODI Change P
Peds QL (parent) total	−0.66 (0.49)	<0.01	0.18	−0.66 (0.45)	<0.01	0.14
Peds QL (child) total	0.20 (0.62)	<0.01	0.75	−0.26 (0.56)	<0.01	0.65
OSA-18 total	3.14 (0.71)	0.05	<0.01	2.87 (0.66)	0.04	<0.01
PSQ-SRBD total	0.05 (0.01)	0.09	<0.01	0.05 (0.01)	0.08	<0.01
PSQL Snoring subscale	0.10 (0.02)	0.09	<0.01	0.10 (0.01)	0.09	<0.01
PSQL Sleepiness subscale	0.04 (0.01)	0.02	<0.01	0.04 (0.01)	0.02	<0.01
PSQL Behavior subscale	0.02 (0.01)	<0.01	0.12	0.02 (0.01)	0.01	0.02
SLSC total (mESS)	0.32 (0.15)	0.01	0.04	0.42 (0.14)	0.02	<0.01

[a] *P* value for change in log ODI adjusting stratified variables only: site, race (African American versus non–African American), age (5–7 vs 8–10 years old), and overweight (≥85th vs < 85th BMI percentile).

[b] *P* value for change in log ODI adjusting for site, race (African American versus non–African American), age (continuous), obese (<95 vs ≥95 BMI percentile), gender, maternal education (less than high school, high school or higher, missing/not sure), income (>$30 000, ≤$30 000, or missing), baseline log AHI, and baseline outcome variable.

domain scores between healthy children and children with a variety of chronic diseases.[37] However, OSAS was not specifically evaluated. Conceivably, children have difficulty recognizing their own sleepiness, irritability, or decreased concentration or do not consider those symptoms as problematic as the pain or physical limitations experienced with other chronic diseases. An alternate explanation is that the improvements reported by caregivers represent a desire to justify surgical interventions.

The major strengths of this study of health-related QoL and OSAS symptoms in pediatric patients undergoing AT for OSAS were a large, diverse sample recruited from multiple pediatric centers and use of a randomized design with a control group and highly rigorous and standardized measurement approaches. The study addressed patient-reported outcomes, which are increasingly recognized as important to patients and other stakeholders in health care. However, it should be noted that measures of QoL are inherently subjective, and in the setting of a surgical trial with an inability to blind participants, it is possible that the larger improvements in QoL and symptom measurements seen in the eAT arm could reflect a surgical placebo effect or variability of caregivers in assessing symptoms. However, the significant (albeit small) correlation with PSG improvement provides support for treatment-associated effects. An additional shortcoming was the limited follow-up period of 7 months.

CONCLUSIONS

This large, multisite, prospective, randomized controlled study of AT for PSG-documented pediatric OSAS found that key parent-reported measures of QoL and symptoms, or "patient- centered outcomes," improved substantially and significantly more in children treated with surgical AT than in children treated with WWSC. Improvements in QoL and OSAS symptoms were associated with improvement in PSG indicators of disease severity; however, only a small proportion of the observed QoL and symptomatic improvement was explained by PSG improvement. This study strongly supports the consideration of metrics beyond those reflected by PSG parameters when evaluating the value of AT in children with symptomatic OSAS.

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Address correspondence to Susan L. Garetz, MD, Department of Otolaryngology-Head and Neck Surgery, University of Michigan Health System, 1540 East Hospital Dr, Ann Arbor, MI 48109-4241. E-mail: garetz@umich.edu

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REFERENCES

1. Brunetti L, Rana S, Lospalluti ML, et al. Prevalence of obstructive sleep apnea syndrome in a cohort of 1,207 children of southern Italy. *Chest*. 2001;120(6):1930–1935
2. Gislason T, Benediktsdóttir B. Snoring, apneic episodes, and nocturnal hypoxemia among children 6 months to 6 years old. An epidemiologic study of lower limit of prevalence. *Chest*. 1995;107(4):963–966
3. Marcus CL, Greene MG, Carroll JL. Blood pressure in children with obstructive sleep apnea. *Am J Respir Crit Care Med*. 1998;157(4 pt 1):1098–1103
4. Amin R, Somers VK, McConnell K, et al. Activity-adjusted 24-hour ambulatory blood pressure and cardiac remodeling in children with sleep disordered breathing. *Hypertension*. 2008;51(1):84–91
5. Ali NJ, Pitson D, Stradling JR. Sleep disordered breathing: effects of adenotonsillectomy on behaviour and psychological functioning. *Eur J Pediatr*. 1996;155(1):56–62
6. Blunden S, Lushington K, Kennedy D, Martin J, Dawson D. Behavior and neurocognitive performance in children aged 5-10 years who snore compared to controls. *J Clin Exp Neuropsychol*. 2000;22(5):554–568
7. Gottlieb DJ, Vezina RM, Chase C, et al. Symptoms of sleep-disordered breathing in 5-year-old children are associated with sleepiness and problem behaviors. *Pediatrics*. 2003;112(4):870–877
8. Kaemingk KL, Pasvogel AE, Goodwin JL, et al. Learning in children and sleep disordered breathing: findings of the Tucson Children's Assessment of Sleep Apnea (tuCASA) prospective cohort study. *J Int Neuropsychol Soc*. 2003;9(7):1016–1026
9. O'Brien LM, Mervis CB, Holbrook CR, et al. Neurobehavioral implications of habitual snoring in children. *Pediatrics*. 2004;114(1):44–49
10. Baldassari CM, Mitchell RB, Schubert C, Rudnick EF. Pediatric obstructive sleep apnea and quality of life: a meta-analysis. *Otolaryngol Head Neck Surg*. 2008;138(3):265–273
11. Georgalas C, Tolley N, Kanagalingam J. Measuring quality of life in children with adenotonsillar disease with the Child Health Questionnaire: a first U.K. study. *Laryngoscope*. 2004;114(10):1849–1855
12. Stewart MG, Friedman EM, Sulek M, et al. Quality of life and health status in pediatric tonsil and adenoid disease. *Arch Otolaryngol Head Neck Surg*. 2000;126(1):45–48
13. Rosen CL, Palermo TM, Larkin EK, Redline S. Health-related quality of life and sleep-disordered breathing in children. *Sleep*. 2002;25(6):657–666
14. Goldstein NA, Fatima M, Campbell TF, Rosenfeld RM. Child behavior and quality of life before and after tonsillectomy and adenoidectomy. *Arch Otolaryngol Head Neck Surg*. 2002;128(7):770–775
15. De Serres LM, Derkay C, Sie K, et al. Impact of adenotonsillectomy on quality of life in children with obstructive sleep disorders. *Arch Otolaryngol Head Neck Surg*. 2002;128(5):489–496
16. Mitchell RB, Kelly J, Call E, Yao N. Long-term changes in quality of life after surgery for pediatric obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2004;130(4):409–412
17. Mitchell RB, Kelly J, Call E, Yao N. Quality of life after adenotonsillectomy for obstructive sleep apnea in children. *Arch Otolaryngol Head Neck Surg*. 2004;130(2):190–194
18. Flanary VA. Long-term effect of adenotonsillectomy on quality of life in pediatric patients. *Laryngoscope*. 2003;113(10):1639–1644
19. Marcus CL, Moore RH, Rosen CL, et al; Childhood Adenotonsillectomy Trial (CHAT). A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med*. 2013;368(25):2366–2376
20. Redline S, Amin R, Beebe D, et al. The Childhood Adenotonsillectomy Trial (CHAT): rationale, design, and challenges of a randomized controlled trial evaluating a standard surgical procedure in a pediatric population. *Sleep*. 2011;34(11):1509–1517

21. Centers for Disease Control and Prevention. Clinical growth charts. Available at: www.cdc.gov/growthcharts/clinical_charts.htm. Accessed November 20, 2014
22. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care*. 2001; 39(8):800–812
23. Franco RA Jr, Rosenfeld RM, Rao M. First place—resident clinical science award 1999. Quality of life for children with obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2000;123(1 pt 1):9–16
24. Bannink N, Maliepaard M, Raat H, Joosten KF, Mathijssen IM. Reliability and validity of the obstructive sleep apnea-18 survey in healthy children and children with syndromic craniosynostosis. *J Dev Behav Pediatr*. 2011;32(1):27–33
25. Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. *Sleep Med*. 2000;1(1):21–32
26. Chervin RD, Ruzicka DL, Giordani BJ, et al. Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. *Pediatrics*. 2006;117(4). Available at: www.pediatrics.org/cgi/content/full/117/4/e769
27. Melendres MC, Lutz JM, Rubin ED, Marcus CL. Daytime sleepiness and hyperactivity in children with suspected sleep-disordered breathing. *Pediatrics*. 2004;114(3):768–775
28. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am J Respir Crit Care Med*. 2010;182(5):676–683
29. Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. *Otolaryngol Head Neck Surg*. 2006; 134(6):979–984
30. Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2009; 140(6):800–808
31. Mitchell RB, Kelly J. Adenotonsillectomy for obstructive sleep apnea in obese children. *Otolaryngol Head Neck Surg*. 2004;131(1):104–108
32. Tran KD, Nguyen CD, Weedon J, Goldstein NA. Child behavior and quality of life in pediatric obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2005; 131(1):52–57
33. Stewart MG, Glaze DG, Friedman EM, Smith EO, Bautista M. Quality of life and sleep study findings after adenotonsillectomy in children with obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2005; 131(4):308–314
34. Mitchell RB, Kelly J. Outcome of adenotonsillectomy for severe obstructive sleep apnea in children. *Int J Pediatr Otorhinolaryngol*. 2004;68(11): 1375–1379
35. Schwimmer JB, Burwinkle TM, Varni JW. Health-related quality of life of severely obese children and adolescents. *JAMA*. 2003;289(14):1813–1819
36. Rosen CL, Larkin EK, Kirchner HL, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. *J Pediatr*. 2003;142(4): 383–389
37. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. *Health Qual Life Outcomes*. 2007;5:43

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Polysomnographic Outcomes Following Lingual Tonsillectomy for Persistent Obstructive Sleep Apnea in Down Syndrome

J. Drew Prosser, MD; Sally R. Shott, MD; Oscar Rodriguez, MD; Narong Simakajornboon, MD; Jareen Meinzen-Derr, PhD; Stacey L. Ishman, MD, MPH

Objectives/Hypothesis: Lingual tonsil hypertrophy is a common cause of persistent airway obstruction in patients with Down syndrome (DS) following adenotonsillectomy (T&A); however, little is known about the effect of lingual tonsillectomy (LT) on polysomnographic outcomes in these patients. Our objective was to describe changes in sleep-related respiratory outcomes following LT in children with DS and persistent obstructive sleep apnea (OSA) following T&A.

Study Design: Retrospective case series.

Methods: We included all children with DS who underwent polysomnography before and after LT at a tertiary care center from 2003 to 2013. Nonparametric analysis of variables was performed.

Results: Forty patients with DS underwent LT; 21 met inclusion criteria. The mean age at surgery was 9.3 $\pm$ 4.3 years and 47.6% were female. The median apnea-hypopnea index (AHI) was 9.1 events/hour (range, 3.8 to 43.8 events/hour) before surgery and 3.7 events/hour (range, 0.5 to 24.4 events/hour) after surgery. The median improvement in overall AHI and the obstructive AHI (oAHI) were 5.1 events/hour (range, -2.9 to 41) and 5.3 events/hour (range, -2.9 to 41), respectively ($P < .0001$). The mean oxygen saturation nadir improved from 84% to 89% ($P = .004$). The mean time with $CO_2 > 50$ mm Hg, central index, and percentage of rapid eye movement sleep were not significantly different. After surgery, the oAHI was <5 events/hour in 61.9% and ≤ 1 in 19% of patients.

Conclusions: In children with DS, persistent OSA after T&A and lingual tonsil hypertrophy, LT significantly improved AHI, oAHI, and O_2 saturation nadir. We recommend that children with DS should be evaluated for lingual tonsil hypertrophy if found to have persistent OSA following T&A.

Key Words: Obstructive sleep apnea, Down syndrome, lingual tonsil hypertrophy, lingual tonsillectomy.

Level of Evidence: 4

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INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder associated with significant morbidity in children, including impaired memory, behavioral disturbances, attention deficit and hyperactivity disorder, and cardiovascular disease.[1,2] Althoughe the prevalence of OSA in the general pediatric population is low (approximately 1%–2%), the prevalence is much higher in children with Down syndrome (DS), where an estimated 40% to 80% are affected.[3,4] Adenotonsillectomy (T&A) is the first-line treatment in children with OSA; however, persistent OSA is common after surgery in children with DS. Studies have shown that in children with DS, T&A results in resolution of OSA, with an obstructive AHI ≤ 1 event/hour, in only 16% to 33% of those treated.[5,6]

Several factors have been implicated in the pathogenesis of persistent OSA in patients with DS. These include muscular hypotonia as well as anatomic features such as macroglossia, relative glossoptosis, midface hypoplasia, hypopharyngeal collapse, and lingual tonsil hypertrophy.[7] Anatomic studies have shown lingual tonsil hypertrophy to be significantly more common in children with DS than in controls, with almost 35% of children with persistent OSA and DS reported to have lingual tonsil hypertrophy, compared to 3% of the general pediatric population.[8,9]

Lingual tonsillectomy (LT) has been shown to improve OSA in patients with lingual tonsil hypertrophy and persistent OSA after T&A.[10] Despite evidence that lingual tonsil hypertrophy plays a significant role in the persistence or recurrent of pediatric OSA, and the recognition that this finding is more prevalent in patients with DS than in children without comorbidities, no

Additional Supporting Information may be found in the online version of this article.

From the Department of Otolaryngology–Head and Neck Surgery (J.D.P.), Georgia Regents University, Augusta, Georgia; Division of Pediatric Otolaryngology–Head and Neck Surgery (S.R.S., S.L.I.), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Department of Otolaryngology–Head and Neck Surgery (S.R.S., S.L.I.), University of Cincinnati College of Medicine, Cincinnati, Ohio; Department of Pediatric Pulmonary and Sleep Medicine (O.R.), University of Mississippi Medical Center, Jackson, Mississippi; Division of Pulmonary and Sleep Medicine (N.S., S.L.I.), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Division of Biostatistics and Epidemiology (J.M.-D.), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, U.S.A.

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Send correspondence to Stacey L. Ishman, MD, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 2018, Cincinnati, Ohio 45229. E-mail: stacey.ishman@cchmc.org

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studies have evaluated the effect of LT on persistent OSA in patients with DS. In light of these findings, it was our goal to evaluate the polysomnographic success of LT to resolve persistent pediatric OSA in our patients with DS.

MATERIALS AND METHODS

Following institutional review board approval at the Cincinnati Children's Hospital Medical Center, we performed a retrospective chart review of patients with DS who were age 18 years and younger who underwent LT using radiofrequency ablation[11] from 2003 to 2013. All patients had previously undergone a T&A and were diagnosed with lingual tonsil hypertrophy using dynamic upper airway cine magnetic resonance imaging (MRI). Patients who completed polysomnography (PSG) before and after LT were included. Patients who did not have both pre- and postoperative PSGs or those whose preoperative obstructive apnea-hypopnea index (oAHI) was <1 event/hour, were excluded.

Charts were reviewed for demographic data and PSG outcomes including the apnea-hypopnea index (AHI), oAHI, O_2 nadir, percent of total sleep time that was rapid eye movement (REM) sleep, percent of sleep study time with CO_2 >50 mm Hg, obstructive apnea index, hypopnea index, maximum end tidal CO_2, and central apnea index.

PSG Recording

PSG was performed with Grass System (Grass Telefactor, West Warwick, RI) for up to 12 hours in a quiet dark room with an ambient temperature of 24°C, in the company of their parents. The standard pediatric montage was used. The following parameters were recorded simultaneously: body position, bilateral electro-occulogram, six-channel electroencephalogram (F3M2, F4M1, C3M2, C4M1, O1M2, O2M1), chin electromyogram, anterior tibialis electromyogram, tracheal microphone, electrocardiogram, pulse oximetry (Masimo, Irvine CA), thoracic and abdominal inductance plethysmography, nasal pressure transducer (Pro-Tech, Mukilteo, WA), and end-tidal CO_2 (BCI, Capnochecks; Smiths Medical, St. Paul, MN). Studies were interpreted by board-certified pediatric sleep medicine physicians at Cincinnati Children's Hospital Medical Center.

PSG Interpretation

All polysomnographs were scored according to the American Academy of Sleep Medicine (AASM) guidelines.[12] An apnea was defined as a reduction of airflow of >90% for at least two breathing cycles. Apneas were identified as obstructive when associated with continued or increased respiratory effort. A mixed apnea was identified when absence of airflow was associated with periods with and without respiratory effort. A hypopnea was defined as a decrease in airflow of ≥50% for at least two breathing cycles followed by a ≥3% decrease in oxygen saturation or an electrocortical arousal from sleep. The obstructive apnea index was calculated as the number of obstructive and mixed apneas divided by the total sleep time. The hypopnea index was calculated as the number of obstructive hypopneas divided by the total sleep time. The AHI was calculated as the number of apneas and hypopneas, divided by the total sleep time. The oAHI was calculated as the sum of the obstructive apneas, mixed apneas, and hypopneas, divided by the total sleep time. Severity of OSA was defined by oAHI. Mild OSA was defined as 1 to <5 events per hour, moderate OSA was defined as 5 to <10 events per hour, and severe OSA was defined as ≥10 events per hour. The saturation nadir was defined as the lowest oxygen saturation reading during a respiratory event.

TABLE I.
Study Population Demographics for Children With Down Syndrome Who Underwent Lingual Tonsillectomy for Obstructive Sleep Apnea After Adenotonsillectomy.

Characteristic	Demographics, n = 21
Age at preoperative PSG, yr, mean (SD), median [range]	8.9 (4.4), 7.8 [3.6–16.9]
Age at surgery, yr, mean (SD), median [range]	9.3 (4.3), 8.1 [4.4–17.2]
Age at postoperative PSG, yr, mean (SD), median [range]	9.7 (4.3), 8.6 [4.6–17.4]
Age at surgery	
3–6 years, n (%)	7 (33.3%)
>6 years, n (%)	14 (66.7%)
Race, white, n (%)	19 (90.5%)
Sex, male, n (%)	11 (52.4%)
BMI percentile, n = 13, mean (SD), median [range]	82.8 (27.4), 92 [1–99]

Mean and median values are reported.
BMI = body mass index; PSG = polysomnography; SD = standard deviation.

Statistical Analysis

Data distributions were reported as means with standard deviations in parentheses and medians with minimum and maximum values in brackets. Due to the fact that the data did not follow a normal distribution, nonparametric statistical analyses were conducted to test postsurgery changes. Changes in measurements pre- and postsurgery were tested using the Wilcoxon signed rank test for continuous variables; changes in categorical variables were tested using the McNemar test.

RESULTS

Forty patients with DS underwent LT, and 21 met the inclusion criteria. The demographics for this study population are displayed in Table I. The mean age at surgery was 9.3 ± 4.3 years (47.6% were female and 90.5% were white). Individual patient PSG data can be found in the Supporting Information, Appendix 1A and 1B, in the online version of this article. The median AHI was 9.1 events/hour (range, 3.8 to 43.8 events/hour) before surgery and 3.7 (range, 0.5 to 24.4 events/hour) after surgery (Table II). The median improvement in overall AHI and the oAHI were 5.1 events/hour (range, −2.9 to 41 events/hour) and 5.3 events/hour (range, −2.9 to 41 events/hour), respectively (P <.0001). The mean oxygen saturation nadir improved from 84% to 89% (P =.004); however, there were no significant changes in the mean percent time with CO_2 >50 mm Hg, central index, or percentage of REM sleep. After surgery, the oAHI was <5 events/hour in 61.9% of patients and ≤1 event/hour in 19%. After LT, 28.5% of patients had moderate OSA, and 14% had severe OSA, as measured by the oAHI. Stratification of patients by age did not affect the PSG outcomes (Table III). Further

TABLE II.
Mean and Median Polysomnography Outcomes for Children With Down Syndrome Who Underwent Lingual Tonsillectomy for Obstructive Sleep Apnea After Adenotonsillectomy.

	Preoperative PSG	Postoperative PSG	Overall Change	*P* Value
AHI, events/hr, mean (SD), median [range]	14.1 (12.2), 9.1 [3.8 to 43.8]	5.9 (6.3), 3.7 [0.5 to 24.4]	5.1 [−2.9 to 41]	<.0001
Obstructive AHI, events/hr, mean (SD), median [range]	13.0 (11.8), 7.6 [2.9 to 43.8]	4.9 (5.7), 2.8 [0 to 22.2]	5.3 [−2.9 to 41]	<.0001
O_2 nadir, %, mean (SD), median [range]	0.84 (0.08), 0.86 [0.58 to 0.91]	0.89 (0.05), 0.91 [0.76 to 0.94]	−0.05 [−0.31 to 0.08]	.004
Percent REM, %, mean (SD), median [range]	19.6 (8.0), 19 [0 to 35]	18.8 (5.3), 19 [8 to 30]	0.02 [−0.15 to 0.18]	.67
% time CO_2 >50 mm Hg, mean (SD), median [range]	41.6 (37.2), 34.5 [0 to 99]	33.6 (42.4), 5 [0 to 100]	8 [−91 to 87.6]	.52
Apnea index, events/hr, mean (SD), median [range]	5.3 (5.9), 2.6 [0.12 to 17.1]	1.9 (2.1), 1.2 [0.16 to 6.6}	1.3 [−1.71 to 14.82]	.013
Hypopnea index, events/hour, mean (SD), median [range]	7.6 (7.5), 5.7 [1.03 to 32.1]	4.1 (4.6), 2.3 [0.58 to 15.5]	3.8 [−8.01 to 29.32]	.012
Maximum ET CO_2, mm Hg, events/hr, mean (SD), median [range]	53.8 (6.6), 53 [44 to 66]	52.3 (6.4), 52 [42.7 to 69]	1 [−12 to 16.3]	.89
Central index, events/hr, mean (SD), median [range]	1.14 (1.14), 0.8 [0 to 3.9]	0.95 (1.24), 0.3 [0 to 4.2]	0 [−2.3 to 3.9]	.57
Postoperative oAHI ≤1 event/hr, n (%)	0	4 (19.1%)		.07
Postoperative oAHI ≤5 events/hr, n (%)	4 (19.1%)	13 (61.9%)		.007

The number for each field is based upon all 21 patients' results unless otherwise noted.
Pre- and postoperative changes in continuous variables were tested with the Wilcoxon signed rank test, whereas changes in categorical variables were tested with the McNemar test.
AHI = apnea-hypopnea index; ET = end tidal; MA = mixed apnea; OA = obstructive apnea; oAHI = obstructive apnea-hypopnea index; PSG = polysomnography; REM = rapid eye movement; SD = standard deviation.

outcomes were stratified by preoperative OSA severity level, which showed a mean improvement in oAHI of 0.93, 4.3, and 17.6 for mild, moderate, and severe disease, respectively (Table IV).

DISCUSSION

In children with DS, lingual tonsil hypertrophy and persistent OSA following T&A, LT significantly improved AHI, oAHI, and the oxygen saturation nadir. After surgery, 19% had complete resolution of OSA, whereas an additional 42.9% had only residual mild disease. At the same time, the median oxygen saturation nadir improved significantly. In this small sample, we did not see any difference in PSG outcomes by age. Fourteen percent of the children had severe OSA after their LT, and all of these patients had moderate or severe disease before surgery. Two patients had worsening of the oAHI following the procedure (oAHI from 6.9 to 10.3 and 6.4 to 6.7), which were not clinically significant and could be a result of test-retest issues with the PSG.

A recent review of non–continuous positive airway pressure treatment options for children with persistent OSA following T&A, found that LT was the most commonly reported surgical intervention.[10] An additional study regarding children who underwent LT reported a mean improvement of the respiratory disturbance index from 14.7 to 8.1 events/hour in 26 patients.[13] This study population was more heterogeneous than our population, as 46% had no comorbidities, and the remaining patients had a variety of syndromes (including DS), although the percentage of patients with DS was not reported. Another study by Abdel-Aziz et al. reviewed 16 children who underwent LT and noted a mean improvement in AHI from 10.5 events/hour before surgery to 3.2 events/hour postoperatively; one patient in the study had DS.[14] Truong et al. reported on 27 children who underwent LT, and demonstrated that this procedure decreased the mean AHI from 18.3 to 9.7 events/hour ($P < .05$).[15] Their population was again heterogeneous, with 26% of patients having comorbidities that included DS, craniofacial syndromes, and other neurologic diseases.

It has been shown that there is a high likelihood that patients with DS have multiples sites of upper airway obstruction associated with their OSA.[9] In addition, airway obstruction in patients with DS is further complicated by the presence of muscular hypotonia with pharyngeal hypotonia, midface hypoplasia, glossoptosis, and relative macroglossia. In light of this, one might expect a significant failure rate and resolution rates to be lower in children with DS when compared to children without comorbidities. When comparing our results to previously published reports, we find similar rates of improvement for our cohort with DS as were seen in mixed patient populations (children with and without comorbidities). One reason for this better than expected resolution rate could be that the patients in our study had lingual tonsil hypertrophy diagnosed with the assistance of a dynamic cine MRI as opposed to drug-induced sleep endoscopy. Although many surgeons use flexible endoscopy to determine the presence or absence of lingual tonsil

TABLE III.
Changes in Polysomnographic Outcomes Before and After Surgery, for Children With Down Syndrome Who Underwent Lingual Tonsillectomy for Obstructive Sleep Apnea After Adenotonsillectomy, Stratified by Age.

	Changes in PSG Outcomes for 3 to 6 Year Olds, N = 7	Changes in PSG Outcomes for Children >6 Years Old, N = 14	*P* Value
AHI, events/hr, mean (SD), median [range]	4.5 [−0.4 to 8.8]	6.4 [−2.9 to 41.0]	.28
Obstructive AHI, events/hr, mean (SD), median [range]	4.3 [−1.4 to 9]	7.1 [−2.1 to 41.0]	.25
O_2 nadir, %, mean (SD), median [range]	−0.02 [−0.06 to 0.08], n = 5	−0.05 [−0.31 to 0.01], n = 11	.078
% REM, mean (SD), median [range]	−2.0 [−12 to 17]	3.0 [−15.0 to 18.0]	.41
% time CO_2 > 50 mm Hg, mean (SD), median [range]	−8.8 [−91 to 34], n = 5	26[−1 to 87.6], n = 6	.12
Apnea index, events/hr, mean (SD), median [range]	−0.14 [−0.22 to 1.57] n = 5	6.73 [−1.71 to 14.82], n = 9	.06
Hypopnea index, events/hr, mean (SD), median [range]	4.8 [−2.96 to 8.61], n = 5	2.78 [−8.01 to 29.32], n = 13	.92
Maximum ET CO_2, mm Hg, events/hr, mean (SD), median [range]	−5 [−11 to 4.0]	1.5 [−12 to 16.3]	.31
Central index, events/hr, mean (SD), median [range]	0.5 [−0.2 to 1.0]	−0.05 [−2.3 to 3.9]	.23

Median differences were tested using the Wilcoxon rank sum test.
AHI = apnea hypopnea index; ET = end tidal; PSG = polysomnography; REM = rapid eye movement; SD = standard deviation.

hypertrophy,[13,15] this method does not allow for quantification of the size, and especially the depth, of lingual tonsil tissue. The MRI is more sensitive than flexible endoscopy for defining the true depth and volume of the lingual tonsillar tissue present[8,9] and may allow for more complete lingual tonsil tissue removal. Although the use of radiofrequency for removal of the lingual tonsils did not allow us to quantify the volume of tissue removed, it is relatively easy to distinguish lymphoid tissue from tongue muscle, which makes complete removal possible.

Limitations of our study include the small sample size, although this is the largest series of LT in children with DS to date, and concerns regarding generalizability, given the fact that 90% of our cohort was white. This study is also limited by its retrospective nature, which likely results in some selection bias. In addition, limiting our evaluation to children who underwent both pre- and postoperative PSG may limit generalizability, as the decision to get these studies may be more common in children with persistent symptoms after both T&A and LT surgery. Furthermore, although we strongly suspect that body mass index (BMI) plays a role in persistent OSA following surgery, there were not enough patients in our study with complete pre- and post-BMI data to make statistical analysis meaningful. Despite these limitations, LT resulted in significant decreases in the oAHI for almost all of these children; however, persistent moderate or severe disease was found in 38%. Futures prospective studies should include standardized PSG outcomes, BMI, and larger sample sizes with sufficient numbers to stratify patients by OSA severity.

CONCLUSION

In children with DS with persistent OSA after T&A and lingual tonsil hypertrophy, LT significantly improved AHI, oAHI, and O_2 saturation nadir, and resolution of the oAHI to <5 events/hour was seen in 62% of children. We recommend that children with DS be evaluated for lingual tonsil hypertrophy if found to have persistent OSA following T&A.

TABLE IV.
Changes in Polysomnographic Outcomes Before and After Surgery, for Children With Down Syndrome Who Underwent Lingual Tonsillectomy for Obstructive Sleep Apnea After Adenotonsillectomy, Stratified by Preoperative Obstructive Sleep Apnea.

OSA Severity	% of Patients (n)	Postoperative AHI, Mean (SD)	Postoperative oAHI, Mean (SD)	oAHI Change, Mean (SD)
Mild OSA	19.0% (4)	3.2 (2.9)	2.5 (2.4)	0.93 (2.2)
Moderate OSA	47.6% (10)	4.0 (3.4)	2.9 (3.1)	4.3 (3.2)
Severe OSA	33.3% (7)	10 (8.9)	9.1 (7.6)	17.6 (12.9)

Mild OSA was defined as 1 to 5 events/hour, moderate OSA was defined as an oAHI of 5 to <10 events/hour, and severe OSA was defined as 10 or more events/hour.
AHI = apnea hypopnea index; oAHI = obstructive apnea hypopnea index; OSA = obstructive sleep apnea; SD = standard deviation.

BIBLIOGRAPHY

1. Blunden S, Lushington K, Kennedy D, et al. Behavior and neurocognitive performance in children aged 5–10 years who snore compared to controls. *J Clin Exp Neurophsychol* 2000;22:554–568.
2. Halbower AC, Deganokar M, Barker PB, et al. Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. *PLoS Med* 2006;3:e301.
3. Shott SR, Amin R, Chini B, et al. Obstructive sleep apnea: should all children with Down syndrome be tested? *Arch Otolarynol Head Neck Surg* 2006;132:432–436.
4. Dyken ME, Lin-Dyken DC, Poulton S, et al. Prospective polysomnographic analysis of obstructive sleep apnea in down syndrome. *Arch Pediatric Adolesc Med* 2003;157:655–660.
5. Thottam PJ, Choi S, Simons JP, et al. Effect of adenotonsillectomy on central and obstructive sleep apnea in children with Down syndrome. *Otolaryngol Head Neck Surg* 2015;153:644–648.
6. Merrell JA, Shott SR. OSAS in Down syndrome: T&A versus T&A plus lateral pharyngoplasty. *Int J Pediatr Otorhinolaryngol* 2007;71:1197–1203.
7. Sedaghat AR, Flax-Goldenberg RB, Gayler BW, et al. A case-control comparison of lingual tonsillar size in children with and without Down syndrome. *Laryngoscope* 2012;122:1165–1169.
8. Fricke BL, Donnelly LF, Shott SR, et al. Comparison of lingual tonsil size as depicted on MR imaging between children with obstructive sleep apnea despite previous tonsillectomy and adenoidectomy and normal controls. *Pediatr Radiol* 2006;36:518–523.
9. Donnelly LF, Shott SR, LaRose CR, et al. Causes of persistent obstructive sleep apnea despite previous T&A in children with Down syndrome as depicted on static and dynamic cine MRI. *Am J Roentgenol* 2004;183: 175–181.
10. Manickam PV, Shott SR, Boss EF, et al. Systematic review of site of obstruction identification and non-CPAP treatment options for children with persistent pediatric obstructive sleep apnea. *Laryngoscope* 2016; 126:491–500.
11. Shott SR. Lingual tonsillectomy. In: Potsic WP, Cotton RT, Handler SD, Zur KB, eds. Surgical Pediatric Otolaryngology. New York, NY: Thieme Medical Publishers; 2016:268–270.
12. Iber C, Ancoli-Israel S, Chesson A, Quan SF; American Academy of Sleep Medicine. The ASSM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine Medicine; 2007.
13. Koltai PJ, Lin AC. Persistent pediatric obstructive sleep apnea and lingual tonsillectomy. *Otolaryngol Head Neck Surg* 2009;141: 81–85.
14. Abdel-Aziz M, Ibrahim N, Ahmed A, et al. Lingual tonsils hypertrophy; a cause of obstructive sleep apnea in children after adenotonsillectomy: operative problems and management. *Int J Pediatr Otorhinolaryngol* 2011;75:1227–1231.
15. Truong MT, Woo VG, Koltai PJ. Sleep endoscopy as a diagnostic tool in pediatric obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol* 2012; 76:722–727.

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Pediatric sinogenic epidural and subdural empyema: The role of endoscopic sinus surgery

A. Garin [a], B. Thierry [a], N. Leboulanger [a], T. Blauwblomme [b], D. Grevent [c], S. Blanot [d], N. Garabedian [a], V. Couloigner [a,*]

[a] Pediatric ENT Department, Hôpital Necker—Enfants Malades, AP-HP, Université Paris Descartes, Paris, France
[b] Pediatric Neurosurgery Department, Hôpital Necker—Enfants Malades, AP-HP, Université Paris Descartes, Paris, France
[c] Pediatric Radiology Department, Hôpital Necker—Enfants Malades, AP-HP, Université Paris Descartes, Paris, France
[d] Department of Anesthesiology, Hôpital Necker—Enfants Malades, AP-HP, Université Paris Descartes, Paris, France

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ABSTRACT

Aim: To analyze the indications and outcomes of open neurosurgical approaches (ONA) and endoscopic transnasal approaches (ETA) in the surgical management of pediatric sinogenic subdural and epidural empyema.

Material and methods: Retrospective single-center study design within a tertiary care referral center setting. Children less than 18 years of age consecutively operated on between January 2012 and February 2014 for drainage of a sinogenic subdural empyema (SE) or epidural (EE) empyema were included. Main outcome measures: success of first surgical procedure, persistent symptoms and sequelae at the end of the follow-up period.

Results: Nine SE (53%) and 8 EE (47%) were observed. Neurological symptoms, especially seizures, were more frequent in the SE group. Perioperative pus samples were positive in 67% of the SE group and in 75% of the EE group. The most frequently isolated bacteria belonged to the *Streptococcus anginosus* group. CT or MR imaging showed that most empyema probably originated from the frontal sinus. However, two cases resulted from an ethmoiditis and one case from a Pott's puffy tumor, without any direct contact with the paranasal sinus. In cases of SE, the most effective surgical technique was ONA with craniotomy. Associated endoscopic sinus drainage was useful for the purpose of bacteriological diagnosis. In cases of EE, effectiveness was noted in both ONA and ETA techniques. In two cases of EE, the ETA procedure encompassed direct drainage of the empyema through the posterior wall of the frontal sinus (Draf III approach). The number of patients successfully treated after a single surgical procedure was higher in the EE group ($p = 0.05$). Regarding outcomes, no mortalities were observed. Persistent disorders at the end of the follow-up period, especially headaches, cognitive, concentration or schooling problems, tended to be more frequent in the SE group than in the EE group (67% vs 29%), and were more commonly observed in cases requiring several surgical procedures (75% vs 12.5%) ($p = 0.05$).

Discussion: Endoscopic sinus surgery plays a critical role in the surgical management of pediatric sinogenic SE and EE. In cases of small volume EE, the endoscopic approach associated with antibiotherapy may be sufficient to treat the infectious process.

1. Introduction

The most commonly applied definition of pediatric acute bacterial sinusitis (PABS) is an upper respiratory infection in which symptoms are not improving after 10–14 days and often worsening after 5–7 days [1]. In a large Northern American study using the "Nationwide Emergency Department Sample 2008 database" and including 101,660 children, complications were documented in 0.7% of children presenting to emergency departments with the diagnosis of PABS [2]. Of those children with complications, 15% had periorbital cellulitis, 76% had orbital complications and 9% had intracranial complications. Orbital complications were associated with a younger mean age (7.3 years versus 11.9 years for intracranial complications). Smaller retrospective studies detailed the distribution of subcategories of intracranial complications. In a cohort of 104

* Corresponding author. Tel.: +33 1 44 49 46 82; fax: +00 33 1 44 49 46 90.
E-mail address: vincent.couloigner@nck.aphp.fr (V. Couloigner).

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children with complicated ABS, 14 intracranial complications including 2 brain abscesses, 7 epidural and 6 subdural empyema were retrieved [3]. In another pediatric series of 11 suppurative intracranial complications of sinusitis, 3 intracranial abscesses (ICA), 3 SE, 2 EE, 2 SE associated with EE, and 1 SE associated with ICA were observed [4]. This data suggests that EE and SE represent the most frequent intracranial complications of pediatric ABS. However, only a few publications have specifically focused on their management, especially concerning the respective roles of ONA and ETA [3–9].

The primary objective of the present study was to compare the outcomes of ONA and ETA in a retrospective pediatric cohort of sinogenic empyema, in order to optimize the indications of surgical treatments of these complications. A secondary end point was to describe the clinical, bacteriological and imaging characteristics of pediatric cases of sinogenic SE and EE.

2. Material and methods

The manuscript was prepared in accordance with STROBE guidelines [10].

2.1. Study design

This single-center retrospective study included all consecutive pediatric cases of epidural or subdural empyema operated in the Pediatric Neurosurgical and ENT Departments of Necker Hospital between January 2012 and February 2014.

2.2. Inclusion criteria

The diagnosis of sinogenic subdural or epidural empyema was based on the association of the following findings: (i) clinical or biological signs of infection, (ii) the observation of an empyema mainly or solely located in the frontal lobe, and of an opacity of the ethmoidal or frontal sinus on CT and MR imaging, (iii) the absence of recent cranial trauma or surgery, and the absence of any other infection (tooth, middle ear.) which could have been responsible for the empyema. Neither the presence of clinical symptoms compatible with sinusitis (fever, headache, facial subcutaneous swelling) nor the contiguity between the sinus opacity and the empyema on imaging were judged necessary to make the diagnosis of sinogenic empyema. Indeed, concerning the latter point, the sinus opacity and the resulting empyema can sometimes be separated from each other due to one of the following mechanisms:

- Indirect spread of infection between the sinus and the epidural or subdural space through the mucosal veins of the sinus to the emissary veins that link the facial and dural venous systems [11,12] or, in cases of EE, through an osteomyelitis of the frontal bone (Pott's puffy tumor)
- Antibiotic treatment prior to brain imaging: often, at the time of diagnosis of empyema, the sinusitis has already been diagnosed and treated for several days with antibiotics. This treatment can modify the extension of the sinus infection and induce a separation between the sinus opacity and the empyema on imaging.

2.3. Exclusion criteria

The exclusion criteria were the following:

- Non-sinogenic empyema.
- Patients older than 18 years.
- Insufficient clinical, biological or imaging data.

2.4. Review of medical records

Clinical charts were retrieved using the institutional database CCAM (Classification Commune des Actes Médicaux). The medical records of children with SE or EE were reviewed for age, gender, underlying conditions before diagnosis, presenting symptoms, duration of symptoms before admission, CRP (C-reactive protein) levels, bacteriological data, CT and MR imaging findings, medical and surgical treatments and final clinical outcomes.

2.5. Data analysis

Quantitative variables were described using their mean or median value and standard deviation, and qualitative variables were described as numbers and percentages. Statistical comparisons were performed using Student's *t*-test or Mann–Whitney *U* test for quantitative variables and Chi-square or Fisher's exact test for qualitative variables. *P* values ≤ 0.05 were considered statistically significant.

3. Results

Out of 23 pediatric cases of SE or EE operated at our institution during the study period, 6 were discarded because of their non-sinogenic origin (5 otogenic and 1 post-traumatic empyema). Nine SE (53%) and 8 EE (47%) cases were finally included. Patients' demographics and symptoms are described in Tables 1–3. The median age was 11 years (8.8–13.5) in the SE group and 10 years (9.0–10.8) in the EE group (NS). The sex ratio was not different between both groups (Table 1).

3.1. Clinical features on admission and before surgery

Clinical features are presented in Tables 1–3. The major difference between both groups was the neurological clinical presentation. Indeed, the number of neurological symptoms per patient (mean ± SD) was 1.8 ± 1.2 in the SE group and 0.4 ± 0.5 in the EE group ($p = 0.01$). The most frequent neurological symptoms were seizures (6 children with SE and 2 with EE) and meningeal syndrome (4 patients with SE and none of those with EE). Among the two patients with EE and seizures, one patient had a frontal subdural aeroma (Table 2), possibly explaining the cortical irritation leading to the seizure. Pott's puffy tumors tended to be more frequent in the EE group (37.5% vs 11%) (NS) (Table 4).

3.2. CRP levels and bacteriological findings

CRP levels and bacteriological data are presented in Tables 2 and 3.

Table 1
Patient clinical characteristics.

	SE ($n=9$)	EE ($n=8$)
Age (years) (median ± SD)	11 ± 3	10 ± 4
Sex ratio (males/females)	4/5	5/3
Fever (n)	3	5
Palpebral edema (n)	1	2
Headaches (n)[a]	4	2
Neurological symptoms findings (n)		
-Aphasia	1	0
-Altered consciousness	1	0
-Meningeal syndrome	4	0
-Focal neurological deficit	2	0
-Seizure	6	2
-Intracranial hypertension	1	1

[a] Headaches were excluded from the list of neurological symptoms as it could have also resulted from sinusitis.

Table 2
Neurological symptoms, CRP levels, size of empyema, surgical treatment and outcomes in patients with SE.

Patient initials	Neurological symptoms[a]	Initial CRP level (mg/ml)	Extension of empyema before 1st surgery[b]	Bacteria	First procedure	Second procedure	Third procedure	Residual symptoms and treatments during the last visit (follow-up duration)
BD	FND DC S MS	72	Extended	Gram positive cocci	ONA (Burr hole drainage)	ONA (frontal and parietal craniotomy)		Speech and motor difficulties (27 months), AEDs
DC	S MS	6	Localized	NG	EEA	ONA (frontal and parietal craniotomy)		Intermittent headaches (22 months)
ID	S	NA	Extended	*Streptococcus constellatus* and *Prevotella species*	EEA	ONA (parietal craniotomy) and FSO		Concentration problems, EEG abnormalities, AEDs (23 months)
LM	MS S	124	Localized	*Streptococcus intermedius*	EEA FSDext	ONA (Burr hole drainage + puncture of frontal BA under US guidance)		Schooling difficulties, headaches (29 months)
PLam	S	NA	Localized	*Fusobacterium necrophorum*	EEA	ONA (parietal craniotomy)	ONA (frontal medial and parietal craniotomies) + FSO	Schooling difficulties, frontal and parietal bone defect, AEDs (20 months)
RM	FND A S	NA	Extended	*Streptococcus constellatus*	EEA and FSDext	ONA (Frontal and parietal craniotomy)		AEDs (24 months)
PLen	MS	86	Extended	NG	EEA			Headaches (27 months)
TL	S ICHS	292	Extended	*Streptococcus species*	ONA (frontal medial craniotomy)			No problem (18 months)
VJ	None	35	Extended	*Fusobacterium necrophorum*	EEA ONA, (frontal medial and parietal craniotomies), FSO			No problem (33 months)

Shaded portion: Cases requiring more than one procedure. Unshaded portion: Cases successfully treated with a single operation. AEDs: antiepileptic drugs BA: brain abscess DC: decreased consciousness EEA: endoscopic ethmoidectomy and antrostomy EEG: electroencephalogram FND: focal neurological deficit FSD: frontal sinus drainage, either through an external (FSDext) or through an endoscopic Draf type III approach (FSDendos) FSO: frontal sinus obliteration ICHS: Intracranial hypertension syndrome MS: Meningeal syndrome NA: not available NG: no bacterium isolated in bacteriological samples ONA: open neurosurgical approach S: seizure.

[a] Headaches were excluded from the list of neurological symptoms as it could have also resulted from sinusitis.

[b] Localized empyema corresponded to empyema located in the front of the polar or basal part of the frontal lobe, next to the infected frontal and anterior ethmoid sinuses. Extended empyema had spread way beyond the polar or basal region of the frontal lobe facing the infected sinus (see also Figs. 1 and 4).

The preoperative CRP levels (mg/l) (mean ± SD) were not different between the SE (102 ± 101) and EE groups (112 ± 119). Nor did the CRP levels differ between patients requiring only one (114 ± 127) or several drainage surgeries (97 ± 75).

Blood cultures were positive in only one patient with SE and in no patients with EE. Perioperative pus samples were positive in 67% ($n = 6$) of SE (3 sinus samples and 3 intracranial samples) and in 75% ($n = 6$) of EE (2 sinus samples and 4 intracranial samples). Lumbar punctures were performed in 4 patients with SE due to meningeal syndrome and did not retrieve any bacteria. In cases of SE, the isolated bacteria were the following: *Streptococcus constellatus* ($n = 2$), Non-specified *Streptococcus* ($n = 2$), *Streptococcus intermedius* ($n = 1$), *Fusobacterium necrophorum* ($n = 1$), *Fusobacterium nucleatum* ($n = 1$) and *Provatella species* ($n = 1$). Bacteria isolated in children with EE were: *S. intermedius* ($n = 4$), *Staphylococcus lugdunensis* ($n = 1$), *Staphylococcus aureus* ($n = 1$), *Staphylococcus capitis* ($n = 1$) and *Propionobacterium acnes* ($n = 1$).

3.3. Radiological findings

The imaging techniques performed before the first surgical procedure were the following: CT scans in 10 cases (59%) (6 SE and 4 EE), MRI in 4 cases (23.5%) (2 SE and 2 EE) and CT scan and MRI in 3 cases (17.5%) (1 SE and 2 EE). There was no clear explanation in the clinical charts concerning the choice of the imaging techniques.

A thickened inflammatory mucosa, possibly associated with the presence of pus, was observed in the maxillary and ethmoidal sinuses in 100% of cases, in the frontal sinus in 88% of cases ($n = 15$), and in the sphenoid sinus in 53% of cases ($n = 9$). Fifty nine percent of cases of maxillary and ethmoidal sinusitis, and 59% of cases of frontal sinusitis were bilateral. Ethmoidal inflammation mostly concerned the interior part of this paranasal sinus. Two cases clearly resulted from the ethmoidal sinus since these patients did not have any frontal sinus. In one case, the EE originated from a Pott's puffy tumor and not directly from a sinus cavity (Fig. 1, D1).

In three cases (2 SE and 1 EE), the empyema and the infected sinus were not contiguous (Fig. 2). An erosion of the posterior wall of the frontal sinus was observed in one case (EE) and an erosion of the ethmoidal roof in two cases (1 SE and 1 EE) (Fig. 3). The locations and extensions of the empyema on the initial imaging and at the time of their maximal expansion are shown in Figs. 1 and 4, respectively. The locations of empyema were as follows:

- For SE, the frontal polar region was involved in 89% of cases ($n = 8$), the frontal basal in one case, the parietal region in 78% of

Table 3
Neurological symptoms, CRP levels, size of empyema, surgical treatment and outcomes in patients with EE.

Patient initials	Neurological symptoms[a]	Initial CRP level (mg/ml)	Size of the empyema before 1st surgery[b]	Bacteria	First procedure	Second procedure	Third procedure	Residual symptoms and treatments during the last visit (follow-up)
CW	S	74	Localized	NG	Endoscopic antrostomy	EEA	ONA (technique not specified) FSO	Slow cognitive procETAing, abnormal EEG, AEDs (11 months)
KK	None	207	Extended	*Staphylococcus lugdunensis*, *Staphylococcus capitis*, and *Propionobacterium acnes*	ONA (frontal craniotomy) + FSO	ONA (frontal craniotomy)		No problem (10 months)
MD	None	339	Localized	*Staphylococcus aureus*	EEA FSDendos Endoscopic transnasal drainage of the empyema			AEDs maintained in spite of normalized EEG (11 months)
CM	S	71	Localized	*Streptococcus intermedius*	EEA FSDendos Endoscopic transnasal drainage of the empyema			AEDs (4 months)
CTK	None	NA	Localized	NG	EEA			No problem (4 months)
KMF	None	53	Extended	*Streptococcus intermedius*	ONA (frontal craniotomy) + FSO			No follow-up
NZM	None	32	Localized	*Streptococcus intermedius*	ONA (frontal craniotomy) + FSO			No problem (4 months)
TE	ICHS[c]	6	Localized	*Streptococcus intermedius*	EEA ONA (frontal craniectomy + BA needle aspiration) FSO[d]			Unsightly secondary displacement of the Palacos® cranioplasty (12 months)

Shaded portion: Cases requiring more than one procedure. Unshaded portion: Cases successfully treated with a single operation. AEDs: antiepileptic drugs BA: brain abscess DC: decreased consciousness EEA: endoscopic ethmoidectomy and antrostomy EEG: electroencephalogram FND: focal neurological deficit FSD: frontal sinus drainage, either through an external (FSDext) or through an endoscopic Draf type III approach (FSDendos) FSO: frontal sinus obliteration ICHS: Intracranial hypertension syndrome NA: not available NG: no bacterium isolated in bacteriological samples ONA: open neurosurgical approach S: Seizure.

[a] Headaches were excluded from the list of neurological symptoms as it could have also resulted from sinusitis.

[b] Localized empyema corresponded to empyema located in the front of the polar or basal part of the frontal lobe, next to the infected frontal and anterior ethmoid sinuses. Extended empyema had spread way beyond the polar or basal region of the frontal lobe facing the infected sinus (see also Figs. 1 and 4).

[c] This intracranial hypertension syndrome with headaches and vomiting was probably mainly due to the presence of a large frontal brain abscess.

[d] This patient was operated on 4.5 months after the initial surgical drainage for frontal cranioplasty using polymethyl-methacrylate (Palacos®).

cases ($n = 7$), and the interhemispheric fissure in 67% of cases ($n = 6$).

- For EE, the frontal polar region was involved in 87.5% of cases ($n = 7$), the frontal basal in two cases, the parietal region in one case and the hemispheric fissure in no cases.

Cerebral, venous, orbital and other lesions associated with the empyema are detailed in Table 4.

Table 4
Lesions associated with the SE or EE.

	SE ($n = 9$)	EE ($n = 8$)
Pott's puffy tumor (n)	1	3
Brain abscess (n)	4	0
Septic thrombophlebitis of the superior longitudinal sinus (n)	2	1
Orbital abscesses (n)	1	1
Other lesions or disorders	Septic pulmonary embolism ($n = 1$) (*F. necrophorum*)	Furunculosis extended over the abdominal skin and 4 limbs one month before empyema ($n = 1$) (*S. aureus*)

3.4. Treatments and outcomes

All patients were hospitalized in a pediatric neurosurgical intensive care unit and were rapidly treated with the following drugs:

- broad spectrum intravenous antibiotherapy active on the bacteria usually involved in these infections and with a good diffusion within the bone, epidural and subdural spaces usually encompassing 3rd generation cephalosporins and metronidazole or clindamycin
- corticosteroids in the presence of cerebral edema
- anticoagulant drugs in case of proven or highly suspected septic thrombophlebitis
- antiepileptic drugs if necessary.

The surgical treatments undergone by our patients are described in Tables 2–5. Even though the mean numbers of surgeries was not different between the SE (1.8 operations/patient) and EE (1.4 operations/patient) groups ($p = 0.18$), the number of patients who recovered after a single surgical procedure was higher in the EE group (Table 5; $p = 0.06$). In both SE and EE groups, the success rate of the first surgical procedure was not significantly influenced by the surgical approach (ONA or ETA). However, in

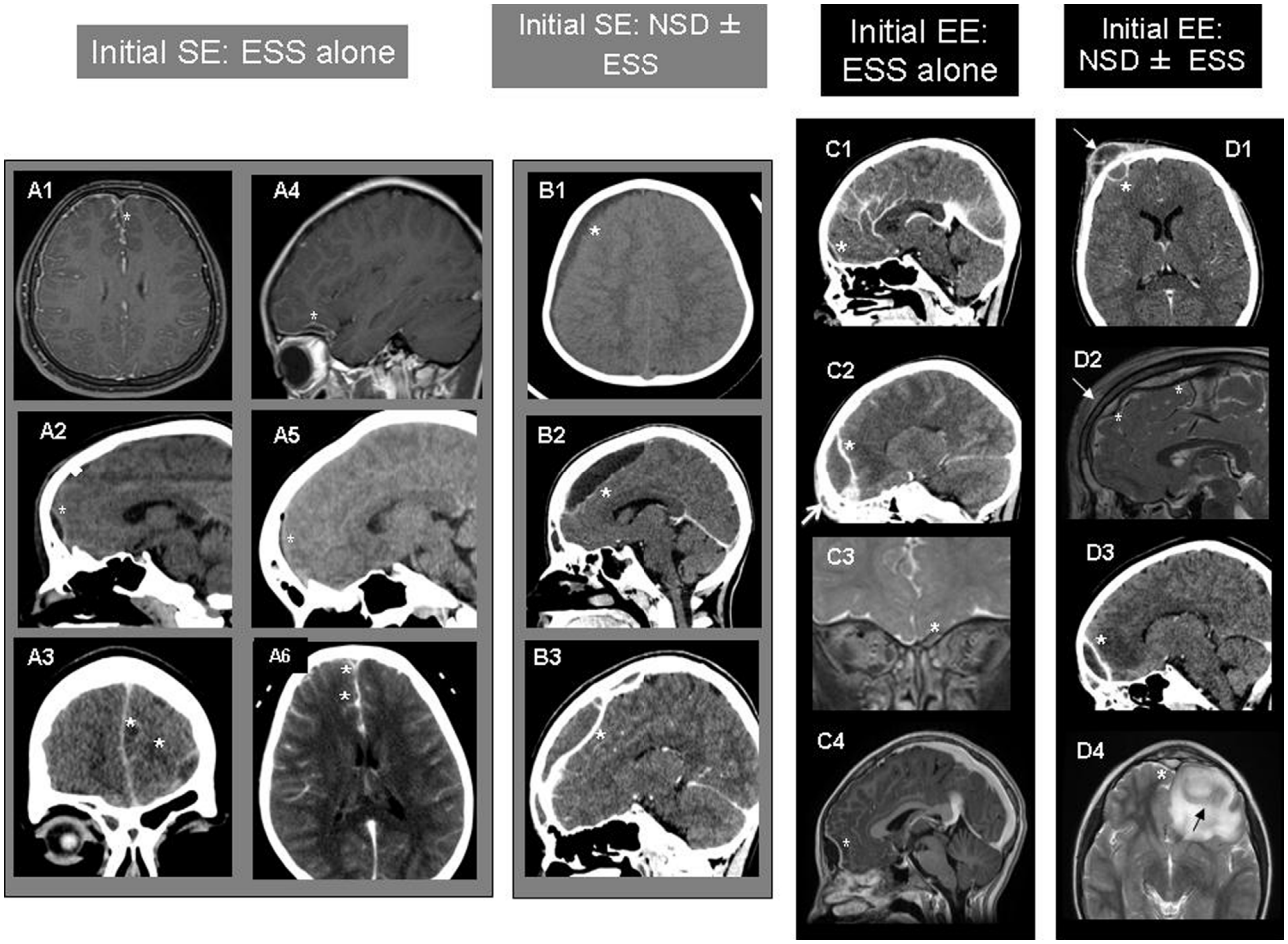

Fig. 1. *Cerebral imaging performed just before the first surgical procedure.* (*) or (◆): Empyema (D1 and D2). White arrows: subcutaneous abscess associated with Pott's puffy tumors (D4). Black arrow: brain abscess. SE initially operated by ETA alone (A1–A7) was smaller than those initially treated by ONA ± ETA (B1–B3). (A3) was the only case of SE that was successfully treated after ETA alone. EE initially operated by ETA alone (C1–C4) was not smaller than those directly treated with ONA ± ETA (D1–D4). In the latter group, the external neurosurgical approach was employed in the case of D1 because the ES originated from a Pott's puffy tumor and remained distant from the infected sinuses, in case B2 because of the size and extensions of the empyema, and in case D4 because of the presence of a large brain abscess requiring direct neurosurgical drainage. The reason why ONA was chosen as an initial procedure in patient D3 is unclear.

patients with SE, ONA tended to be more effective: 67% (2/3) of children who recovered after a single surgical procedure were operated on using ONA while only 17% (1/6) of children who recovered after requiring several surgeries were operated on using ONA ($p = 0.22$). In the EE group, the corresponding percentages were 50% (3/6) and 50% (1/2), respectively. Regarding frontal sinus surgery, in SE cases, 33% (1/3) of children who had a single surgical procedure and 33% (2/6) of those who had several operations had drainage or an obliteration of the frontal sinus. In the EE group, the corresponding percentages were 50% (3/6) and 50% (1/2), respectively. Thus, in both SE and EE groups, frontal sinus surgery did not improve the effectiveness of the first surgical procedure.

In SE, the most effective procedure was ONA with craniotomy (Table 2)

- During the first surgical procedure, its success rate was 100% (2/2) versus 14% (1/7) using other techniques ($p = 0.08$).
- If we consider all surgical procedures, its success rate was 88% (7/8) versus (25%) (2/8) using other techniques ($p = 0.04$).

No mortalities were observed in the present study. The follow-up duration was longer in the SE group (Table 5). Persistent symptoms and disorders at the end of the follow-up period are detailed in Tables 2 and 3. They tended to be more frequent in the SE group than in the EE group (67% vs 29%) (Table 5). The most frequent symptoms observed were headaches and cognitive, concentration, or schooling problems. 44% of patients with SE (4/9) and 43% of those with EE (3/7) were still being treated with antiepileptic drugs during their latest follow-up visit.

4. Discussion

The clinical expressions of SE and EE are dramatically different. Subdural empyema often presents itself in neurosurgical emergencies whereas epidural empyema is often diagnosed on imaging studies. Therefore, the place of the ENT surgeon may differ according to the localization of the empyema.

The aim of the present study was to describe the clinical characteristics of pediatric sinogenic EE and SE, and to discuss their optimal treatment strategies.

Since most cases of empyema were associated with an infection of both the ethmoidal and frontal sinuses, it was often impossible to determine with certainty from which sinus the SE or EE had developed from. The observation of an erosion of the posterior wall of the frontal sinus or the superior wall of the ethmoidal sinus was rarely contributive in the determination of ethmoidal or frontal sinus involvement as it was present in only three cases (Fig. 3). The presence of Pott's puffy tumors in 4 patients did not allow the ruling out of an ethmoidal origin as osteomyelitis of the frontal bone can result from ethmoiditis [13]. However, two arguments

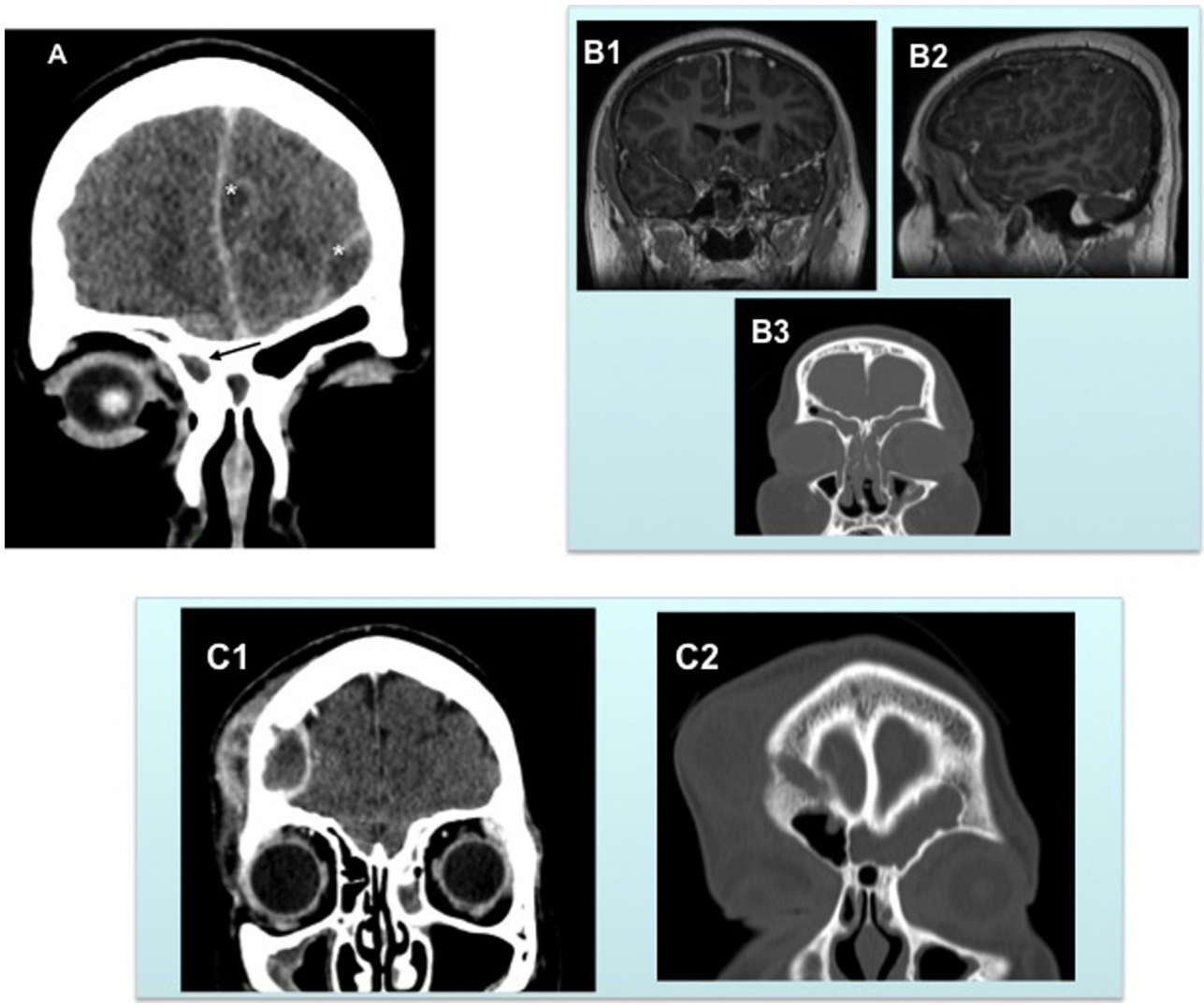

Fig. 2. *CT and MR imaging of empyema not in contact with the infected sinus.* (A) In this patient, only the right frontal sinus was infected (black arrow) even though the SE was located on the opposite side (*). (B1–B3) SE with no visible continuity with the frontal or ethmoid sinuses. (C1–C2) Left frontal sinusitis and right frontal EE originated from Pott's puffy tumor.

strongly support the responsibility of frontal sinusitis in most cases:

- the mean age of our patients (11 years for SE and 10 years for EE), which was similar to those previously reported in the literature [3,4,14], corresponds to the age of development of the frontal sinus
- 82% of empyema (8 SE and 6 EE) were at least partly located in the polar part of the frontal lobe and not in its basal part, i.e. they faced the frontal and not the ethmoid sinus.

Two cases clearly originated from the ethmoidal sinus since these patients did not have any frontal sinus. In one case, the EE originated from a Pott's puffy tumor and not directly from a sinus cavity (Fig. 2).

With regards to imaging techniques, in the present work as well as in other publications [15], CT scans were more often prescribed than MRI (76.5% versus 41% of cases). This is mostly due to the fact that they are easier to obtain in an emergency setting and also easier to perform on children. However, CT scans may fail in revealing intracranial complications [16,17]. The American College of Radiology considers that MRI with contrast and contrast-enhanced CT are complementary examinations when evaluating potential complications of sinusitis [18]. CT scans are less effective in detecting empyema and in distinguishing SE from EE as compared to MRI, but its specificity for the diagnosis of thrombophlebitis is higher and it better shows absent sinuses and bony erosions of sinus walls or cranial vault. Concerning MRI, gadolinium-enhanced T1-weighted sequences are particularly useful in distinguishing EE from SE, since in these sequences, the dura mater clearly appears as a thick enhanced layer. The distinction is usually quite obvious in extended forms (Fig. 4), but can be more difficult at the beginning of the evolution (Fig. 1): SE inner contours are rather irregular, following the form of underlying cerebral gyri. They often have a multilocular appearance, are frequently spread way beyond the infected sinus and are often partly localized in the interhemispheric fissure.

Concerning microbiological data, a striking trend noted was the frequent involvement of *Streptococcus anginosus.* Indeed, this group of streptococci has long been recognized to cause invasive pyogenic infections in various tissues [19]. In pediatric studies of intracranial complications of rhinosinusitis, *S. anginosus* was not only the most frequently involved bacterium, but it also increased

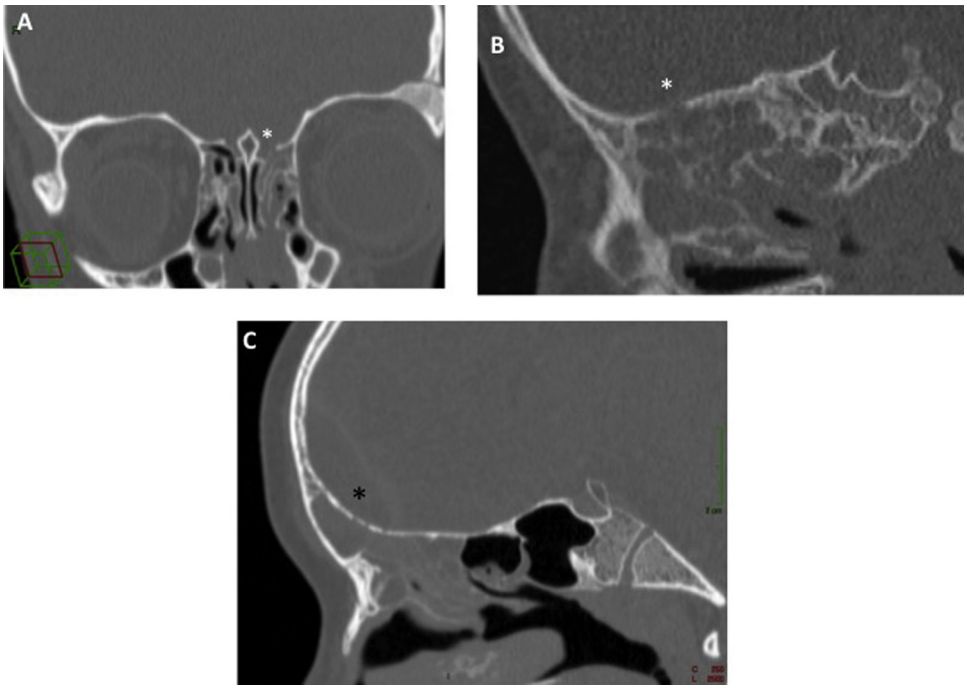

Fig. 3. CT scans showing an erosion of the ethmoidal roof ((A) SE, (B) EE) or of the posterior wall of the frontal bone (*) ((C) EE).

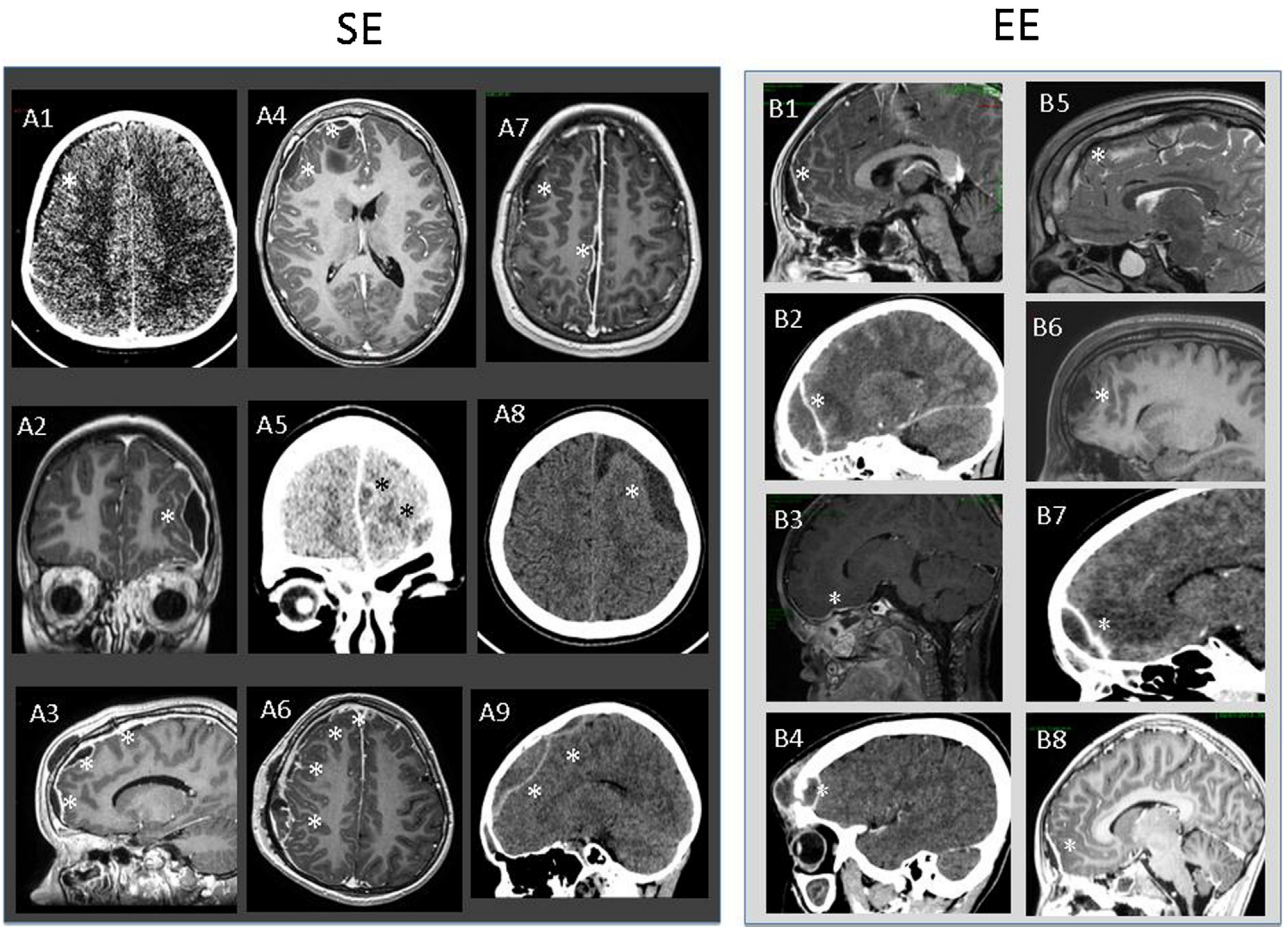

Fig. 4. *Cerebral imaging at the time of maximal extension of empyema* (*). These images show that SE is usually larger than EE, reaches areas situated way above the ethmoid and frontal sinuses and, also often extends to the interhemispheric region. While EE shows typical biconvex contours, SE has a more irregular shape, sometimes displaying a multilocular appearance (A3, A4, A5, A6, A7, and A9).

Table 5
Treatments and outcomes.

	SE ($n=9$)	EE ($n=8$)	p
Follow-up (months)[a]	25 ± 5	7 ± 4.5	$<10^{-6}$
Duration of hospital stay (days)[a]	23 ± 9	22 ± 6	NS
IV antibiotics (days)[a]	22 ± 7	17 ± 7	NS
Success of initial surgical procedure	33% (3/9)	75% (6/8)	0.06
-ETA ($n=6$)	17% (1/6)	75% (3/4)	
-ONA ($n=2$)	50% (1/2)	67% (2/3)	
-ONA combined with ETA ($n=1$)	100% (1/1)	100% (1/1)	
Mean number of surgical procedures[a]	1.8 ± 0.7	1.4 ± 0.7	0.18
Hospitalization duration (days)[a]	23 ± 9	22 ± 6	NS
All surgical procedures			
Children with persistent symptoms at the end of the follow-up period	67% (6/9)	29% (2/7)[b]	NS
-Headaches	3	0	
-Concentration, cognitive or schooling problems	3	1	
-Abnormal EEG	1	1	
-Speech difficulties	1	0	
-Motor difficulties	1	0	
-Unsightly cranial vault deformity	1	1	

NS: not significant.
[a] Values are expressed as means ± SD.
[b] In the calculation of the percentage of persistent symptoms at the end of the follow-up period in the EE group, the denominator was reduced to 7 as one patient never attended the scheduled follow-up visits.

the probability of neurosurgical intervention and long-term neurologic deficits [9]. Some bacteriological differences between SE and EE result from the more anaerobic environment of SE due to its reduced connection to the pneumatized paranasal sinuses. Hence why staphylococci are more frequently observed in EE and anaerobic bacteria in SE (present study, [4,5,9]). This microbiological data differs from those observed in uncomplicated PABS, where *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are isolated in about 30%, 30%, and 10% of cases, respectively [15].

SE and EE always require hospitalization in a pediatric neurosurgical intensive care unit and the rapid institution of a medical treatment. With regards to surgical indications and modalities, our data strongly suggests that they considerably differ between SE and EE. In SE, the most effective procedure is a direct and large drainage through a craniotomy. ETA alone is not advisable: in the present work, out of 7 patients with SE treated this way, only one recovered while the 6 others required additional surgery with ONA (Fig. 1, A3). As shown in Fig. 1, the poor results from ETA in the case of this indication were observed even when the initial extension of the SE was very limited. However, the adjunction of ETA to ONA was useful for the purpose of bacteriological diagnosis as in our series of patients with SE, half of the positive bacteriological samples were harvested from paranasal sinuses during the ETA procedure. Hence, we recommend rapid surgery combining ETA and ONA in pediatric cases of SE.

In EE, as shown by the present data, more patients will recover after a single surgical procedure than in cases of SE. ETA may be an alternative to ONA, especially when a direct drainage of the EE can be performed through a Draf III approach and an opening of the posterior wall of the frontal sinus. In some instances however, a direct endoscopic drainage is impossible due to the location and extensions of the EE, or due to the presence of associated lesions requiring ONA (Fig. 1, cases D1, D2 and D4). One of our cases (Fig. 1, C2) and other literature data [20] show that the presence of a Pott's puffy tumor does not contraindicate an exclusively endoscopic approach. Finally, the drainage or obliteration of the frontal sinus did not influence surgical outcomes in patients with EE as well as in those with SE.

Regarding outcomes, in accordance with literature data [3–6], no mortalities were observed. Persistent disorders at the end of the follow-up period, especially headaches and cognitive, concentration, or schooling problems, tended to be more frequent in the SE group than in the EE group (67% vs 29%). As a consequence of their more uneventful postoperative course, children with EE were followed up for a shorter period of time (Table 5, $p < 10^{-6}$). The probability of persistent symptoms was higher when several surgical procedures were needed ($p = 0.05$).

The present study contains some limitations and drawbacks:

- it is a single-center and retrospective study
- it includes a small number of patients, even if it represents the second largest published series of pediatric sinogenic intracranial complications [9]
- only children who underwent surgery for SE and EE were retrieved meaning that empyema cases which did not require surgery were not included.

5. Conclusions

Intracranial empyema and particularly subdural empyema are severe infections that require a multimodal approach, involving neurosurgeons, ENT surgeons, radiologists and infectiologists.

ETA has an important role in the management of intracranial empyema. If its role may be limited to microbiological diagnosis in SE, it can sometimes successfully treat EE, especially when the EE can be directly drained by opening of the posterior wall of the frontal sinus or of the ethmoidal roof.

References

[1] M.J. Abzug, Acute sinusitis in children: do antibiotics have any role? J. Infect. 68 (Suppl. 1) (2014) S33–S37.
[2] A.R. Sedaghat, C.O. Wilke, M.J. Cunningham, S.L. Ishman, Socioeconomic disparities in the presentation of acute bacterial sinusitis complications in children, Laryngoscope 124 (2014) 1700–1706.
[3] L.E. Oxford, J. McClay, Complications of acute sinusitis in children, Otolaryngol. Head Neck Surg. 133 (2005) 32–37.
[4] D. Kombogiorgas, R. Seth, R. Athwal, J. Modha, J. Singh, Suppurative intracranial complications of sinusitis in adolescence, single institute experience and review of literature, Br. J. Neurosurg. 21 (2007) 603–609.
[5] N. Adame, G. Hedlund, C.L. Byington, Sinogenic intracranial empyema in children, Pediatrics 116 (2005) e461–e467.
[6] M. Calik, A. Iscan, M. Abuhandan, I. Yetkin, F. Bozkuş, M.F. Torun, Masked subdural empyema secondary to frontal sinusitis, Am. J. Emerg. Med. 30 (2012) 1657.e1–1657.e4.
[7] P.K. Sharma, B. Saikia, R. Sharma, Orbitocranial complications of acute sinusitis in children, J. Emerg. Med. 47 (2014) 282–285.

[8] M. Legrand, T. Roujeau, P. Meyer, P. Carli, G. Orliaguet, S. Blanot, Paediatric intracranial empyema: differences according to age, Eur. J. Pediatr. 168 (2009) 1235–1241.
[9] M.W. Deutschmann, D. Livingstone, J.J. Cho, O.G. Vanderkooi, J.T. Brookes, The significance of *Streptococcus anginosus* group in intracranial complications of pediatric rhinosinusitis, JAMA Otolaryngol. Head Neck Surg. 139 (2013) 157–160.
[10] E. Elmvon, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gøtzsche, J.P. Vandenbroucke, The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies, Lancet 370 (2007) 1453–1457.
[11] C.B. Courville, Subdural empyema secondary to purulent frontal sinusitis, Arch. Otolaryngol. 39 (1944) 211–230.
[12] Y.S. Bhandari, N.B. Sarkari, Subdural empyema. A review of 37 cases, J. Neurosurg. 32 (1970) 35–39.
[13] E. Hitti, E. Love, Pott's puffy tumor in a six-year-old female, J. Hosp. Med. 5 (2010) E4–E5.
[14] V.K. Goytia, C.M. Giannoni, M.S. Edwards, Intraorbital and intracranial extension of sinusitis: comparative morbidity, J. Pediatr. 158 (2011) 486–491.
[15] E.R. Wald, K.E. Applegate, C. Bordley, D.H. Darrow, M.P. Glode, S.M. Marcy, et al., American academy of pediatrics, clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years, Pediatrics 132 (2013) e262–e280.
[16] R.T. Younis, V.K. Anand, B. Davidson, The role of computed tomography and magnetic resonance imaging in patients with sinusitis with complications, Laryngoscope 112 (2002) 224–229.
[17] D. McIntosh, M. Mahadevan, Failure of contrast enhanced computed tomography scans to identify an orbital abscess. The benefit of magnetic resonance imaging, J. Laryngol. Otol. 122 (2008) 639–640.
[18] American College of Radiology, Appropriateness Criteria for Sinonasal Disease, American College of Radiology, 2009 Available at ⟨www.acr.org/~/media/8172B4DE503149248E64856857674BB5.pdf.AccETAed⟩ (November 6, 2012).
[19] B.Y. Sunwoo, W.T. Miller Jr., *Streptococcus anginosus* infections: crossing tissue planes, Chest 146 (2014) e121–e125.
[20] P.K. Parida, G. Surianarayanan, S. Ganeshan, S.K. Saxena, Pott's puffy tumor in pediatric age group: a retrospective study, Int. J. Pediatr. Otorhinolaryngol. 76 (2012) 1274–1277.

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Quantitative evaluation of facial growth in children after unilateral ESS for subperiosteal orbital abscess drainage☆

Lihi Sagi [a], Ephraim Eviatar [a], Paul Gottlieb [b], Haim Gavriel [a,*]

[a] Department of Otolaryngology Head and Neck Surgery, Assaf Harofeh Medical Center, Zerifin 70300, Israel[1]
[b] Department of Diagnostic Imaging, Assaf Harofeh Medical Center, Zerifin 7030070300, Israel[1]

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ABSTRACT

Objective: To determine the effects of unilateral endoscopic sinus surgery (ESS) on facial skeletal growth in children.
Design: Retrospective controlled study.
Setting: Academic tertiary referral medical center.
Materials and methods: Included were children who underwent a unilateral ESS procedure between 1995 and 2006 to evacuate a subperiosteal orbital abscess (SPOA) and several years later went through cephalometric measurements comparing their facial development between the surgical and nonsurgical sides.
Results: A total of 6 children were recruited for this study (3 girls and 3 boys), between the ages 3 to 10 at time of surgery, and from 9.5 to 23 years of age today. Four of the children had surgery on the right side and 2 on the left. No statistically significant difference was found when evaluating all planes in the cephalometric radiographs according to age at surgery, age today and years from surgery.
Conclusion: In our study, no significant differences were found in craniofacial growth between the sides of the face in children who underwent ESS for the same medical indication on one side of the face, suggesting that ESS might be safely performed even in young children.
Level of evidence: –2c

1. Introduction

Insufficient reports and animal studies have raised concerns and debate regarding the impact of surgical intervention of the nasal sinuses on facial development in the pediatric population [1–8]. Most of these studies were conducted on piglets, showing interruption of facial growth on the side of the endoscopic surgery. However, the animals did not show any clinical evidence of abnormal growth [9,10]. The effects of sinus surgery on facial growth in human beings has been even less frequently reported due to the significant quantity of parameters to be evaluated including patient age, the various pathologies treated, the surgical procedure performed and the need for further imaging for accurate evaluation of the facial skeleton post-surgery. For example, Kosko et al. reported maxillary sinus hypoplasia on CT scan after endoscopic sinus surgery (ESS), but with no apparent clinical facial asymmetry [11]. In addition to this, very aggressive surgical management of mid-face lesions was not associated with interruption of facial growth as was suggested by Lund et al. [12]. In another study conducted by Wolf et al., no evidence of facial growth interruption was reported; however, these two latter studies did not perform accurate measurements of the facial skeleton.

The purpose of this study is to evaluate the effect of extensive unilateral removal of the ethmoid cells and the lamina papyracea by ESS on mid-facial growth in a unique group of children having a subperiosteal orbital abscess (SPOA), and compare this to the non-operated side using antero-posterior (AP) cephalometric radiographs (soft tissue and bone intensity).

2. Materials and methods

The study was approved by the IRB.

☆ There is no direct or indirect commercial financial incentive associated with publishing the article; there is no extra-institutional funding; there are no possible conflicts of interest; there are no sources of financial support, corporate involvement, patent holdings, etc. for our research/study; and there is no ethical problem.

* Corresponding author. Tel.: +972 8 9779417; fax: +972 8 9779421.
E-mail address: haim.ga@012.net.il (H. Gavriel).
[1] Affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel.

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0165-5876/

The study population consisted of children who underwent ESS for drainage of an SPOA between the years 1995 and 2006. Children with significant congenital syndromes such as Down's syndrome and cystic fibrosis [13], a history of significant maxillofacial trauma, nasal fractures, or previous nasoseptal surgery were excluded. All children underwent a CT scan demonstrating sinusitis and an SPOA. All ESS procedures for drainage of the abscess were performed by the same surgeon, using the same approach and technique.

2.1. Surgical procedure

ESS was performed using 4-mm 0° and 30° telescopes under general anesthesia. The lamina papyracea was completely exposed and removed after removal of the uncinate process, bulla ethmoidalis and anterior and posterior ethmoid cells. A small pack was left in the middle meatus until the following morning [14].

2.2. Patient evaluation

All patients were contacted for initial assessment by phone for collecting epidemiologic data, including queries regarding any imaging modality of the head region performed since the ESS procedure.

The next step was to invite the child (and his parents when appropriate) for medical history, including nasal history, face trauma and additional surgery in the sinuses and nose along the years, and a complete head and neck examination at the outpatient clinic. An informed consent was provided by the patient (or his parents when appropriate).

2.3. Cephalometric radiography and measurement

All patients had an AP cephalometric radiograph for evaluation of any asymmetry between the two sides of the face.

The cephalometric images are the 2D interpretation of 3D structures. In cephalometry, the X-ray source was fixed at a distance of 152.4 cm from the mid sagittal plane, and the film was placed at a distance of 15 cm from the mid sagittal plane. The ear rods were inserted into the external auditory canals, while the Frankfort plane was parallel to the floor. The central X-ray beam penetrated the patient's skull in an AP direction and bisected the trans-meatal axis perpendicularly. In lateral and frontal cephalograms, many structures overlap as complex 3D structures are projected on a 2D plane. The magnification and distortion inherent in conventional radiography make it difficult to accurately assess the patient's anatomy [15]. The properly adjusted cephalostat cannot prevent a slight translation or rotation of the mid-sagittal plane. These variations in skull position may lead to variations in cephalometric measurements.

One investigator (blinded to the side of operation) evaluated 7 reference points on the cephalometric radiograph and compared the two sides of the face. Cephalograms were traced and measured by hand, and all measurements made by one investigator. Five transverse linear measurements were measured on each radiograph. These are shown in Fig. 1 (see legend for definitions of abbreviations).

The linear transverse measurements used in the study were as follows:

Our 4 anatomic landmark reference points used for the measurements (Fig. 1):

1. MO – medio-orbitale – the point on the medial orbital margin that is closest to the median lane (left and right);

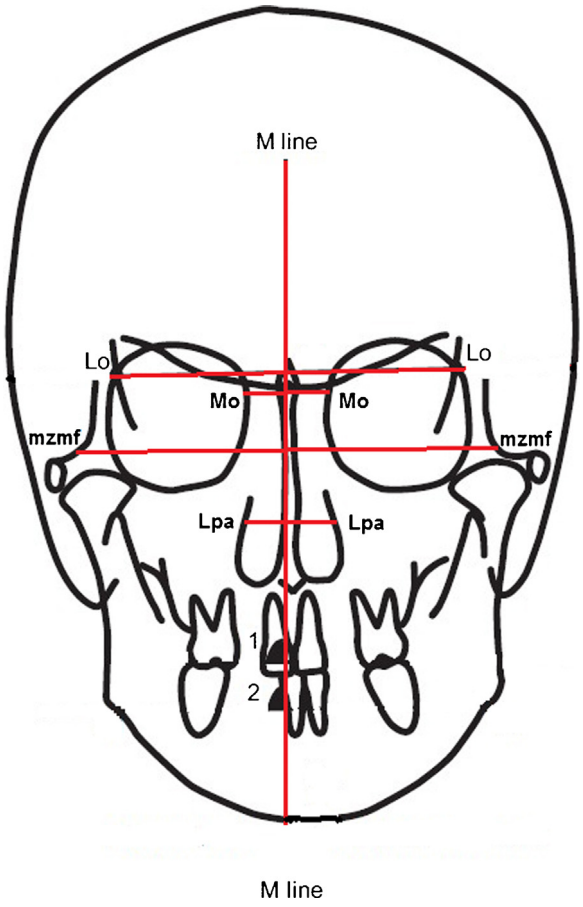

Fig. 1. Illustration of the five transverse linear measurements.

2. LO – latero-orbitale – the intersection of the lateral orbital contour with the innominate line (left and right);
3. LPA – lateral piriform aperture – the most lateral aspect of the piriform aperture (left and right);
4. ZFMA – zygomatico-frontal medial suture point – point at the medial margin of the zygomatico-frontal suture (left and right).

The midsagittal plane (the 5th plane), from which all other planes were calculated was drawn through:

Top: OM – orbital midpoint – the projection on the line LO–LO of the top of the nasal septum at the base of the crista galli;
TNS – top nasal septum – the highest point on the superior aspect of the nasal septum;
Bottom: ANS—anterior nasal spine.

2.4. Statistical evaluation

Categorical variables were reported as frequency and percentages, and continuous variables as medians and interquartile ranges (IQR). We used the Wilcoxon test to study the difference between the two sides of the face, using the four variables measured. Spearman Correlation Coefficient was used to assess the correlation between age at surgery, age at evaluation, time of follow up and the difference between the measurements of the two facial sided. A two-tailed $p < 0.05$ were considered statistically significant. Analyses were performed with SPSS version 21.

Table 1
Patients' age at surgery and now (chronological order).

No.	Age at surgery (years)	Age today (years)	Time from surgery (years)
1	10	23	13
2	3	12.5	9.5
3	7	12.5	5.5
4	3	9.5	6.5
5	9	15.5	6.5
6	4	13	9

3. Results

Eighteen children underwent evacuation of SPOA during the study period. Excluded were 2 who were no operated upon by the same surgeon and 5 more who were lost to follow-up and could not be reached. Out of the remaining 11 children, 5 strongly refused to have further imaging and hence were also excluded. A total of 6 patients were finally recruited for this study (3 females and 3 males), all between the ages of 3 and 10 at the time of surgery, and between 9.5 and 23 years of age today (Table 1). Four of the children had surgery on the right side and 2 on the left.

Table 2 shows the AP cephalometric combined means, standard deviations, medians, and minimum and maximum values of eight linear transverse measurements (right and left four transverse planes) for all 6 subjects.

The mean distance between the MO reference point and the mid-sagittal plane on the right was 10.67 mm and on the left 12.17 mm. There was no significant statistical difference between the sides in all patients ($p = 0.447$).

The mean distance between the LO reference point and the mid-sagittal plane on the right was 45.33 mm and on the left 45.00 mm. There was no significant statistical difference between the sides in all patients ($p = 0.819$).

The mean distance between the LPA reference point and the mid-sagittal plane on the right was 11.17 mm and on the left 14.00 mm. There was no significant statistical difference between the sides in all patients ($p = 0.56$).

The mean distance between the ZFMA reference point and the MO reference point on the right was 38.67 mm and on the left 42.0 mm. again, there was no statistical difference between the sides in all patients (Table 3).

It is important here to emphasis that out of the 6 patients, 4 were operated on the right and 2 on the left. All measurements except LPA measured on the left in both cases that were operated on the left and LO measured on the right for 1 case operated on the right, showed that the transverse plane on the side that was operated on was smaller than the other side; however, these changes were not found to be statistically significant.

No statistically significant difference was found when evaluating the differences for all four planes according to age at surgery, age today and years from surgery. We did find a non-significant difference ($p = 0.088$) between the two sides when measuring the ZFMA/MO planes when considering the years from surgery – the longer the time that passed from surgery – the less the difference.

Table 3
.

	Line measured	*r* Value	*p* Value
Age at surgery	diff_mo	−0.162	0.759
	diff_lo	−0.03	0.955
	diff_lpa	0.309	0.551
	diff_mzmd_div_mo	0.132	0.803
Age today	diff_mo	−0.209	0.691
	diff_lo	0.076	0.887
	diff_lpa	−0.209	0.691
	diff_mzmd_div_mo	−0.388	0.447
Years from surg	diff_mo	−0.388	0.447
	diff_lo	0.121	0.819
	diff_lpa	−0.299	0.56
	diff_mzmd_div_mo	−0.746	0.088

4. Discussion

ESS in the pediatric populations is becoming more common in recent years, but concern has been raised regarding the possible influence on mid facial growth due to the disturbance of the bony structures of the sinuses. While evidence of mal development of the mid facial region in animal studies has been reported, controversy exists as to possible development alterations in humans [10,13].

Although the craniofacial skeleton in the growing child is suggested by some to be responsive to changing functional demands and environmental factors, several studies have shown no significant changes of mid-facial growth in children even following ESS [2]. In the latter study, Wolf et al. documented the largest series reported thus far of 124 children who underwent ESS. Even though the follow-up varied (4–14 years), and cephalometric measurements were not taken, they concluded that no clinically significant disturbances were observed in facial bone development. Bothwell et al. reported a 13.2 year follow-up of 67 children with a mean age of 3.1 years, 46 who had ESS and 21 children who did not. Quantitative and qualitative analyses showed no statistical significance in facial growth between children who underwent ESS and those who did not [3].

In this study, we present quantitative evidence that unilateral sinus surgery can be performed safely in the pediatric patient without causing significant facial asymmetry. All of our subjects were young children at the time of the surgery (ages 3–10), and today (time of evaluation), at least 6 years after surgery, in the age range of 9.5–23 years. We report no statistically significant differences in the measured transverse planes on cephalometry radiographs between the operated and non-operated sides.

Although there are a reasonable number of studies on the impact of ESS on facial growth in the pediatric population, using different methods of measurements and comparisons, none

Table 2
The values of the anatomic landmarks measured.

Anatomic landmark side	mo		lo		lpa		zfma_div_mo	
	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
Mean	10.67	12.17	45.33	45	11.17	14	38.67	42
SD	1.37	1.72	3.5	2.83	1.94	3.41	3.88	6.69
	mo		Lo		lpa		zfma_div_mo	
Operated(O), non-operated (NO)	O	NO	O	NO	O	NO	O	NO
Mean	10	13	45	46	12	13	36.8	43.8

related to this type of procedure nor did they use *AP* cephalometry transverse measurements. Only one other study was found using CT tomography with the aim of comparing facial growth between 8 children who had unilateral surgical treatment including the external approach, ESS and the combined approach for orbital complications (mainly, but not only SPOA) to 19 adults with or without sinusitis [1]. In another study by Van Peteghem et al., lateral cephalometric measurements were reported for a very specific group of cystic fibrosis children having extensive functional endoscopic sinus surgery, reporting no statistically significant differences between different age groups [15]. However, AP cephalometry was not performed and all patients have had bilateral surgery.

In our study, only minimal changes in facial volume measurements were found, confirming the clinical impression that ESS in the pediatric population is safe.

Our study design has contributed substantially to our conclusion in several ways. First of all, only one side was operated upon, saving the other side to serve as a control group in the same patient. Second, all patients had comparable significant endoscopic surgery in which the ethmoid cells and the lamina papyracea were resected extensively. Needless to say, such an extensive uniform procedure is not common in the pediatric population. Third, all procedures were performed by the same surgeon, and last of all, the cephalometric imaging provides the major advantage of better enabling evaluation of facial measurements.

The study had limitations, and the results should be interpreted with caution. The sample size was small, cephalometric measurements are prone to errors (due to the technique and measurement process), and lastly, the children were of different ages at surgery, and as a consequence different ages at the time of cephalometry and evaluation of measurements.

5. Conclusions

In the present study sample, no significant differences were found in craniofacial growth between the sides of the face in children. These children went through ESS for the same medical indication on one side of the face, and this side was compared to the other non-operable side, with measurements using anterior-posterior cephalometry.

References

[1] B. Senior, A. Wirtschafter, C. Mai, C. Becker, W. Belenky, Quantitative impact of pediatric sinus surgery on facial growth, Laryngoscope 110 (11) (2000) 1866–1870.
[2] G. Wolf, K. Greistorfer, J.A. Jebeles, The endoscopic endonasal technique in the treatment of chronic recurring sinusitis, Rhinology 33 (Jun (2)) (1995) 97–103.
[3] M.R. Bothwell, J.F. Piccirillo, R.P. Lusk, B.D. Ridenour, Long-term outcome of facial growth after functional endoscopic sinus surgery, Otolaryngol. Head Neck Surg. 126 (6) (2002) 628–634.
[4] E.A. Mair, W.E. Bolger, E.A. Breisch, Sinus and facial growth after pediatric endoscopic sinus surgery, Arch Otolaryngol. Head Neck Surg. 121 (1995) 547–552.
[5] G. Wolf, W. Anderhuber, F. Kuhn, The development of the paranasal sinus in children: implications for paranasal sinus surgery, Ann. Otol. Rhinol. Laryngol. 102 (1993) 70.
[6] L.G. Farkas, Craniofacial Examination in Medicine Anthropometric Measurement, Raven Press, New York, NY, 1994.
[7] R.P. Lusk, H.R. Muntz, Endoscopic sinus surgery in children with chronic sinusitis: a pilot study, Laryngoscope 100 (1990) 654–658.
[8] C.W. Gross, M.J. Gurucharri, R.H. Lazar, T.E. Long, Functional endoscopic sinus surgery (FESS) in the pediatric age group, Laryngoscope 99 (3) (1989) 272–275.
[9] K.M. Carpenter, S.M. Graham, R.J. Smith, Facial skeletal growth after endoscopic sinus surgery in the piglet model, Am J Rhinol 11 (1997) 211–217.
[10] E.A. Mair, W.E. Bolger, E.A. Breisch, Sinus and facial growth after pediatric endoscopic sinus surgery, Arch. Otolaryngol. Head Neck Surg. 121 (1995) 547–552.
[11] J.R. Kosko, B.E. Hall, D.E. Tunkel, Acquired maxillary sinus hypoplasia: a consequence of endoscopic sinus surgery, Laryngoscope 106 (1996) 1210–1213.
[12] V.J. Lund, D.J. Howard, W.I. Wei, A.D. Cheesman, Craniofacial resection for tumors of the nasal cavity and paranasal sinuses—a 17 year experience, Head Neck 20 (1999) 97–105.
[13] A. Van Peteghem, P.A. Clement, Influence of extensive functional endoscopic sinus surgery (FESS) on facial growth in children with cystic fibrosis. Comparison of 10 cephalometric parameters of the midface for three study groups, Int. J. Pediatr. Otorhinolaryngol. 70 (2006) 1407–1413.
[14] E. Eviatar, T. Lazarovitch, H. Gavriel, The correlation of microbiology growth between subperiosteal orbital abscess and affected sinuses in young children, Am. J. Rhinol. Allergy 26 (Nov–Dec (6)) (2012) 489–492.
[15] A. Van Peteghem, P.A. Clement, Influence of extensive functional endoscopic sinus surgery (FESS) on facial growth in children with cystic fibrosis. Comparison of 10 cephalometric parameters of the midface for three study groups, Int. J. Pediatr. Otorhinolaryngol. 70 (8) (2006) 1407–1413.

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CLINICAL PRACTICE GUIDELINE

Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 Years

abstract

FREE

OBJECTIVE: To update the American Academy of Pediatrics clinical practice guideline regarding the diagnosis and management of acute bacterial sinusitis in children and adolescents.

METHODS: Analysis of the medical literature published since the last version of the guideline (2001).

RESULTS: The diagnosis of acute bacterial sinusitis is made when a child with an acute upper respiratory tract infection (URI) presents with (1) persistent illness (nasal discharge [of any quality] or daytime cough or both lasting more than 10 days without improvement), (2) a worsening course (worsening or new onset of nasal discharge, daytime cough, or fever after initial improvement), or (3) severe onset (concurrent fever [temperature ≥39°C/102.2°F] and purulent nasal discharge for at least 3 consecutive days). Clinicians should not obtain imaging studies of any kind to distinguish acute bacterial sinusitis from viral URI, because they do not contribute to the diagnosis; however, a contrast-enhanced computed tomography scan of the paranasal sinuses should be obtained whenever a child is suspected of having orbital or central nervous system complications. The clinician should prescribe antibiotic therapy for acute bacterial sinusitis in children with severe onset or worsening course. The clinician should either prescribe antibiotic therapy or offer additional observation for 3 days to children with persistent illness. Amoxicillin with or without clavulanate is the first-line treatment of acute bacterial sinusitis. Clinicians should reassess initial management if there is either a caregiver report of worsening (progression of initial signs/symptoms or appearance of new signs/symptoms) or failure to improve within 72 hours of initial management. If the diagnosis of acute bacterial sinusitis is confirmed in a child with worsening symptoms or failure to improve, then clinicians may change the antibiotic therapy for the child initially managed with antibiotic or initiate antibiotic treatment of the child initially managed with observation.

CONCLUSIONS: Changes in this revision include the addition of a clinical presentation designated as "worsening course," an option to treat immediately or observe children with persistent symptoms for 3 days before treating, and a review of evidence indicating that imaging is not necessary in children with uncomplicated acute bacterial sinusitis. *Pediatrics* 2013;132:e262–e280

Ellen R. Wald, MD, FAAP, Kimberly E. Applegate, MD, MS, FAAP, Clay Bordley, MD, FAAP, David H. Darrow, MD, DDS, FAAP, Mary P. Glode, MD, FAAP, S. Michael Marcy, MD, FAAP, Carrie E. Nelson, MD, MS, Richard M. Rosenfeld, MD, FAAP, Nader Shaikh, MD, MPH, FAAP, Michael J. Smith, MD, MSCE, FAAP, Paul V. Williams, MD, FAAP, and Stuart T. Weinberg, MD, FAAP

KEY WORDS

acute bacterial sinusitis, sinusitis, antibiotics, imaging, sinus aspiration

ABBREVIATIONS

AAP—American Academy of Pediatrics
AOM—acute otitis media
CT—computed tomography
PCV-13—13-valent pneumococcal conjugate vaccine
RABS—recurrent acute bacterial sinusitis
RCT—randomized controlled trial
URI—upper respiratory tract infection

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INTRODUCTION

Acute bacterial sinusitis is a common complication of viral upper respiratory infection (URI) or allergic inflammation. Using stringent criteria to define acute sinusitis, it has been observed that between 6% and 7% of children seeking care for respiratory symptoms has an illness consistent with this definition.[1–4]

This clinical practice guideline is a revision of the clinical practice guideline published by the American Academy of Pediatrics (AAP) in 2001.[5] It has been developed by a subcommittee of the Steering Committee on Quality Improvement and Management that included physicians with expertise in the fields of primary care pediatrics, academic general pediatrics, family practice, allergy, epidemiology and informatics, pediatric infectious diseases, pediatric otolaryngology, radiology, and pediatric emergency medicine. None of the participants had financial conflicts of interest, and only money from the AAP was used to fund the development of the guideline. The guideline will be reviewed in 5 years unless new evidence emerges that warrants revision sooner.

The guideline is intended for use in a variety of clinical settings (eg, office, emergency department, hospital) by clinicians who treat pediatric patients. The data on which the recommendations are based are included in a companion technical report, published in the electronic pages.[6] The Partnership for Policy Implementation has developed a series of definitions using accepted health information technology standards to assist in the implementation of this guideline in computer systems and quality measurement efforts. This document is available at: http://www2.aap.org/informatics/PPI.html.

This revision focuses on the diagnosis and management of acute sinusitis in children between 1 and 18 years of age. It does not apply to children with subacute or chronic sinusitis. Similar to the previous guideline, this document does not consider neonates and children younger than 1 year or children with anatomic abnormalities of the sinuses, immunodeficiencies, cystic fibrosis, or primary ciliary dyskinesia. The most significant areas of change from the 2001 guideline are in the addition of a clinical presentation designated as "worsening course," inclusion of new data on the effectiveness of antibiotics in children with acute sinusitis,[4] and a review of evidence indicating that imaging is not necessary to identify those children who will benefit from antimicrobial therapy.

METHODS

The Subcommittee on Management of Sinusitis met in June 2009 to identify research questions relevant to guideline revision. The primary goal was to update the 2001 report by identifying and reviewing additional studies of pediatric acute sinusitis that have been performed over the past decade.

Searches of PubMed were performed by using the same search term as in the 2001 report. All searches were limited to English-language and human studies. Three separate searches were performed to maximize retrieval of the most recent and highest-quality evidence for pediatric sinusitis. The first limited results to all randomized controlled trials (RCTs) from 1966 to 2009, the second to all meta-analyses from 1966 to 2009, and the third to all pediatric studies (limited to ages <18 years) published since the last technical report (1999–2009). Additionally, the Web of Science was queried to identify studies that cited the original AAP guidelines. This literature search was replicated in July 2010

Evidence Quality	Preponderance of Benefit or Harm	Balance of Benefit and Harm
A. Well-designed RCTs or diagnostic studies on relevant population	Strong Recommendation	Option
B. RCTs or diagnostic studies with minor limitations;overwhelmingly consistent evidence from observational studies	Recommendation	
C. Observational studies (case-control and cohort design)		
D. Expert opinion, case reports, reasoning from first principles	Option	No Rec
X. Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm	Strong Recommendation / Recommendation	

FIGURE 1
Levels of recommendations. Rec, recommendation.

and November 2012 to capture recently published studies. The complete results of the literature review are published separately in the technical report.[6] In summary, 17 randomized studies of sinusitis in children were identified and reviewed. Only 3 trials met inclusion criteria. Because of significant heterogeneity among these studies, formal meta-analyses were not pursued.

The results from the literature review were used to guide development of the key action statements included in this document. These action statements were generated by using BRIDGE-Wiz (Building Recommendations in a Developers Guideline Editor, Yale School of Medicine, New Haven, CT), an interactive software tool that leads guideline development through a series of questions that are intended to create a more actionable set of key action statements.[7] BRIDGE-Wiz also incorporates the quality of available evidence into the final determination of the strength of each recommendation.

The AAP policy statement "Classifying Recommendations for Clinical Practice Guidelines" was followed in designating levels of recommendations (Fig 1).[8] Definitions of evidence-based statements are provided in Table 1. This guideline was reviewed by multiple groups in the AAP and 2 external organizations. Comments were compiled and reviewed by the subcommittee, and relevant changes were incorporated into the guideline.

KEY ACTION STATEMENTS

Key Action Statement 1

Clinicians should make a presumptive diagnosis of acute bacterial sinusitis when a child with an acute URI presents with the following:

- **Persistent illness, ie, nasal discharge (of any quality) or daytime cough or both lasting more than 10 days without improvement;**

OR

- **Worsening course, ie, worsening or new onset of nasal discharge, daytime cough, or fever after initial improvement;**

OR

- **Severe onset, ie, concurrent fever (temperature ≥39°C/102.2°F) and purulent nasal discharge for at least 3 consecutive days (Evidence Quality: B; Recommendation).**

KAS Profile 1

Aggregate evidence quality: B	
Benefit	Diagnosis allows decisions regarding management to be made. Children likely to benefit from antimicrobial therapy will be identified.
Harm	Inappropriate diagnosis may lead to unnecessary treatment. A missed diagnosis may lead to persistent infection or complications
Cost	Inappropriate diagnosis may lead to unnecessary cost of antibiotics. A missed diagnosis leads to cost of persistent illness (loss of time from school and work) or cost of caring for complications.
Benefits-harm assessment	Preponderance of benefit.
Value judgments	None.
Role of patient preference	Limited.
Intentional vagueness	None.
Exclusions	Children aged <1 year or older than 18 years and with underlying conditions.
Strength	Recommendation.

TABLE 1 Guideline Definitions for Evidence-Based Statements

Statement	Definition	Implication
Strong recommendation	A strong recommendation in favor of a particular action is made when the anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting evidence is excellent. In some clearly identified circumstances, strong recommendations may be made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation in favor of a particular action is made when the anticipated benefits exceed the harms but the quality of evidence is not as strong. Again, in some clearly identified circumstances, recommendations may be made when high-quality evidence is impossible to obtain but the anticipated benefits outweigh the harms.	Clinicians would be prudent to follow a recommendation, but should remain alert to new information and sensitive to patient preferences.
Option	Options define courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to one approach over another.	Clinicians should consider the option in their decision-making, and patient preference may have a substantial role.
No recommendation	No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear.	Clinicians should be alert to new published evidence that clarifies the balance of benefit versus harm.

The purpose of this action statement is to guide the practitioner in making a diagnosis of acute bacterial sinusitis on the basis of stringent clinical criteria. To develop criteria to be used in distinguishing episodes of acute bacterial sinusitis from other common respiratory infections, it is helpful to describe the features of an uncomplicated viral URI. Viral URIs are usually characterized by nasal symptoms (discharge and congestion/obstruction) or cough or both. Most often, the nasal discharge begins as clear and watery. Often, however, the quality of nasal discharge changes during the course of the illness. Typically, the nasal discharge becomes thicker and more mucoid and may become purulent (thick, colored, and opaque) for several days. Then the situation reverses, with the purulent discharge becoming mucoid and then clear again or simply resolving. The transition from clear to purulent to clear again occurs in uncomplicated viral URIs without the use of antimicrobial therapy.

Fever, when present in uncomplicated viral URI, tends to occur early in the illness, often in concert with other constitutional symptoms such as headache and myalgias. Typically, the fever and constitutional symptoms disappear in the first 24 to 48 hours, and the respiratory symptoms become more prominent (Fig 2).

The course of most uncomplicated viral URIs is 5 to 7 days.[9–12] As shown in Fig 2, respiratory symptoms usually peak in severity by days 3 to 6 and then begin to improve; however, resolving symptoms and signs may persist in some patients after day 10.[9,10]

Symptoms of acute bacterial sinusitis and uncomplicated viral URI overlap considerably, and therefore it is their persistence without improvement that suggests a diagnosis of acute sinusitis.[9,10,13] Such symptoms include nasal discharge (of any quality: thick or thin, serous, mucoid, or purulent) or daytime cough (which may be worse at night) or both. Bad breath, fatigue, headache, and decreased appetite, although common, are not specific indicators of acute sinusitis.[14] Physical examination findings are also not particularly helpful in distinguishing sinusitis from uncomplicated URIs. Erythema and swelling of the nasal turbinates are nonspecific findings.[14] Percussion of the sinuses is not useful. Transillumination of the sinuses is difficult to perform correctly in children and has been shown to be unreliable.[15,16] Nasopharyngeal cultures do not reliably predict the etiology of acute bacterial sinusitis.[14,16]

Only a minority (~6%–7%) of children presenting with symptoms of URI will meet criteria for persistence.[3,4,11] As a result, before diagnosing acute bacterial sinusitis, it is important for the practitioner to attempt to (1) differentiate between sequential episodes of uncomplicated viral URI (which may seem to coalesce in the mind of the patient or parent) from the onset of acute bacterial sinusitis with persistent symptoms and (2) establish whether the symptoms are clearly not improving.

A worsening course of signs and symptoms, termed "double sickening," in the context of a viral URI is another presentation of acute bacterial sinusitis.[13,17] Affected children experience substantial and acute worsening of respiratory symptoms (nasal discharge or nasal congestion or daytime cough) or a new fever, often on the sixth or seventh day of illness, after initial signs of recovery from an uncomplicated viral URI. Support for this definition comes from studies in children and adults, for whom antibiotic treatment of worsening symptoms after a period of apparent improvement was associated with better outcomes.[4]

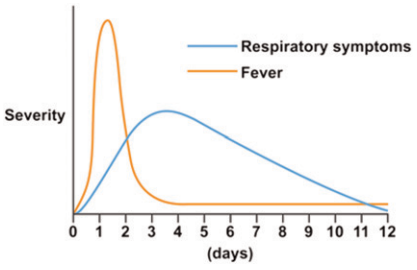

FIGURE 2
Uncomplicated viral URI.

Finally, some children with acute bacterial sinusitis may present with severe onset, ie, concurrent high fever (temperature >39°C) and purulent nasal discharge. These children usually are ill appearing and need to be distinguished from children with uncomplicated viral infections that are unusually severe. If fever is present in uncomplicated viral URIs, it tends to be present early in the illness, usually accompanied by other constitutional symptoms, such as headache and myalgia.[9,13,18] Generally, the constitutional symptoms resolve in the first 48 hours and then the respiratory symptoms become prominent. In most uncomplicated viral infections, including influenza, purulent nasal discharge does not appear for several days. Accordingly, it is the concurrent presentation of high fever and purulent nasal discharge for the first 3 to 4 days of an acute URI that helps to define the severe onset of acute bacterial sinusitis.[13,16,18] This presentation in children is the corollary to acute onset of headache, fever, and facial pain in adults with acute sinusitis.

Allergic and nonallergic rhinitis are predisposing causes of some cases of acute bacterial sinusitis in childhood. In addition, at their onset, these conditions may be mistaken for acute bacterial sinusitis. A family history of atopic conditions, seasonal occurrences, or occurrences with exposure to common allergens and other

allergic diatheses in the index patient (eczema, atopic dermatitis, asthma) may suggest the presence of noninfectious rhinitis. The patient may have complaints of pruritic eyes and nasal mucosa, which will provide a clue to the likely etiology of the condition. On physical examination, there may be a prominent nasal crease, allergic shiners, cobblestoning of the conjunctiva or pharyngeal wall, or pale nasal mucosa as other indicators of the diagnosis.

Key Action Statement 2A

Clinicians should not obtain imaging studies (plain films, contrast-enhanced computed tomography [CT], MRI, or ultrasonography) to distinguish acute bacterial sinusitis from viral URI (Evidence Quality: B; Strong Recommendation).

KAS Profile 2A

Aggregate evidence quality: B; overwhelmingly consistent evidence from observational studies.

Benefit	Avoids exposure to radiation and costs of studies. Avoids unnecessary therapy for false-positive diagnoses.
Harm	None.
Cost	Avoids cost of imaging.
Benefits-harm assessment	Exclusive benefit.
Value judgments	Concern for unnecessary radiation and costs.
Role of patient preference	Limited. Parents may value a negative study and avoidance of antibiotics as worthy of radiation but panel disagrees.
Intentional vagueness	None.
Exclusions	Patients with complications of sinusitis.
Strength	Strong recommendation.

The purpose of this key action statement is to discourage the practitioner from obtaining imaging studies in children with uncomplicated acute bacterial sinusitis. As emphasized in Key Action Statement 1, acute bacterial sinusitis in children is a diagnosis that is made on the basis of stringent clinical criteria that describe signs, symptoms, and temporal patterns of a URI. Although historically imaging has been used as a confirmatory or diagnostic modality in children suspected to have acute bacterial sinusitis, it is no longer recommended.

The membranes that line the nose are continuous with the membranes (mucosa) that line the sinus cavities, the middle ear, the nasopharynx, and the oropharynx. When an individual experiences a viral URI, there is inflammation of the nasal mucosa and, often, the mucosa of the middle ear and paranasal sinuses as well. The continuity of the mucosa of the upper respiratory tract is responsible for the controversy regarding the usefulness of images of the paranasal sinuses in contributing to a diagnosis of acute bacterial sinusitis.

As early as the 1940s, observations were made regarding the frequency of abnormal sinus radiographs in healthy children without signs or symptoms of current respiratory disease.[19] In addition, several investigators in the 1970s and 1980s observed that children with uncomplicated viral URI had frequent abnormalities of the paranasal sinuses on plain radiographs.[20–22] These abnormalities were the same as those considered to be diagnostic of acute bacterial sinusitis (diffuse opacification, mucosal swelling of at least 4 mm, or an air-fluid level).[16]

As technology advanced and CT scanning of the central nervous system and skull became prevalent, several studies reported on incidental abnormalities of the paranasal sinuses that were observed in children.[23,24] Gwaltney et al[25] showed striking abnormalities (including air-fluid levels) in sinus CT scans of young adults with uncomplicated colds. Manning et al[26] evaluated children undergoing either CT or MRI of the head for indications other than respiratory complaints or suspected sinusitis. Each patient underwent rhinoscopy and otoscopy before imaging and each patient's parent was asked to fill out a questionnaire regarding recent symptoms of URI. Sixty-two percent of patients overall had physical findings or history consistent with an upper respiratory inflammatory process, and 55% of the total group showed some abnormalities on sinus imaging; 33% showed pronounced mucosal thickening or an air-fluid level. Gordts et al[27] made similar observations in children undergoing MRI. Finally, Kristo et al[28] performed MRI in children with URIs and confirmed the high frequency (68%) of major abnormalities seen in the paranasal sinuses.

In summary, when the paranasal sinuses are imaged, either with plain radiographs, contrast-enhanced CT, or MRI in children with uncomplicated URI, the majority of studies will be significantly abnormal with the same kind of findings that are associated with bacterial infection of the sinuses. Accordingly, although normal radiographs or CT or MRI results can ensure that a patient with respiratory symptoms does not have acute bacterial sinusitis, an abnormal image cannot confirm the diagnosis. Therefore, it is not necessary to perform imaging in children with uncomplicated episodes of clinical sinusitis. Similarly, the high likelihood of an abnormal imaging result in a child with an uncomplicated URI indicates that radiographic studies

not be performed in an attempt to eliminate the diagnosis of sinusitis.

Key Action Statement 2B

Clinicians should obtain a contrast-enhanced CT scan of the paranasal sinuses and/or an MRI with contrast whenever a child is suspected of having orbital or central nervous system complications of acute bacterial sinusitis (Evidence Quality: B; Strong Recommendation).

KAS Profile 2B

Aggregate evidence quality: B; overwhelmingly consistent evidence from observational studies.	
Benefit	Determine presence of abscesses, which may require surgical intervention; avoid sequelae because of appropriate aggressive management.
Harm	Exposure to ionizing radiation for CT scans; need for sedation for MRI.
Cost	Direct cost of studies.
Benefits-harm assessment	Preponderance of benefit.
Value judgments	Concern for significant complication that may be unrecognized and, therefore, not treated appropriately.
Role of patient preference	Limited.
Intentional vagueness	None.
Exclusions	None.
Strength	Strong recommendation.

The purpose of this key action statement is to have the clinician obtain contrast-enhanced CT images when children are suspected of having serious complications of acute bacterial sinusitis. The most common complication of acute sinusitis involves the orbit in children with ethmoid sinusitis who are younger than 5 years.[29–31] Orbital complications should be suspected when the child presents with a swollen eye, especially if accompanied by proptosis or impaired function of the extraocular muscles. Orbital complications of acute sinusitis have been divided into 5 categories: sympathetic effusion, subperiosteal abscess, orbital cellulitis, orbital abscess, and cavernous sinus thrombosis.[32] Although sympathetic effusion (inflammatory edema) is categorized as an orbital complication, the site of infection remains confined to the sinus cavities; eye swelling is attributable to the impedance of venous drainage secondary to congestion within the ethmoid sinuses. Alternative terms for sympathetic effusion (inflammatory edema) are preseptal or periorbital cellulitis. The remaining "true" orbital complications are best visualized by contrast-enhanced CT scanning.

Intracranial complications of acute sinusitis, which are substantially less common than orbital complications, are more serious, with higher morbidity and mortality than those involving the orbit. Intracranial complications should be suspected in the patient who presents with a very severe headache, photophobia, seizures, or other focal neurologic findings. Intracranial complications include subdural empyema, epidural empyema, venous thrombosis, brain abscess, and meningitis.[29] Typically, patients with intracranial complications of acute bacterial sinusitis are previously healthy adolescent males with frontal sinusitis.[33,34]

There have been no head-to-head comparisons of the diagnostic accuracy of contrast-enhanced CT scanning to MRI with contrast in the evaluation of orbital and intracranial complications of sinusitis in children. In general, the contrast-enhanced CT scan has been the preferred imaging study when complications of sinusitis are suspected.[35,36] However, there are documented cases in which a contrast-enhanced CT scan has not revealed the abnormality responsible for the clinical presentation and the MRI with contrast has, especially for intracranial complications and rarely for orbital complications.[37,38] Accordingly, the most recent appropriateness criteria from the American College of Radiology endorse both MRI with contrast and contrast-enhanced CT as complementary examinations when evaluating potential complications of sinusitis.[35] The availability and speed of obtaining the contrast-enhanced CT are desirable; however, there is increasing concern regarding exposure to radiation. The MRI, although very sensitive, takes longer than the contrast-enhanced CT and often requires sedation in young children (which carries its own risks). In older children and adolescents who may not require sedation, MRI with contrast, if available, may be preferred when intracranial complications are likely. Furthermore, MRI with contrast should be performed when there is persistent clinical concern or incomplete information has been provided by the contrast-enhanced CT scan.

Key Action Statement 3

Initial Management of Acute Bacterial Sinusitis

3A: "Severe onset and worsening course" acute bacterial sinusitis. The clinician should prescribe antibiotic therapy for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms, or both) (Evidence Quality: B; Strong Recommendation).

KAS Profile 3A

Aggregate evidence quality: B; randomized controlled trials with limitations.	
Benefit	Increase clinical cures, shorten illness duration, and may prevent suppurative complications in a high-risk patient population.
Harm	Adverse effects of antibiotics.
Cost	Direct cost of therapy.
Benefits-harm assessment	Preponderance of benefit.
Value judgments	Concern for morbidity and possible complications if untreated.
Role of patient preference	Limited.
Intentional vagueness	None.
Exclusions	None.
Strength	Strong recommendation.

3B: "Persistent illness." The clinician should either prescribe antibiotic therapy OR offer additional outpatient observation for 3 days to children with persistent illness (nasal discharge of any quality or cough or both for at least 10 days without evidence of improvement) (Evidence Quality: B; Recommendation).

The purpose of this section is to offer guidance on initial management of persistent illness sinusitis by helping clinicians choose between the following 2 strategies:

1. Antibiotic therapy, defined as initial treatment of acute bacterial sinusitis with antibiotics, with the intent of starting antibiotic therapy as soon as possible after the encounter.
2. Additional outpatient observation, defined as initial management of acute bacterial sinusitis limited to continued observation for 3 days, with commencement of antibiotic therapy if either the child does not improve clinically within several days of diagnosis or if there is clinical worsening of the child's condition at any time.

KAS Profile 3B

Aggregate evidence quality: B; randomized controlled trials with limitations.	
Benefit	Antibiotics increase the chance of improvement or cure at 10 to 14 days (number needed to treat, 3–5); additional observation may avoid the use of antibiotics with attendant cost and adverse effects.
Harm	Antibiotics have adverse effects (number needed to harm, 3) and may increase bacterial resistance. Observation may prolong illness and delay start of needed antibiotic therapy.
Cost	Direct cost of antibiotics as well as cost of adverse reactions; indirect costs of delayed recovery when observation is used.
Benefits-harm assessment	Preponderance of benefit (because both antibiotic therapy and additional observation with rescue antibiotic, if needed, are appropriate management).
Value judgments	Role for additional brief observation period for selected children with persistent illness sinusitis, similar to what is recommended for acute otitis media, despite the lack of randomized trials specifically comparing additional observation with immediate antibiotic therapy and longer duration of illness before presentation.
Role of patient preference	Substantial role in shared decision-making that should incorporate illness severity, child's quality of life, and caregiver values and concerns.
Intentional vagueness	None.
Exclusions	Children who are excluded from randomized clinical trials of acute bacterial sinusitis, as defined in the text.
Strength	Recommendation.

In contrast to the 2001 AAP guideline,[5] which recommended antibiotic therapy for all children diagnosed with acute bacterial sinusitis, this guideline allows for additional observation of children presenting with persistent illness (nasal discharge of any quality or daytime cough or both for at least 10 days without evidence of improvement). In both guidelines, however, children presenting with severe or worsening illness (which was not defined explicitly in the 2001 guideline[5]) are to receive antibiotic therapy. The rationale for this approach (Table 2) is discussed below.

Antibiotic Therapy for Acute Bacterial Sinusitis

In the United States, antibiotics are prescribed for 82% of children with acute sinusitis.[39] The rationale for antibiotic therapy of acute bacterial sinusitis is based on the recovery of bacteria in high density ($\geq 10^4$ colony-forming units/mL) in 70% of maxillary sinus aspirates obtained from children with a clinical syndrome characterized by persistent nasal discharge, daytime cough, or both.[16,40] Children who present with severe-onset acute bacterial sinusitis are presumed to have bacterial infection, because a temperature of at least 39°C/102.2°F coexisting for at least 3 consecutive days with purulent nasal discharge is not consistent with the well-documented pattern of acute viral URI. Similarly, children with worsening-course acute bacterial sinusitis have a clinical course that is also not consistent with the steady improvement that characterizes an uncomplicated viral URI.[9,10]

Three RCTs have compared antibiotic therapy with placebo for the initial management of acute bacterial sinusitis in children. Two trials by Wald et al[4,41] found an increase in cure or improvement after antibiotic therapy compared with placebo with a number needed to treat of 3 to 5 children. Most children in these studies had persistent acute bacterial sinusitis, but children with severe or worsening illness were also included. Conversely, Garbutt et al,[42] who studied only children with persistent acute bacterial sinusitis, found no difference in outcomes for antibiotic versus placebo. Another RCT by Kristo et al,[43] often cited as showing no benefit from antibiotics for acute bacterial sinusitis, will not be considered further because of methodologic flaws, including weak entry criteria and inadequate dosing of antibiotic treatment.

The guideline recommends antibiotic therapy for severe or worsening acute bacterial sinusitis because of the benefits revealed in RCTs[4,41] and a theoretically higher risk of suppurative complications than for children who present with persistent symptoms. Orbital and intracranial complications of acute bacterial sinusitis have not been observed in RCTs, even when placebo was administered; however, sample sizes have inadequate power to preclude an increased risk. This risk, however, has caused some investigators to exclude children with severe acute bacterial sinusitis from trial entry.[42]

Additional Observation for Persistent Onset Acute Bacterial Sinusitis

The guideline recommends either antibiotic therapy or an additional brief period of observation as initial management strategies for children with persistent acute bacterial sinusitis because, although there are benefits to antibiotic therapy (number needed to treat, 3–5), some children improve on their own, and the risk of suppurative complications is low.[4,41] Symptoms of persistent acute bacterial sinusitis may be mild and have varying effects on a given child's quality of life, ranging from slight (mild cough, nasal discharge) to significant (sleep disturbance, behavioral changes, school or child care absenteeism). The benefits of antibiotic therapy in some trials[4,41] must also be balanced against an increased risk of adverse events (number need to harm, 3), most often self-limited diarrhea, but also including occasional rash.[4]

Choosing between antibiotic therapy or additional observation for initial management of persistent illness sinusitis presents an opportunity for shared decision-making with families (Table 2). Factors that might influence this decision include symptom severity, the child's quality of life, recent antibiotic use, previous experience or outcomes with acute bacterial sinusitis, cost of antibiotics, ease of administration, caregiver concerns about potential adverse effects of antibiotics, persistence of respiratory symptoms, or development of complications. Values and preferences expressed by the caregiver should be taken into consideration (Table 3).

Children with persistent acute bacterial sinusitis who received antibiotic therapy in the previous 4 weeks, those with concurrent bacterial infection (eg, pneumonia, suppurative cervical adenitis, group A streptococcal pharyngitis, or acute otitis media), those with actual or suspected complications of acute bacterial sinusitis, or those with underlying conditions should generally be managed with antibiotic therapy. The latter group includes children with asthma, cystic fibrosis, immunodeficiency, previous sinus surgery, or anatomic abnormalities of the upper respiratory tract.

Limiting antibiotic use in children with persistent acute bacterial sinusitis who may improve on their own reduces common antibiotic-related adverse events, such as diarrhea, diaper dermatitis, and skin rash. The most recent RCT of acute bacterial sinusitis in children[4] found adverse events of 44% with antibiotic and 14% with placebo.

Limiting antibiotics may also reduce the prevalence of resistant bacterial pathogens. Although this is always a desirable goal, no increase in resistant bacterial species was observed within the group of children treated with a single course of antimicrobial agents (compared with those receiving placebo) in 2 recent large studies of antibiotic versus placebo for children with acute otitis media.[44,45]

Key Action Statement 4

Clinicians should prescribe amoxicillin with or without clavulanate as first-line treatment when a decision has been made to initiate antibiotic treatment of acute bacterial sinusitis (Evidence Quality: B; Recommendation).

KAS Profile 4

Aggregate evidence quality: B; randomized controlled trials with limitations.

Benefit	Increase clinical cures with narrowest spectrum drug; stepwise increase in broadening spectrum as risk factors for resistance increase.
Harm	Adverse effects of antibiotics including development of hypersensitivity.
Cost	Direct cost of antibiotic therapy.
Benefits-harm assessment	Preponderance of benefit.
Value judgments	Concerns for not encouraging resistance if possible.
Role of patient preference	Potential for shared decision-making that should incorporate the caregiver's experiences and values.
Intentional vagueness	None.
Exclusions	May include allergy or intolerance.
Strength	Recommendation.

TABLE 2 Recommendations for Initial Use of Antibiotics for Acute Bacterial Sinusitis

Clinical Presentation	Severe Acute Bacterial Sinusitis[a]	Worsening Acute Bacterial Sinusitis[b]	Persistent Acute Bacterial Sinusitis[c]
Uncomplicated acute bacterial sinusitis without coexisting illness	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation for 3 days[d]
Acute bacterial sinusitis with orbital or intracranial complications	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy
Acute bacterial sinusitis with coexisting acute otitis media, pneumonia, adenitis, or streptococcal pharyngitis	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy

[a] Defined as temperature ≥39°C and purulent (thick, colored, and opaque) nasal discharge present concurrently for at least 3 consecutive days.

[b] Defined as nasal discharge or daytime cough with sudden worsening of symptoms (manifested by new-onset fever ≥38°C/100.4°F or substantial increase in nasal discharge or cough) after having experienced transient improvement of symptoms.

[c] Defined as nasal discharge (of any quality), daytime cough (which may be worse at night), or both, persisting for >10 days without improvement.

[d] Opportunity for shared decision-making with the child's family; if observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens at any time or fails to improve within 3 days of observation.

The purpose of this key action statement is to guide the selection of antimicrobial therapy once the diagnosis of acute bacterial sinusitis has been made. The microbiology of acute bacterial sinusitis was determined nearly 30 years ago through direct maxillary sinus aspiration in children with compatible signs and symptoms. The major bacterial pathogens recovered at that time were *Streptococcus pneumoniae* in approximately 30% of children and nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis* in approximately 20% each.[16,40] Aspirates from the remaining 25% to 30% of children were sterile.

Maxillary sinus aspiration is rarely performed at the present time unless the course of the infection is unusually prolonged or severe. Although some authorities have recommended obtaining cultures from the middle meatus to determine the cause of a maxillary sinus infection, there are no data in children with acute bacterial sinusitis that have compared such cultures with cultures of a maxillary sinus aspirate. Furthermore, there are data indicating that the middle meatus in healthy children is commonly colonized with *S pneumoniae*, *H influenzae*, and *M catarrhalis*.[46]

Recent estimates of the microbiology of acute sinusitis have, of necessity, been based primarily on that of acute otitis media (AOM), a condition with relatively easy access to infective fluid through performance of tympanocentesis and one with a similar pathogenesis to acute bacterial sinusitis.[47,48] The 3 most common bacterial pathogens recovered from the middle ear fluid of children with AOM are the same as those that have been associated with acute bacterial sinusitis: *S pneumoniae*, nontypeable *H influenzae*, and *M catarrhalis*.[49] The proportion of each has varied from study to study depending on criteria used for diagnosis of AOM, patient characteristics, and bacteriologic techniques. Recommendations since the year 2000 for the routine use in infants of 7-valent and, more recently, 13-valent pneumococcal conjugate vaccine (PCV-13) have been associated with a decrease in recovery of *S pneumoniae* from ear fluid of children with AOM and a relative increase in the incidence of infections attributable to *H influenzae*.[50] Thus, on the basis of the proportions of bacteria found in middle ear infections, it is estimated that *S pneumoniae* and *H influenzae* are currently each responsible for approximately 30% of cases of acute bacterial sinusitis in children, and *M catarrhalis* is responsible for approximately 10%. These percentages are contingent on the assumption that approximately one-quarter of aspirates of maxillary sinusitis would still be sterile, as reported in earlier studies. *Staphylococcus aureus* is rarely isolated from sinus aspirates in children with acute bacterial sinusitis, and with the exception of acute maxillary sinusitis associated with infections of dental origin,[51] respiratory anaerobes are also rarely recovered.[40,52] Although *S aureus* is a very infrequent cause of acute bacterial sinusitis in children, it is a significant pathogen in the orbital and intracranial complications of sinusitis. The reasons for this discrepancy are unknown.

Antimicrobial susceptibility patterns for *S pneumoniae* vary considerably from community to community. Isolates obtained from surveillance centers nationwide indicate that, at the present time, 10% to 15% of upper respiratory tract isolates of *S pneumoniae* are nonsusceptible to penicillin[53,54]; however, values for penicillin nonsusceptibility as high as 50% to 60% have been reported in some areas.[55,56] Of the organisms that are resistant, approximately half are highly resistant to penicillin and the remaining half are intermediate in resistance.[53,54,56–59] Between 10% and 42% of *H influenzae*[56–59] and close to 100% of *M catarrhalis* are likely to be β-lactamase positive and nonsusceptible to amoxicillin. Because of dramatic geographic variability in the prevalence of β-lactamase–positive *H influenzae*, it is extremely desirable for the practitioner to be familiar with local patterns of susceptibility. Risk factors for the presence of organisms

likely to be resistant to amoxicillin include attendance at child care, receipt of antimicrobial treatment within the previous 30 days, and age younger than 2 years.[50,55,60]

Amoxicillin remains the antimicrobial agent of choice for first-line treatment of uncomplicated acute bacterial sinusitis in situations in which antimicrobial resistance is not suspected. This recommendation is based on amoxicillin's effectiveness, safety, acceptable taste, low cost, and relatively narrow microbiologic spectrum. For children aged 2 years or older with uncomplicated acute bacterial sinusitis that is mild to moderate in degree of severity who do not attend child care and who have not been treated with an antimicrobial agent within the last 4 weeks, amoxicillin is recommended at a standard dose of 45 mg/kg per day in 2 divided doses. In communities with a high prevalence of nonsusceptible *S pneumoniae* (>10%, including intermediate- and high-level resistance), treatment may be initiated at 80 to 90 mg/kg per day in 2 divided doses, with a maximum of 2 g per dose.[55] This high-dose amoxicillin therapy is likely to achieve sinus fluid concentrations that are adequate to overcome the resistance of *S pneumoniae,* which is attributable to alteration in penicillin-binding proteins on the basis of data derived from patients with AOM.[61] If, within the next several years after licensure of PCV-13, a continuing decrease in isolates of *S pneumoniae* (including a decrease in isolates of nonsusceptible *S pneumoniae)* and an increase in β-lactamase–producing *H influenzae* are observed, standard-dose amoxicillin-clavulanate (45 mg/kg per day) may be most appropriate.

Patients presenting with moderate to severe illness as well as those younger than 2 years, attending child care, or who have recently been treated with an antimicrobial may receive high-dose amoxicillin-clavulanate (80–90 mg/kg per day of the amoxicillin component with 6.4 mg/kg per day of clavulanate in 2 divided doses with a maximum of 2 g per dose). The potassium clavulanate levels are adequate to inhibit all β-lactamase–producing *H influenzae* and *M catarrhalis*.[56,59]

A single 50-mg/kg dose of ceftriaxone, given either intravenously or intramuscularly, can be used for children who are vomiting, unable to tolerate oral medication, or unlikely to be adherent to the initial doses of antibiotic.[62–64] The 3 major bacterial pathogens involved in acute bacterial sinusitis are susceptible to ceftriaxone in 95% to 100% of cases.[56,58,59] If clinical improvement is observed at 24 hours, an oral antibiotic can be substituted to complete the course of therapy. Children who are still significantly febrile or symptomatic at 24 hours may require additional parenteral doses before switching to oral therapy.

The treatment of patients with presumed allergy to penicillin has been controversial. However, recent publications indicate that the risk of a serious allergic reaction to second- and third-generation cephalosporins in patients with penicillin or amoxicillin allergy appears to be almost nil and no greater than the risk among patients without such allergy.[65–67] Thus, patients allergic to amoxicillin with a non–type 1 (late or delayed, >72 hours) hypersensitivity reaction can safely be treated with cefdinir, cefuroxime, or cefpodoxime.[66–68] Patients with a history of a serious type 1 immediate or accelerated (anaphylactoid) reaction to amoxicillin can also safely be treated with cefdinir, cefuroxime, or cefpodoxime. In both circumstances, clinicians may wish to determine individual tolerance by referral to an allergist for penicillin and/or cephalosporin skin-testing before initiation of therapy.[66–68] The susceptibility of *S pneumoniae* to cefdinir, cefpodoxime, and cefuroxime varies from 60% to 75%,[56–59] and the susceptibility of *H influenzae* to these agents varies from 85% to 100%.[56,58] In young children (<2 years) with a serious type 1 hypersensitivity to penicillin and moderate or more severe sinusitis, it may be prudent to use a combination of clindamycin (or linezolid) and cefixime to achieve the most comprehensive coverage against both resistant *S pneumoniae* and *H influenzae*. Linezolid has excellent activity against all *S pneumoniae*, including penicillin-resistant strains, but lacks activity against *H influenzae* and *M catarrhalis*. Alternatively, a quinolone, such as levofloxacin, which has a high level of activity against both *S pneumoniae* and *H influenzae*, may be prescribed.[57,58] Although the use of quinolones is usually restricted because of concerns for toxicity, cost, and emerging resistance, their use in this circumstance can be justified.

Pneumococcal and *H influenzae* surveillance studies have indicated that resistance of these organisms to trimethoprim-sulfamethoxazole and azithromycin is sufficient to preclude their use for treatment of acute bacterial sinusitis in patients with penicillin hypersensitivity.[56,58,59,69]

The optimal duration of antimicrobial therapy for patients with acute bacterial sinusitis has not received systematic study. Recommendations based on clinical observations have varied widely, from 10 to 28 days of treatment. An alternative suggestion has been made that antibiotic therapy be continued for 7 days after the patient becomes free of signs and symptoms.[5] This strategy has the advantage of individualizing the treatment of each patient, results in a minimum course of 10 days, and

avoids prolonged antimicrobial therapy in patients who are asymptomatic and therefore unlikely to adhere to the full course of treatment.[5]

Patients who are acutely ill and appear toxic when first seen (see below) can be managed with 1 of 2 options. Consultation can be requested from an otolaryngologist for consideration of maxillary sinus aspiration (with appropriate analgesia/anesthesia) to obtain a sample of sinus secretions for Gram stain, culture, and susceptibility testing so that antimicrobial therapy can be adjusted precisely. Alternatively, inpatient therapy can be initiated with intravenous cefotaxime or ceftriaxone, with referral to an otolaryngologist if the patient's condition worsens or fails to show improvement within 48 hours. If a complication is suspected, management will differ depending on the site and severity.

A recent guideline was published by the Infectious Diseases Society of America for acute bacterial rhinosinusitis in children and adults.[70] Their recommendation for initial empirical antimicrobial therapy for acute bacterial sinusitis in children was amoxicillin-clavulanate based on the concern that there is an increasing prevalence of *H influenzae* as a cause of sinusitis since introduction of the pneumococcal conjugate vaccines and an increasing prevalence of β-lactamase production among these strains. In contrast, this guideline from the AAP allows either amoxicillin or amoxicillin-clavulanate as first-line empirical therapy and is therefore inclusive of the Infectious Diseases Society of America's recommendation. Unfortunately, there are scant data available regarding the precise microbiology of acute bacterial sinusitis in the post–PCV-13 era. Prospective surveillance of nasopharyngeal cultures may be helpful in completely aligning these recommendations in the future.

Key Action Statement 5A

Clinicians should reassess initial management if there is either a caregiver report of worsening (progression of initial signs/symptoms or appearance of new signs/symptoms) OR failure to improve (lack of reduction in all presenting signs/symptoms) within 72 hours of initial management (Evidence Quality: C; Recommendation).

KAS Profile 5A

Aggregate evidence quality: C; observational studies	
Benefits	Identification of patients who may have been misdiagnosed, those at risk of complications, and those who require a change in management.
Harm	Delay of up to 72 hours in changing therapy if patient fails to improve.
Cost	Additional provider and caregiver time and resources.
Benefits-harm assessment	Preponderance of benefit.
Value judgments	Use of 72 hours to assess progress may result in excessive classification as treatment failures if premature; emphasis on importance of worsening illness in defining treatment failures.
Role of patient preferences	Caregivers determine whether the severity of the patient's illness justifies the report to clinician of the patient's worsening or failure to improve.
Intentional vagueness	None.
Exclusions	Patients with severe illness, poor general health, complicated sinusitis, immune deficiency, previous sinus surgery, or coexisting bacterial illness.
Strength	Recommendation.

The purpose of this key action statement is to ensure that patients with acute bacterial sinusitis who fail to improve symptomatically after initial management are reassessed to be certain that they have been correctly diagnosed and to consider initiation of alternate therapy to hasten resolution of symptoms and avoid complications. "Worsening" is defined as progression of presenting signs or symptoms of acute bacterial sinusitis or onset of new signs or symptoms. "Failure to improve" is lack of reduction in presenting signs or symptoms of acute bacterial sinusitis by 72 hours after diagnosis and initial management; patients with persistent but improving symptoms do not meet this definition.

The rationale for using 72 hours as the time to assess treatment failure for acute bacterial sinusitis is based on clinical outcomes in RCTs. Wald et al[41] found that 18 of 35 patients (51%) receiving placebo demonstrated symptomatic improvement within 3 days of initiation of treatment; only an additional 3 patients receiving placebo (9%) improved between days 3 and 10. In the same study, 48 of 58 patients (83%) receiving antibiotics were cured or improved within 3 days; at 10 days, the overall rate of improvement was 79%, suggesting that no additional patients improved between days 3 and 10. In a more recent study, 17 of 19 children who ultimately failed initial therapy with either antibiotic or placebo demonstrated failure to improve within 72 hours.[4] Although Garbutt et al[42] did not report the percentage of patients who improved by day 3, they did demonstrate that the majority of improvement in symptoms occurred within

the first 3 days of study entry whether they received active treatment or placebo.

Reporting of either worsening or failure to improve implies a shared responsibility between clinician and caregiver. Although the clinician should educate the caregiver regarding the anticipated reduction in symptoms within 3 days, it is incumbent on the caregiver to appropriately notify the clinician of concerns regarding worsening or failure to improve. Clinicians should emphasize the importance of reassessing those children whose symptoms are worsening whether or not antibiotic therapy was prescribed. Reassessment may be indicated before the 72-hour mark if the patient is substantially worse, because it may indicate the development of complications or a need for parenteral therapy. Conversely, in some cases, caregivers may think that symptoms are not severe enough to justify a change to an antibiotic with a less desirable safety profile or even the time, effort, and resources required for reassessment. Accordingly, the circumstances under which caregivers report back to the clinician and the process by which such reporting occurs should be discussed at the time the initial management strategy is determined.

Key Action Statement 5B

If the diagnosis of acute bacterial sinusitis is confirmed in a child with worsening symptoms or failure to improve in 72 hours, then clinicians may change the antibiotic therapy for the child initially managed with antibiotic OR initiate antibiotic treatment of the child initially managed with observation (Evidence Quality: D; Option based on expert opinion, case reports, and reasoning from first principles).

KAS Profile 5B

Aggregate evidence quality: D; expert opinion and reasoning from first principles.	
Benefit	Prevention of complications, administration of effective therapy.
Harm	Adverse effects of secondary antibiotic therapy.
Cost	Direct cost of medications, often substantial for second-line agents.
Benefits-harm assessment	Preponderance of benefit.
Value judgments	Clinician must determine whether cost and adverse effects associated with change in antibiotic is justified given the severity of illness.
Role of patient preferences	Limited in patients whose symptoms are severe or worsening, but caregivers of mildly affected children who are failing to improve may reasonably defer change in antibiotic.
Intentional vagueness	None.
Exclusions	None.
Strength	Option.

The purpose of this key action statement is to ensure optimal antimicrobial treatment of children with acute bacterial sinusitis whose symptoms worsen or fail to respond to the initial intervention to prevent complications and reduce symptom severity and duration (see Table 4).

Clinicians who are notified by a caregiver that a child's symptoms are worsening or failing to improve should confirm that the clinical diagnosis of acute bacterial sinusitis corresponds to the patient's pattern of illness, as defined in Key Action Statement 1. If caregivers report worsening of symptoms at any time in a patient for whom observation was the initial intervention, the clinician should begin treatment as discussed in Key Action Statement 4. For patients whose symptoms are mild and who have failed to improve but have not worsened, initiation of antimicrobial agents or continued observation (for up to 3 days) is reasonable.

If caregivers report worsening of symptoms after 3 days in a patient initially treated with antimicrobial agents, current signs and symptoms should be reviewed to determine whether acute bacterial sinusitis is still the best diagnosis. If sinusitis is still the best diagnosis, infection with drug-resistant bacteria is probable, and an alternate antimicrobial agent may be administered. Face-to-face reevaluation of the patient is desirable. Once the decision is made to change medications, the clinician should consider the limitations of the initial antibiotic coverage, the anticipated susceptibility of residual bacterial pathogens, and the ability of antibiotics to adequately penetrate the site of infection. Cultures of sinus or nasopharyngeal secretions in patients with initial antibiotic failure have identified a large percentage of bacteria with resistance to the original antibiotic.[71,72] Furthermore, multidrug-resistant *S pneumoniae* and β-lactamase–positive *H influenzae* and *M catarrhalis* are more commonly isolated after previous antibiotic exposure.[73–78] Unfortunately, there are no studies in children that have investigated the microbiology of treatment failure in acute bacterial sinusitis or cure rates using second-line antimicrobial agents. As a result, the likelihood of adequate antibiotic coverage for resistant organisms must be

addressed by extrapolations from studies of acute otitis media in children and sinusitis in adults and by using the results of data generated in vitro. A general guide to management of the child who worsens in 72 hours is shown in Table 4.

NO RECOMMENDATION

Adjuvant Therapy

Potential adjuvant therapy for acute sinusitis might include intranasal corticosteroids, saline nasal irrigation or lavage, topical or oral decongestants, mucolytics, and topical or oral antihistamines. A recent Cochrane review on decongestants, antihistamines, and nasal irrigation for acute sinusitis in children found no appropriately designed studies to determine the effectiveness of these interventions.[79]

Intranasal Steroids

The rationale for the use of intranasal corticosteroids in acute bacterial sinusitis is that an antiinflammatory agent may reduce the swelling around the sinus ostia and encourage drainage, thereby hastening recovery. However, there are limited data on how much inflammation is present, whether the inflammation is responsive to steroids, and whether there are differences in responsivity according to age. Nonetheless, there are several RCTs in adolescents and adults, most of which do show significant differences compared with placebo or active comparator that favor intranasal steroids in the reduction of symptoms and the patient's global assessment of overall improvement.[80–85] Several studies in adults with acute bacterial sinusitis provide data supporting the use of intranasal steroids as either monotherapy or adjuvant therapy to antibiotics.[81,86] Only one study did not show efficacy.[85]

There have been 2 trials of intranasal steroids performed exclusively in children: one comparing intranasal corticosteroids versus an oral decongestant[87] and the other comparing intranasal corticosteroids with placebo.[88] These studies showed a greater rate of complete resolution[87] or greater reduction in symptoms in patients receiving the steroid preparation, although the effects were modest.[88] It is important to note that nearly all of these studies (both those reported in children and adults) suffered from substantial methodologic problems. Examples of these methodologic problems are as follows: (1) variable inclusion criteria for sinusitis, (2) mixed populations of allergic and nonallergic subjects, and (3) different outcome criteria. All of these factors make deriving a clear conclusion difficult. Furthermore, the lack of stringent criteria in selecting the subject population increases the chance that the subjects had viral URIs or even persistent allergies rather than acute bacterial sinusitis.

The intranasal steroids studied to date include budesonide, flunisolide, fluticasone, and mometasone. There is no reason to believe that one steroid would be more effective than another, provided equivalent doses are used.

Potential harm in using nasal steroids in children with acute sinusitis includes the increased cost of therapy, difficulty in effectively administering nasal sprays in young children, nasal irritation and epistaxis, and potential systemic adverse effects of steroid use. Fortunately, no clinically significant steroid adverse effects have been discovered in studies in children.[89–96]

Saline Irrigation

Saline nasal irrigation or lavage (not saline nasal spray) has been used to remove debris from the nasal cavity and temporarily reduce tissue edema (hypertonic saline) to promote drainage from the sinuses. There have been very few RCTs using saline nasal irrigation or lavage in acute sinusitis, and these have had mixed results.[97,98] The 1 study in children showed greater improvement in nasal airflow and quality of life as well as a better rate of improvement in total symptom score when compared with placebo in patients treated with antibiotics and decongestants.[98] There are 2 Cochrane reviews published on the use of saline nasal irrigation in acute sinusitis in adults that showed variable results. One review published in 2007[99] concluded that it is a beneficial adjunct, but the other, published in 2010,[100] concluded that most trials were too small or contained too high a risk of bias to be confident about benefits.

Nasal Decongestants, Mucolytics, and Antihistamines

Data are insufficient to make any recommendations about the use of oral or topical nasal decongestants, mucolytics, or oral or nasal spray antihistamines as adjuvant therapy for acute bacterial sinusitis in children.[79] It is the opinion of the expert panel that antihistamines should not be used for the primary indication of acute bacterial sinusitis in any child, although such therapy might be helpful in reducing typical allergic symptoms in patients with atopy who also have acute sinusitis.

OTHER RELATED CONDITIONS

Recurrence of Acute Bacterial Sinusitis

Recurrent acute bacterial sinusitis (RABS) is an uncommon occurrence in healthy children and must be distinguished from recurrent URIs, exacerbations of allergic rhinitis, and chronic sinusitis. The former is defined by episodes of bacterial infection of the paranasal sinuses lasting fewer than 30 days and separated by intervals of

TABLE 3 Parent Information Regarding Initial Management of Acute Bacterial Sinusitis

How common are sinus infections in children?	Thick, colored, or cloudy mucus from your child's nose frequently occurs with a common cold or viral infection and does not by itself mean your child has sinusitis. In fact, fewer than 1 in 15 children get a true bacterial sinus infection during or after a common cold.
How can I tell if my child has bacterial sinusitis or simply a common cold?	Most colds have a runny nose with mucus that typically starts out clear, becomes cloudy or colored, and improves by about 10 d. Some colds will also include fever (temperature >38°C [100.4°F]) for 1 to 2 days. In contrast, acute bacterial sinusitis is likely when the pattern of illness is persistent, severe, or worsening. 1. *Persistent* sinusitis is the most common type, defined as runny nose (of any quality), daytime cough (which may be worse at night), or both for at least 10 days without improvement. 2. *Severe* sinusitis is present when fever (temperature ≥39°C [102.2°F]) lasts for at least 3 days in a row and is accompanied by nasal mucus that is thick, colored, or cloudy. 3. *Worsening* sinusitis starts with a viral cold, which begins to improve but then worsens when bacteria take over and cause new-onset fever (temperature ≥38°C [100.4°F]) or a substantial increase in daytime cough or runny nose.
If my child has sinusitis, should he or she take an antibiotic?	Children with *persistent* sinusitis may be managed with either an antibiotic or with an additional brief period of observation, allowing the child up to another 3 days to fight the infection and improve on his or her own. The choice to treat or observe should be discussed with your doctor and may be based on your child's quality of life and how much of a problem the sinusitis is causing. In contrast, all children diagnosed with *severe* or *worsening* sinusitis should start antibiotic treatment to help them recover faster and more often.
Why not give all children with acute bacterial sinusitis an immediate antibiotic?	Some episodes of *persistent* sinusitis include relatively mild symptoms that may improve on their own in a few days. In addition, antibiotics can have adverse effects, which may include vomiting, diarrhea, upset stomach, skin rash, allergic reactions, yeast infections, and development of resistant bacteria (that make future infections more difficult to treat).

at least 10 days during which the patient is asymptomatic. Some experts require at least 4 episodes in a calendar year to fulfill the criteria for this condition. Chronic sinusitis is manifest as 90 or more uninterrupted days of respiratory symptoms, such as cough, nasal discharge, or nasal obstruction.

Children with RABS should be evaluated for underlying allergies, particularly allergic rhinitis; quantitative and functional immunologic defect(s), chiefly immunoglobulin A and immunoglobulin G deficiency; cystic fibrosis; gastroesophageal reflux disease; or dysmotile cilia syndrome.[101] Anatomic abnormalities obstructing one or more sinus ostia may be present. These include septal deviation, nasal polyps, or concha bullosa (pneumatization of the middle turbinate); atypical ethmoid cells with compromised drainage; a lateralized middle turbinate; and intrinsic ostiomeatal anomalies.[102] Contrast-enhanced CT, MRI, or endoscopy or all 3 should be performed for detection of obstructive conditions, particularly in children with genetic or acquired craniofacial abnormalities.

The microbiology of RABS is similar to that of isolated episodes of acute bacterial sinusitis and warrants the same treatment.[72] It should be recognized that closely spaced sequential courses of antimicrobial therapy may foster the emergence of antibiotic-resistant bacterial species as the causative agent in recurrent episodes. There are no systematically evaluated options for prevention of RABS in children. In general, the use of prolonged prophylactic antimicrobial therapy should be avoided and is not usually recommended for children with recurrent acute otitis media. However, when there are no recognizable predisposing conditions to remedy in children with RABS, prophylactic antimicrobial agents may be used for several months during the respiratory season. Enthusiasm for this strategy is tempered by concerns regarding the encouragement of bacterial resistance. Accordingly, prophylaxis should only be considered in carefully selected children whose infections have been thoroughly documented.

Influenza vaccine should be administered annually, and PCV-13 should be administered at the recommended ages for all children, including those with RABS. Intranasal steroids and nonsedating antihistamines can be helpful for children with allergic rhinitis, as can antireflux medications for those with gastroesophageal reflux disease. Children with anatomic abnormalities may require endoscopic surgery for removal of or reduction in ostiomeatal obstruction.

The pathogenesis of chronic sinusitis is poorly understood and appears to be multifactorial; however, many of the conditions associated with RABS

TABLE 4 Management of Worsening or Lack of Improvement at 72 Hours

Initial Management	Worse in 72 Hours	Lack of Improvement in 72 Hours
Observation	Initiate amoxicillin with or without clavulanate	Additional observation or initiate antibiotic based on shared decision-making
Amoxicillin	High-dose amoxicillin-clavulanate	Additional observation or high-dose amoxicillin-clavulanate based on shared decision-making
High-dose amoxicillin-clavulanate	Clindamycin[a] and cefixime OR linezolid and cefixime OR levofloxacin	Continued high-dose amoxicillin-clavulanate OR clindamycin[a] and cefixime OR linezolid and cefixime OR levofloxacin

[a] Clindamycin is recommended to cover penicillin-resistant *S pneumoniae*. Some communities have high levels of clindamycin-resistant *S pneumoniae*. In these communities, linezolid is preferred.

have also been implicated in chronic sinusitis, and it is clear that there is an overlap between the 2 syndromes.[101,102] In some cases, there may be episodes of acute bacterial sinusitis superimposed on a chronic sinusitis, warranting antimicrobial therapy to hasten resolution of the acute infection.

Complications of Acute Bacterial Sinusitis

Complications of acute bacterial sinusitis should be diagnosed when the patient develops signs or symptoms of orbital and/or central nervous system (intracranial) involvement. Rarely, complicated acute bacterial sinusitis can result in permanent blindness, other neurologic sequelae, or death if not treated promptly and appropriately. Orbital complications have been classified by Chandler et al.[32] Intracranial complications include epidural or subdural abscess, brain abscess, venous thrombosis, and meningitis.

Periorbital and intraorbital inflammation and infection are the most common complications of acute sinusitis and most often are secondary to acute ethmoiditis in otherwise healthy young children. These disorders are commonly classified in relation to the orbital septum; periorbital or preseptal inflammation involves only the eyelid, whereas postseptal (intraorbital) inflammation involves structures of the orbit. Mild cases of preseptal cellulitis (eyelid <50% closed) may be treated on an outpatient basis with appropriate oral antibiotic therapy (high-dose amoxicillin-clavulanate for comprehensive coverage) for acute bacterial sinusitis and daily follow-up until definite improvement is noted. If the patient does not improve within 24 to 48 hours or if the infection is progressive, it is appropriate to admit the patient to the hospital for antimicrobial therapy. Similarly, if proptosis, impaired visual acuity, or impaired and/or painful extraocular mobility is present on examination, the patient should be hospitalized, and a contrast-enhanced CT should be performed. Consultation with an otolaryngologist, an ophthalmologist, and an infectious disease expert is appropriate for guidance regarding the need for surgical intervention and the selection of antimicrobial agents.

Intracranial complications are most frequently encountered in previously healthy adolescent males with frontal sinusitis.[33,34] In patients with altered mental status, severe headache, or Pott's puffy tumor (osteomyelitis of the frontal bone), neurosurgical consultation should be obtained. A contrast-enhanced CT scan (preferably coronal thin cut) of the head, orbits, and sinuses is essential to confirm intracranial or intraorbital suppurative complications; in such cases, intravenous antibiotics should be started immediately. Alternatively, an MRI may also be desirable in some cases of intracranial abnormality. Appropriate antimicrobial therapy for intraorbital complications include vancomycin (to cover possible methicillin-resistant *S aureus* or penicillin-resistant *S pneumoniae*) and either ceftriaxone, ampicillin-sulbactam, or piperacillin-tazobactam.[103] Given the polymicrobial nature of sinogenic abscesses, coverage for anaerobes (ie, metronidazole) should also be considered for intraorbital complications and should be started in all cases of intracranial complications if ceftriaxone is prescribed.

Patients with small orbital, subperiosteal, or epidural abscesses and minimal ocular and neurologic abnormalities may be managed with intravenous antibiotic treatment for 24 to 48 hours while performing frequent visual and mental status checks.[104] In patients who develop progressive signs and symptoms, such as impaired visual acuity, ophthalmoplegia, elevated intraocular pressure (>20 mm), severe proptosis (>5 mm), altered mental status, headache, or vomiting, as well as those who fail to improve within 24 to 48 hours while receiving antibiotics, prompt surgical intervention and drainage of the abscess should be undertaken.[104] Antibiotics can be tailored to the results of culture and sensitivity studies when they become available.

AREAS FOR FUTURE RESEARCH

Since the publication of the original guideline in 2001, only a small number of high-quality studies of the diagnosis and treatment of acute bacterial sinusitis in children have been published.[5] Ironically, the number of published guidelines on the topic (5) exceeds the number of prospective,

placebo-controlled clinical trials of either antibiotics or ancillary treatments of acute bacterial sinusitis. Thus, as was the case in 2001, there are scant data on which to base recommendations. Accordingly, areas for future research include the following:

Etiology

1. Reexamine the microbiology of acute sinusitis in children in the postpneumococcal conjugate vaccine era and determine the value of using newer polymerase chain reaction–based respiratory testing to document viral, bacterial, and polymicrobial disease.
2. Correlate cultures obtained from the middle meatus of the maxillary sinus of infected children with cultures obtained from the maxillary sinus by puncture of the antrum.
3. Conduct more and larger studies to more clearly define and correlate the clinical findings with the various available diagnostic criteria of acute bacterial sinusitis (eg, sinus aspiration and treatment outcome).
4. Develop noninvasive strategies to accurately diagnose acute bacterial sinusitis in children.
5. Develop imaging technology that differentiates bacterial infection from viral infection or allergic inflammation, preferably without radiation.

Treatment

1. Determine the optimal duration of antimicrobial therapy for children with acute bacterial sinusitis.
2. Evaluate a "wait-and-see prescription" strategy for children with persistent symptom presentation of acute sinusitis.
3. Determine the optimal antimicrobial agent for children with acute bacterial sinusitis, balancing the incentives of choosing narrow-spectrum agents against the known microbiology of the disease and resistance patterns of likely pathogens.
4. Determine the causes and treatment of subacute, recurrent acute, and chronic bacterial sinusitis.
5. Determine the efficacy of prophylaxis with antimicrobial agents to prevent RABS.
6. Determine the effects of bacterial resistance among *S pneumoniae*, *H influenzae*, and *M catarrhalis* on outcome of treatment with antibiotics by the performance of randomized, double-blind, placebo-controlled studies in well-defined populations of patients.
7. Determine the role of adjuvant therapies (antihistamines, nasal corticosteroids, mucolytics, decongestants, nasal irrigation, etc) in patients with acute bacterial sinusitis by the performance of prospective, randomized clinical trials.
8. Determine whether early treatment of acute bacterial sinusitis prevents orbital or central nervous system complications.
9. Determine the role of complementary and alternative medicine strategies in patients with acute bacterial sinusitis by performing systematic, prospective, randomized clinical trials.
10. Develop new bacterial and viral vaccines to reduce the incidence of acute bacterial sinusitis.

SUBCOMMITTEE ON ACUTE SINUSITIS

Ellen R. Wald, MD, FAAP (Chair, Pediatric Infectious Disease Physician: no financial conflicts; published research related to sinusitis)
Kimberly E. Applegate, MD, MS, FAAP (Radiologist, AAP Section on Radiology: no conflicts)
Clay Bordley, MD, MPH, FAAP (Pediatric Emergency and Hospitalist Medicine physician: no conflicts)
David H. Darrow, MD, FAAP (Otolaryngologist, AAP Section on Otolaryngology–Head and Neck Surgery: no conflicts)
Mary P. Glode, MD, FAAP (Pediatric Infectious Disease Physician, AAP Committee on Infectious Disease: no conflicts)
S. Michael Marcy, MD, FAAP (General Pediatrician with Infectious Disease Expertise, AAP Section on Infectious Diseases: no conflicts)
Nader Shaikh, MD, FAAP (General Academic Pediatrician: no financial conflicts; published research related to sinusitis)
Michael J. Smith, MD, MSCE, FAAP (Epidemiologist, Pediatric Infectious Disease Physician: research funding for vaccine clinical trials from Sanofi Pasteur and Novartis)
Paul V. Williams, MD, FAAP (Allergist, AAP Section on Allergy, Asthma, and Immunology: no conflicts)
Stuart T. Weinberg, MD, FAAP (PPI Informatician, General Academic Pediatrician: no conflicts)
Carrie E. Nelson, MD, MS (Family Physician, American Academy of Family Physicians: employed by McKesson Health Solutions)
Richard M. Rosenfeld, MD, MPH, FAAP (Otolaryngologist, AAP Section on Otolaryngology–Head and Neck Surgery, American Academy of Otolaryngology–Head and Neck Surgery: no financial conflicts; published research related to sinusitis)

CONSULTANT

Richard N. Shiffman, MD, FAAP (Informatician, Guideline Methodologist, General Academic Pediatrician: no conflicts)

STAFF

Caryn Davidson, MA

REFERENCES

1. Aitken M, Taylor JA. Prevalence of clinical sinusitis in young children followed up by primary care pediatricians. *Arch Pediatr Adolesc Med.* 1998;152(3):244–248
2. Kakish KS, Mahafza T, Batieha A, Ekteish F, Daoud A. Clinical sinusitis in children attending primary care centers. *Pediatr Infect Dis J.* 2000;19(11):1071–1074
3. Ueda D, Yoto Y. The ten-day mark as a practical diagnostic approach for acute paranasal sinusitis in children. *Pediatr Infect Dis J.* 1996;15(7):576–579

4. Wald ER, Nash D, Eickhoff J. Effectiveness of amoxicillin/clavulanate potassium in the treatment of acute bacterial sinusitis in children. *Pediatrics*. 2009;124(1):9–15
5. American Academy of Pediatrics, Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. *Pediatrics*. 2001;108(3):798–808
6. Smith MJ. AAP technical report: evidence for the diagnosis and treatment of acute uncomplicated sinusitis in children: a systematic review. 2013, In press.
7. Shiffman RN, Michel G, Rosenfeld RM, Davidson C. Building better guidelines with BRIDGE-Wiz: development and evaluation of a software assistant to promote clarity, transparency, and implementability. *J Am Med Inform Assoc*. 2012;19 (1):94–101
8. American Academy of Pediatrics, Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114(3):874–877
9. Gwaltney JM, Jr, Hendley JO, Simon G, Jordan WS Jr. Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. *JAMA*. 1967;202(6):494–500
10. Pappas DE, Hendley JO, Hayden FG, Winther B. Symptom profile of common colds in school-aged children. *Pediatr Infect Dis J*. 2008;27(1):8–11
11. Wald ER, Guerra N, Byers C. Frequency and severity of infections in day care: three-year follow-up. *J Pediatr*. 1991;118(4 pt 1): 509–514
12. Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: duration of and frequency of complications. *Pediatrics*. 1991;87(2):129–133
13. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. *J Allergy Clin Immunol*. 2004;114(6 suppl): 155–212
14. Shaikh N, Wald ER. Signs and symptoms of acute sinusitis in children. *Pediatr Infect Dis J*. 2013; in press
15. Wald ER. The diagnosis and management of sinusitis in children: diagnostic considerations. *Pediatr Infect Dis*. 1985;4(6 suppl):S61–S64
16. Wald ER, Milmoe GJ, Bowen A, Ledesma-Medina J, Salamon N, Bluestone CD. Acute maxillary sinusitis in children. *N Engl J Med*. 1981;304(13):749–754
17. Lindbaek M, Hjortdahl P, Johnsen UL. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. *Fam Med*. 1996;28(3):183–188
18. Wald ER. Beginning antibiotics for acute rhinosinusitis and choosing the right treatment. *Clin Rev Allergy Immunol*. 2006; 30(3):143–152
19. Maresh MM, Washburn AH. Paranasal sinuses from birth to late adolescence. II. Clinical and roentgenographic evidence of infection. *Am J Dis Child*. 1940;60:841–861
20. Glasier CM, Mallory GB, Jr, Steele RW. Significance of opacification of the maxillary and ethmoid sinuses in infants. *J Pediatr*. 1989;114(1):45–50
21. Kovatch AL, Wald ER, Ledesma-Medina J, Chiponis DM, Bedingfield B. Maxillary sinus radiographs in children with nonrespiratory complaints. *Pediatrics*. 1984; 73(3):306–308
22. Shopfner CE, Rossi JO. Roentgen evaluation of the paranasal sinuses in children. *Am J Roentgenol Radium Ther Nucl Med*. 1973;118(1):176–186
23. Diament MJ, Senac MO, Jr, Gilsanz V, Baker S, Gillespie T, Larsson S. Prevalence of incidental paranasal sinuses opacification in pediatric patients: a CT study. *J Comput Assist Tomogr*. 1987;11(3):426–431
24. Glasier CM, Ascher DP, Williams KD. Incidental paranasal sinus abnormalities on CT of children: clinical correlation. *AJNR Am J Neuroradiol*. 1986;7(5):861–864
25. Gwaltney JM, Jr, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. *N Engl J Med*. 1994;330 (1):25–30
26. Manning SC, Biavati MJ, Phillips DL. Correlation of clinical sinusitis signs and symptoms to imaging findings in pediatric patients. *Int J Pediatr Otorhinolaryngol*. 1996;37(1):65–74
27. Gordts F, Clement PA, Destryker A, Desprechins B, Kaufman L. Prevalence of sinusitis signs on MRI in a non-ENT paediatric population. *Rhinology*. 1997;35(4): 154–157
28. Kristo A, Uhari M, Luotonen J, et al. Paranasal sinus findings in children during respiratory infection evaluated with magnetic resonance imaging. *Pediatrics*. 2003;111(5 pt 1):e586–e589
29. Brook I. Microbiology and antimicrobial treatment of orbital and intracranial complications of sinusitis in children and their management. *Int J Pediatr Otorhinolaryngol*. 2009;73(9):1183–1186
30. Sultesz M, Csakanyi Z, Majoros T, Farkas Z, Katona G. Acute bacterial rhinosinusitis and its complications in our pediatric otolaryngological department between 1997 and 2006. *Int J Pediatr Otorhinolaryngol*. 2009;73(11):1507–1512
31. Wald ER. Periorbital and orbital infections. *Infect Dis Clin North Am*. 2007;21(2):393–408
32. Chandler JR, Langenbrunner DJ, Stevens ER. The pathogenesis of orbital complications in acute sinusitis. *Laryngoscope*. 1970;80(9):1414–1428
33. Kombogiorgas D, Seth R, Modha J, Singh J. Suppurative intracranial complications of sinusitis in adolescence. Single institute experience and review of the literature. *Br J Neurosurg*. 2007;21(6):603–609
34. Rosenfeld EA, Rowley AH. Infectious intracranial complications of sinusitis, other than meningitis in children: 12 year review. *Clin Infect Dis*. 1994;18(5):750–754
35. American College of Radiology. Appropriateness criteria for sinonasal disease. 2009. Available at: www.acr.org/~/media/8172B4DE503149248E64856857674BB5.pdf. Accessed November 6, 2012
36. Triulzi F, Zirpoli S. Imaging techniques in the diagnosis and management of rhinosinusitis in children. *Pediatr Allergy Immunol*. 2007;18(suppl 18):46–49
37. McIntosh D, Mahadevan M. Failure of contrast enhanced computed tomography scans to identify an orbital abscess. The benefit of magnetic resonance imaging. *J Laryngol Otol*. 2008;122(6):639–640
38. Younis RT, Anand VK, Davidson B. The role of computed tomography and magnetic resonance imaging in patients with sinusitis with complications. *Laryngoscope*. 2002;112(2):224–229
39. Shapiro DJ, Gonzales R, Cabana MD, Hersh AL. National trends in visit rates and antibiotic prescribing for children with acute sinusitis. *Pediatrics*. 2011;127(1): 28–34
40. Wald ER, Reilly JS, Casselbrant M, et al. Treatment of acute maxillary sinusitis in childhood: a comparative study of amoxicillin and cefaclor. *J Pediatr*. 1984;104(2): 297–302
41. Wald ER, Chiponis D, Ledesma-Medina J. Comparative effectiveness of amoxicillin and amoxicillin-clavulanate potassium in acute paranasal sinus infections in children: a double-blind, placebo-controlled trial. *Pediatrics*. 1986;77(6):795–800
42. Garbutt JM, Goldstein M, Gellman E, Shannon W, Littenberg B. A randomized, placebo-controlled trial of antimicrobial treatment for children with clinically diagnosed acute sinusitis. *Pediatrics*. 2001; 107(4):619–625

43. Kristo A, Uhari M, Luotonen J, Ilkko E, Koivunen P, Alho OP. Cefuroxime axetil versus placebo for children with acute respiratory infection and imaging evidence of sinusitis: a randomized, controlled trial. *Acta Paediatr*. 2005;94(9): 1208–1213
44. Hoberman A, Paradise JL, Rockette HE, et al. Treatment of acute otitis media in children under 2 years of age. *N Engl J Med*. 2011;364(2):105–115
45. Tahtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med*. 2011;364(2):116–126
46. Gordts F, Abu Nasser I, Clement PA, Pierard D, Kaufman L. Bacteriology of the middle meatus in children. *Int J Pediatr Otorhinolaryngol*. 1999;48(2):163–167
47. Parsons DS, Wald ER. Otitis media and sinusitis: similar diseases. *Otolaryngol Clin North Am*. 1996;29(1):11–25
48. Revai K, Dobbs LA, Nair S, Patel JA, Grady JJ, Chonmaitree T. Incidence of acute otitis media and sinusitis complicating upper respiratory tract infection: the effect of age. *Pediatrics*. 2007;119(6). Available at: www.pediatrics.org/cgi/content/full/119/6/e1408
49. Klein JO, Bluestone CD. *Textbook of Pediatric Infectious Diseases*. 6th ed. Philadelphia, PA: Saunders; 2009
50. Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. *Pediatr Infect Dis J*. 2010;29(4): 304–309
51. Brook I, Gober AE. Frequency of recovery of pathogens from the nasopharynx of children with acute maxillary sinusitis before and after the introduction of vaccination with the 7-valent pneumococcal vaccine. *Int J Pediatr Otorhinolaryngol*. 2007;71(4):575–579
52. Wald ER. Microbiology of acute and chronic sinusitis in children. *J Allergy Clin Immunol*. 1992;90(3 pt 2):452–456
53. Centers for Disease Control and Prevention. Effects of new penicillin susceptibility breakpoints for *Streptococcus pneumoniae*—United States, 2006-2007. *MMWR Morb Mortal Wkly Rep*. 2008;57 (50):1353–1355
54. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs): Emerging Infections Program Network. 2011. Available at: www.cdc.gov/abcs/reports-findings/survreports/spneu09.html. Accessed November 6, 2012
55. Garbutt J, St Geme JW, III, May A, Storch GA, Shackelford PG. Developing community-specific recommendations for first-line treatment of acute otitis media: is high-dose amoxicillin necessary? *Pediatrics*. 2004;114(2):342–347
56. Harrison CJ, Woods C, Stout G, Martin B, Selvarangan R. Susceptibilities of *Haemophilus influenzae, Streptococcus pneumoniae*, including serotype 19A, and *Moraxella catarrhalis* paediatric isolates from 2005 to 2007 to commonly used antibiotics. *J Antimicrob Chemother*. 2009; 63(3):511–519
57. Critchley IA, Jacobs MR, Brown SD, Traczewski MM, Tillotson GS, Janjic N. Prevalence of serotype 19A Streptococcus pneumoniae among isolates from U.S. children in 2005-2006 and activity of faropenem. *Antimicrob Agents Chemother*. 2008;52(7):2639–2643
58. Jacobs MR, Good CE, Windau AR, et al. Activity of ceftaroline against recent emerging serotypes of *Streptococcus pneumoniae* in the United States. *Antimicrob Agents Chemother*. 2010;54(6):2716–2719
59. Tristram S, Jacobs MR, Appelbaum PC. Antimicrobial resistance in *Haemophilus influenzae*. *Clin Microbiol Rev*. 2007;20(2): 368–389
60. Levine OS, Farley M, Harrison LH, Lefkowitz L, McGeer A, Schwartz B. Risk factors for invasive pneumococcal disease in children: a population-based case-control study in North America. *Pediatrics*. 1999; 103(3). Available at: www.pediatrics.org/cgi/content/full/103/3/e28
61. Seikel K, Shelton S, McCracken GH Jr. Middle ear fluid concentrations of amoxicillin after large dosages in children with acute otitis media. *Pediatr Infect Dis J*. 1997;16(7):710–711
62. Cohen R, Navel M, Grunberg J, et al. One dose ceftriaxone vs. ten days of amoxicillin/clavulanate therapy for acute otitis media: clinical efficacy and change in nasopharyngeal flora. *Pediatr Infect Dis J*. 1999;18(5):403–409
63. Green SM, Rothrock SG. Single-dose intramuscular ceftriaxone for acute otitis media in children. *Pediatrics*. 1993;91(1): 23–30
64. Leibovitz E, Piglansky L, Raiz S, Press J, Leiberman A, Dagan R. Bacteriologic and clinical efficacy of one day vs. three day intramuscular ceftriaxone for treatment of nonresponsive acute otitis media in children. *Pediatr Infect Dis J*. 2000;19(11): 1040–1045
65. DePestel DD, Benninger MS, Danziger L, et al. Cephalosporin use in treatment of patients with penicillin allergies. *J Am Pharm Assoc*. 2008;48(4):530–540
66. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics*. 2005;115(4): 1048–1057
67. Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: a meta-analysis. *Otolaryngol Head Neck Surg*. 2007;136(3): 340–347
68. Park MA, Koch CA, Klemawesch P, Joshi A, Li JT. Increased adverse drug reactions to cephalosporins in penicillin allergy patients with positive penicillin skin test. *Int Arch Allergy Immunol*. 2010;153(3): 268–273
69. Jacobs MR. Antimicrobial-resistant Streptococcus pneumoniae: trends and management. *Expert Rev Anti Infect Ther*. 2008; 6(5):619–635
70. Chow AW, Benninger MS, Brook I, et al; Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis*. 2012;54(8):e72–e112
71. Brook I, Gober AE. Resistance to antimicrobials used for therapy of otitis media and sinusitis: effect of previous antimicrobial therapy and smoking. *Ann Otol Rhinol Laryngol*. 1999;108(7 pt 1):645–647
72. Brook I, Gober AE. Antimicrobial resistance in the nasopharyngeal flora of children with acute maxillary sinusitis and maxillary sinusitis recurring after amoxicillin therapy. *J Antimicrob Chemother*. 2004;53(2):399–402
73. Dohar J, Canton R, Cohen R, Farrell DJ, Felmingham D. Activity of telithromycin and comparators against bacterial pathogens isolated from 1,336 patients with clinically diagnosed acute sinusitis. *Ann Clin Microbiol Antimicrob*. 2004;3(3): 15–21
74. Jacobs MR, Bajaksouzian S, Zilles A, Lin G, Pankuch GA, Appelbaum PC. Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 U.S. surveillance study. *Antimicrob Agents Chemother*. 1999;43(8):1901–1908
75. Jacobs MR, Felmingham D, Appelbaum PC, Gruneberg RN. The Alexander Project 1998-2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. *J Antimicrob Chemother*. 2003;52(2):229–246

76. Lynch JP, III, Zhanel GG. *Streptococcus pneumoniae*: epidemiology and risk factors, evolution of antimicrobial resistance, and impact of vaccines. *Curr Opin Pulm Med.* 2010;16(3):217–225
77. Sahm DF, Jones ME, Hickey ML, Diakun DR, Mani SV, Thornsberry C. Resistance surveillance of *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* isolated in Asia and Europe, 1997-1998. *J Antimicrob Chemother.* 2000; 45(4):457–466
78. Sokol W. Epidemiology of sinusitis in the primary care setting: results from the 1999-2000 respiratory surveillance program. *Am J Med.* 2001;111(suppl 9A):19S–24S
79. Shaikh N, Wald ER, Pi M. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. *Cochrane Database Syst Rev.* 2010;(12):CD007909
80. Dolor RJ, Witsell DL, Hellkamp AS, Williams JW, Jr, Califf RM, Simel DL. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. *JAMA.* 2001;286(24):3097–3105
81. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. *J Allergy Clin Immunol.* 2005;116(6):1289–1295
82. Meltzer EO, Charous BL, Busse WW, Zinreich SJ, Lorber RR, Danzig MR. Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. The Nasonex Sinusitis Group. *J Allergy Clin Immunol.* 2000;106 (4):630–637
83. Meltzer EO, Orgel HA, Backhaus JW, et al. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. *J Allergy Clin Immunol.* 1993;92(6):812–823
84. Nayak AS, Settipane GA, Pedinoff A, et al. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. *Ann Allergy Asthma Immunol.* 2002;89(3):271–278
85. Williamson IG, Rumsby K, Benge S, et al. Antibiotics and topical nasal steroid for treatment of acute maxillary sinusitis: a randomized controlled trial. *JAMA.* 2007; 298(21):2487–2496
86. Zalmanovici A, Yaphe J. Intranasal steroids for acute sinusitis. *Cochrane Database Syst Rev.* 2009;(4):CD005149
87. Yilmaz G, Varan B, Yilmaz T, Gurakan B. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Eur Arch Otorhinolaryngol.* 2000;257(5):256–259
88. Barlan IB, Erkan E, Bakir M, Berrak S, Basaran MM. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Ann Allergy Asthma Immunol.* 1997;78(6):598–601
89. Bruni FM, De Luca G, Venturoli V, Boner AL. Intranasal corticosteroids and adrenal suppression. *Neuroimmunomodulation.* 2009;16 (5):353–362
90. Kim KT, Rabinovitch N, Uryniak T, Simpson B, O'Dowd L, Casty F. Effect of budesonide aqueous nasal spray on hypothalamic-pituitary-adrenal axis function in children with allergic rhinitis. *Ann Allergy Asthma Immunol.* 2004;93(1):61–67
91. Meltzer EO, Tripathy I, Maspero JF, Wu W, Philpot E. Safety and tolerability of fluticasone furoate nasal spray once daily in paediatric patients aged 6-11 years with allergic rhinitis: subanalysis of three randomized, double-blind, placebo-controlled, multicentre studies. *Clin Drug Investig.* 2009;29(2):79–86
92. Murphy K, Uryniak T, Simpson B, O'Dowd L. Growth velocity in children with perennial allergic rhinitis treated with budesonide aqueous nasal spray. *Ann Allergy Asthma Immunol.* 2006;96(5):723–730
93. Ratner PH, Meltzer EO, Teper A. Mometasone furoate nasal spray is safe and effective for 1-year treatment of children with perennial allergic rhinitis. *Int J Pediatr Otorhinolaryngol.* 2009;73(5):651–657
94. Skoner DP, Gentile DA, Doyle WJ. Effect on growth of long-term treatment with intranasal triamcinolone acetonide aqueous in children with allergic rhinitis. *Ann Allergy Asthma Immunol.* 2008;101(4): 431–436
95. Weinstein S, Qaqundah P, Georges G, Nayak A. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in children aged 2 to 5 years with perennial allergic rhinitis: a randomized, double-blind, placebo-controlled study with an open-label extension. *Ann Allergy Asthma Immunol.* 2009;102(4):339–347
96. Zitt M, Kosoglou T, Hubbell J. Mometasone furoate nasal spray: a review of safety and systemic effects. *Drug Saf.* 2007;30(4): 317–326
97. Adam P, Stiffman M, Blake RL Jr. A clinical trial of hypertonic saline nasal spray in subjects with the common cold or rhinosinusitis. *Arch Fam Med.* 1998;7(1):39–43
98. Wang YH, Yang CP, Ku MS, Sun HL, Lue KH. Efficacy of nasal irrigation in the treatment of acute sinusitis in children. *Int J Pediatr Otorhinolaryngol.* 2009;73(12): 1696–1701
99. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2007;(3):CD006394
100. Kassel JC, King D, Spurling GK. Saline nasal irrigation for acute upper respiratory tract infections. *Cochrane Database Syst Rev.* 2010;(3):CD006821
101. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. *Pediatrics.* 1991;87(3):311–316
102. Wood AJ, Douglas RG. Pathogenesis and treatment of chronic rhinosinusitis. *Postgrad Med J.* 2010;86(1016):359–364
103. Liao S, Durand ML, Cunningham MJ. Sinogenic orbital and subperiosteal abscesses: microbiology and methicillin-resistant Staphylococcus aureus incidence. *Otolaryngol Head Neck Surg.* 2010;143(3):392–396
104. Oxford LE, McClay J. Medical and surgical management of subperiosteal orbital abscess secondary to acute sinusitis in children. *Int J Pediatr Otorhinolaryngol.* 2006;70(11):1853–1861

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Cost–benefit analysis of targeted hearing directed early testing for congenital cytomegalovirus infection

Anna Bergevin [a], Cathleen D. Zick [b,*], Stephanie Browning McVicar [c], Albert H. Park [d]

[a] Center for Public Policy & Administration, University of Utah, Salt Lake City, UT, United States
[b] Department of Family & Consumer Studies, University of Utah, Salt Lake City, UT, United States
[c] Utah Department of Health, Salt Lake City, UT, United States
[d] Division of Otolaryngology—Head and Neck Surgery, University of Utah, Salt Lake City, UT, United States

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ABSTRACT

Objectives: In this study, we estimate an *ex ante* cost–benefit analysis of a Utah law directed at improving early cytomegalovirus (CMV) detection.
Study design: We use a differential cost of treatment analysis for publicly insured CMV-infected infants detected by a statewide hearing-directed CMV screening program.
Methods: Utah government administrative data and multi-hospital accounting data are used to estimate and compare costs and benefits for the Utah infant population.
Results: If antiviral treatment succeeds in mitigating hearing loss for one infant per year, the public savings will offset the public costs incurred by screening and treatment. If antiviral treatment is not successful, the program represents a net cost, but may still have non-monetary benefits such as accelerated achievement of diagnostic milestones.
Conclusions: The CMV education and treatment program costs are modest and show potential for significant cost savings.

1. Introduction

Cytomegalovirus (CMV) is the most common infectious cause of congenital sensorineural hearing loss (SNHL) [1]. Morton et al., Grosse et al., and our group have reported that 15–30% of pediatric hearing loss can be attributed to CMV [2–4]. The consequences of hearing loss for affected children include speech and language delay, low education, and poor occupational performance in adulthood [5]. The lifetime cost for each child with hearing loss is estimated to be over three hundred thousand dollars accounting for the lost productivity, the need for special education, vocational rehabilitation, assistive devices and medical costs [6]. One study estimates the total costs associated with congenital CMV infection to be $4 billion a year [7]. Preventing the sequelae of progressive hearing loss would significantly reduce the personal and societal costs for these children.

Research has shown that early identification and intervention before the hearing-impaired infant reaches 6 months of age are associated with better language outcomes [8,9]. A recent paper also reported that early antiviral intervention may improve CMV-related hearing and neurocognitive outcomes [10]. The National Institute of Allergy and Infectious Disease Collaborative Antiviral Study Group (CASG) presented results comparing 6 weeks versus 6 months of oral valganciclovir (VGC) therapy for CMV infected children less than one month of age. Specifically, 64% of the children who underwent 6 weeks of VGC therapy had improved or normal hearing versus 77% who underwent 6 months of oral VGC therapy. These better audiologic and neurocognitive outcomes apply to symptomatic congenitally infected infants, however, and may not apply to the CMV infected hearing impaired infants identified from a hearing targeted early CMV approach [10].

A critical challenge in diagnosing congenital CMV is that most newborns do not present with any signs of infection. The diagnosis requires laboratory testing of neonatal samples within the first three weeks of life since postnatal CMV infection is not associated with SNHL. Thus, ideally, at-risk infants should be identified early to permit targeted monitoring and intervention so that they can achieve normal speech and language skills. One testing approach utilizes a targeted hearing loss driven screening method to determine which infants should undergo CMV testing. This approach became the basis of a bill Representative Ronda Menlove, with the support of the Utah CMV working group, introduced to the

* Corresponding author. Tel.: +1 801 581 3147; fax: +1 801 581 5156.
E-mail address: zick@fcs.utah.edu (C.D. Zick).

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Utah legislature in February, 2013 [11]. This bill mandated CMV testing of newborns under three weeks of age who fail their newborn hearing screen(s). Utah became the first state to implement this targeted hearing loss driven testing approach for CMV diagnosis when the bill was signed into law in June 2013.

Data from Utah's newborn hearing screening program show that during the first year of implementation of the law 89% of newborns underwent the two hearing screens and that 63% of the children who failed the two newborn hearing screens were screened for CMV ($n = 244$). Among the children screened, 5% (12 infants) tested positive for CMV. Some of these CMV positive infants were found to have normal hearing following audiologic evaluation.

The enormous potential health burden of congenital CMV suggests that it is vital that we assess the benefits of early detection relative to the potentially significant costs of early CMV testing and treatment. To date, only one such cost analysis has been done and the authors found targeted newborn screening in the United Kingdom to be cost effective [12]. Given the differences in health insurance in the United Kingdom, it is unclear if these study findings would extrapolate to the United States. As other states, including Texas, Hawaii, Illinois and Connecticut, consider or have recently passed similar legislation, there is a need to perform a cost–benefit analysis to inform public policy in the United States. This analysis uses an ex-ante approach and a governmental accounting perspective to assess the projected costs and benefits of the Utah law.

2. Materials and methods

2.1. Determining costs & benefits

Costs fell cleanly into two categories: administrative costs and medical costs. Administrative costs were those incurred by the Department of Health for both the education and screening components of the program. The government also bears the medical costs for those affected infants covered by the public insurance programs (CHIP & Medicaid). Medical costs include both the CMV screening test and the differential cost of treatment for CMV-positive infants. Benefits were narrowly defined as medical costs avoided that would have otherwise been incurred had there not been early screening and intervention. Benefits to individuals, families, and private insurers were not considered and cases of CMV prevented entirely through education and prevention efforts were also not captured in this analysis. The analysis thus provides a conservative estimate, as societal and even governmental benefits from the law certainly exceed what is captured here.

2.2. Quantifying costs and benefits

Administrative costs were drawn from the legislative fiscal note accompanying the original bill [13]. Department of Health officials confirmed the fiscal note was an accurate estimate of actual program costs. The figures used in the analysis include a one-time startup cost of $4000 and an annual ongoing appropriation of $30,800[1].

Calculating medical costs and cost avoidance (benefits) required calculating the number of estimated screenings each year as well as the rate of positive screenings that would be referred for further evaluation and treatment. For infants who tested positive but who were found to have normal hearing following audiological evaluation, only the cost of their screening is included in the analysis. Screening costs and additional treatment costs are included for infants with confirmed hearing loss[2]. The cost of the screening itself was $66 per infant[3].

The analysis only considers the costs for those children likely to be on public insurance because we are using a governmental perspective. We estimated the proportion of publicly insured infants using a range of values and varied them in our sensitivity analysis to test the impact of our assumptions[4].

All infants with confirmed hearing loss will incur medical treatment costs. This analysis considers the added costs to the government per patient with confirmed congenital CMV and a diagnosis of sensorineural hearing loss. Treatment of CMV-induced hearing loss will likely be identical to other types of hearing loss in infants except for the prescription of antiviral medication and tests to monitor the patient during treatment[5]. The cost data presented here represent the cost to the provider without any markup for profit margins and include $4453 for the antiviral medication for 6 months and $385.63 for testing. As such they may underestimate the costs from a private insurance perspective but may overestimate the costs from a Medicaid reimbursement perspective. Absent the ability to secure Medicaid reimbursement rates, these cost data were our best estimates.

We present different hypothetical models that include avoiding cochlear implantation in patients treated with antiviral therapy. Cochlear implantation is one of the most costly factors in the analysis. Cochlear implants cost $47,800 per year ($95,600 for bilateral) whereas hearing aids are $2000; thus, avoiding implants will save anywhere from $46,800 to $93,600 per patient [5].

A transparent cost benefit analysis must include several iterations of the analysis, varying the assumptions to illustrate how sensitive the results are to particular choices made. Because most costs related to newborn hearing loss are incurred in the first year or two of life, no discounting is necessary for this analysis as all costs and benefits occur more or less in the present. Many of the costs and benefits that will accrue in the future are to individuals, families and educational institutions rather than to the government. In our estimation, the society-wide benefits of early detection and intervention far exceed those presented here. For the following models, all calculations project forward two years into the program.

3. Results

The initial model presented in Table 1 provides a baseline. It assumes that the rate of public insurance coverage for infants will

[1] In the second year additional funding was given, but administrators note this funding was to be used exclusively for the educational component of the law and was thus excluded from our analysis, which evaluates the screening component alone.

[2] Of these 9 CMV positive children, 5 had confirmed hearing loss after further testing. All of these children are at risk of developing more extensive hearing loss in early childhood as CMV induced hearing loss is progressive, but we are unable to consider these more distant potential costs for the subgroup without confirmed hearing loss ($n = 4$) due to lack of data.

[3] Medical costs were calculated using a multi-hospital cost accounting database. Though we'd prefer to use Medicaid/CHIP cost reimbursement figures, limited access to such data required we use hospital cost as a proxy.

[4] Data from the Census Bureau indicates that 23% of Utah children (all ages) are on public insurance, but national data broken down by age indicates that insurance rates for the youngest children tend to be much higher, 45.2% [14] 2013 Annual Social and Economic Supplement Current Population Survey, City, 2013. Utah Department of Health data indicates that 37.5% of children born in 2013 were born on public insurance [15] Bergevin A, Personal Communication with Kobi Young at the Utah Department of Health, City, 2014. All of these data points represent historical coverage rates and do not account for changes caused by the Affordable Care Act (ACA) and potential Medicaid expansion in the state. Even without Medicaid expansion, the state estimates that using current eligibility guidelines, 63.5–80% of children are eligible for CHIP or Medicaid; if larger numbers of individuals start taking advantage of their eligibility from the ACA, then state public insurance for infants could reach higher rates than ever before.

[5] Use of antiviral medications to treat hearing loss in otherwise asymptomatic CMV patients is still experimental. We assume a majority of patients will choose to undergo antivirals because preliminary data shows that to be the case in Utah.

Table 1
Cost–benefit figures of mandatory CMV testing for infants who fail two newborn hearing screenings using different model assumptions.

	Baseline model[a]		No cochlear implants avoided		One cochlear implant avoided		80% of newborns on public insurance	
	2014	2015	2014	2015	2014	2015	2014	2015
Costs								
Program setup	$4,000		$4000		$4000		$4,000	
Fixed administrative	$30,800	$30,800	$30,800	$30,800	$30,800	$30,800	$30,800	$30,800
Screenings	$7,260	$7,260	$7260	$7260	$7260	$7,260	$7,260	$7,260
Antiviral treatment and monitoring tests	$4,839	$4,839	$4839	$4839	$4839	$4,839	$9,678	$9,678
Total costs	$46,899	$42,899	$46,899	$42,899	$46,899	$42,899	$57,348	$53,348
Benefits								
Treatment savings	$93,600	$93,600	$0	$0	$46,800	$46,800	$140,400	$140,400
Benefits–costs	$46,691	$50,701	($46,899)	($42,899)	($99)	$3,901	$83,052	$87,052

[a] The base model chooses values near the middle of the ranges provided for the costs/benefits for which we have ranges and uses precise estimates where available. Program setup & fixed administrative costs are those outlined in the fiscal note incurred directly by the Department of Health, screening costs are the costs to the government through Medicaid/CHIP for the proportion of screening costs expected to be publicly funded, and antiviral treatment and monitoring tests are likewise those incurred only by the patients who are publicly funded and elect to undergo those procedures. This model assumes one child covered by Medicaid/CHIP and diagnosed with CMV-related sensorineural hearing loss each year, that child takes antivirals, and s/he would have needed cochlear implants without the intervention.

mimic the rate nationwide for children under age three. It also assumes that the one publicly funded patient who pursues antiviral therapy will mitigate hearing loss to an extent that s/he will only require hearing aids rather than bilateral cochlear implants. The model shows a large net benefit.

The next two models that appear in Table 1 illustrate the difference if, under the same set of assumptions, no cochlear implants are avoided or only a single implant (unilateral) is avoided. In the case where no cochlear implants are avoided, there is a net cost to the government, and in the case of a single cochlear implant avoided, the costs and benefits essentially cancel each other out.

The final model considers how costs and benefits might differ if the number of publicly insured infants increases as individuals take advantage of their public insurance eligibility to avoid tax penalties for the uninsured or as increased numbers of individuals are eligible for public insurance under currently debated Medicaid expansion in Utah. This model considers the extreme scenario of 80% of infants on public insurance (using the high end of the Department of Health data on current eligibility). All other assumptions follow the base model. While this increases dramatically the public dollars paid for CMV screenings, it only increases the number of CMV-positive children that take VGC on public insurance from one to two children per year. At most it might mean that two children avoid cochlear implantation each year rather than one. The model above calculates the benefit if one of those two children would have had a single CI and the other would have been bilateral and both are able to avoid cochlear implantation. Overall, this model illustrates that the effect of increased public insurance is not as significant a factor in the calculation as the potential cost–savings if VGC treatment proves effective.

In sum, we found the implementation of Utah's hearing-targeted CMV screening program to have a net public benefit in three of the four cost–benefit scenarios we investigated. Only in the instance where no cochlear implant is avoided in a year does the program show a net public cost, albeit a modest one.

4. Discussion

The enormous societal costs of congenital CMV must be balanced against the costs incurred from any early CMV screening program. A targeted hearing early CMV testing approach was a compromise to identify infants at greatest risk to develop progressive SNHL. A targeted approach requires CMV testing of a small number of infants per year as compared to testing thousands of infants if a universal program was implemented.

Williams et al., estimated the cost of a targeted CMV screening program within the United Kingdom [12]. They utilized data from the national hearing screening program in England and from a recently completed study using saliva swabs. The costs of screening time, PCR testing, and treatment were calculated. They estimated that the cost for this approach would be $10,693 per child and concluded this amount would be favorable compared to other screening programs.

The costs per child determined from our analysis would be much less than that from the Williams et al., study although a direct comparison is difficult given the different health care systems. Much of the cost from screening and treatment of the congenitally infected hearing impaired infants will come from antiviral therapy and from cochlear implantation. Eighteen months since implementation of this approach, eight of fourteen infants diagnosed with CMV have undergone antiviral therapy. Kimberlin et al., reported one child who underwent 6 months of VGC therapy requiring cochlear implantation compared to three children who underwent 6 week VGC therapy requiring this surgical procedure at the 12 month follow up period [10]. At the 24 month follow up period, four children undergoing 6 months of VGC therapy required cochlear implantation compared to six children requiring the same procedure undergoing 6 weeks of VGC therapy.

It may be that our cost–benefit estimates are overly generous as only a minority of children who would qualify for cochlear implants in the United States actually receive them [10]. This potential over-estimation however, is likely offset by the fact that we did not include the familial and educational benefits of early intervention that will be attributable to the Utah law. Nor did we account for the benefits of the preventive educational programming mandated by the legislation. Both of these omissions make our analyses conservative.

5. Conclusion

Our results support a possible societal savings from early identification and treatment of CMV. This analysis considers only the impact of the screening portion of the program. Overall, the results suggest that there is reason for optimism about the return on investment to the government associated with the Utah law.

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References

[1] M.L. Engman, G. Malm, L. Engstrom, K. Petersson, E. Karltorp, K. Tear Fahnehjelm, et al. Scand. J. Infect. Dis. 40 (2008) 935–942.
[2] C.C. Morton, W.E. Nance, N. Engl. J. Med. 354 (2006) 2151–2164.
[3] S.D. Grosse, D.S. Ross, S.C. Dollard, J. Clin. Virol. 41 (2008) 57–62.
[4] A.H. Park, M. Duval, S. McVicar, J.F. Bale Jr., N. Hohler, J.C. Carey, Laryngoscope 124 (11) (2014) 2624–2629.
[5] American Academy of Pediatrics, Joint Committee on Infant Hearing, Pediatrics 120 (2007) 898–921.
[6] A. Honeycutt, S.D. Grosse, L. Dunlap, Economic Costs of Mental Retardation, Cerebral Palsy, Hearing Loss, and Vision Impairment, Elsevier Science Ltd, London, England, 2003.
[7] K.R. Stratton, J.S. Durch, R.S. e. Lawrence, Vaccines for the 21st Century: a Tool for Decision Making, National Academy Press, Washington DC, 2001.
[8] C. Yoshinaga-Itano, D. Coulter, V. Thomson, J. Perinatol. 20 (2000) S132–S137.
[9] C. Yoshinaga-Itano, D. Coulter, V. Thomson, Semin. Neonatol. 6 (2001) 521–529.
[10] D.W. Kimberlin, P.M. Jester, P.J. Sánchez, A. Ahmed, R. Arav-Boger, M.G. Michaels, et al. New Engl. J. Med. 372 (2015) 933–943.
[11] Ronda Rudd Menlove, in: UHo (Ed.), Cytomegalovirus Public Health Initiative, Utah House of Representatives, Salt Lake City, 2013.
[12] E.J. Williams, J. Gray, S. Luck, C. Atkinson, N.D. Embleton, S. Kadambari, et al. *First Estimates of the Potential Cost of Targeted Screening for Congenital CMV*, Arch. Dis. Child. Fetal. Neonatal. Ed. published online doi: 10.1136/archdischild-2014-306756.
[13] Utah State Legislature, Fiscal Note HB0081 S02 Cytomegalovirus Public Health Initiative, Utah State Legislature, Salt Lake City, 2013.
[14] U.S. Census Bureau. Annual Social and Economic Supplement Current Population Survey, 2013.
[15] A. Bergevin, Personal Communication with Kobi Young at the Utah Department of Health, Utah Department of Health, Salt Lake City, 2014.

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The effect of age on pediatric tympanoplasty outcomes: A comparison of preschool and older children

Melanie Duval *, J. Fredrik Grimmer, Jeremy Meier, Harlan R. Muntz, Albert H. Park

Division of Otolaryngology, University of Utah, 50 N Medical Drive, SOM 3C120, Salt Lake City, UT 84132, USA

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ABSTRACT

Objectives: Determine whether the outcome of tympanoplasty in preschool children is different from that of older children.
Study design: Retrospective case series.
Methods: Retrospective review of children having undergone a primary tympanoplasty by 4 surgeons for a tympanic membrane perforation between 2002 and 2013.
Results: Data from 50 children age 2–4, 130 children age 5–7 and 105 children age 8–13 years old were reviewed. Median follow-up was 7.5 months. On crude analysis, the incidence of anatomical success was not significantly different between the different age groups ($p = 0.38$), the success rate was respectively 69.4%, 68.5% and 79.1% with an overall rate of 72.5%. 5.9% of all children required later insertion of tympanostomy tubes, 10.2% in preschool children. The post-operative audiology results were similar for all groups with a mean improvement of 9 dB in the air-bone gap. When limiting the analysis to the 155 children having at least 6 months of follow-up, the rate of success was respectively 50.0%, 60.8% and 74.0% ($p = 0.10$). After multivariate analysis controlling for the effect of surgeon, approach and etiology, the odds ratio of perforation was respectively 5.48, 2.27 and 1.00 for the different age groups.
Conclusion: Children younger than 4 years of age have the worst outcome after tympanoplasty. It remains uncertain whether the benefits of hearing improvement and quality of life may outweigh that of a high rate of a residual, usually smaller, perforation. Prospective studies are needed to confirm these results and delineate the patient characteristics and technique most likely to lead to successful results.

1. Introduction

Tympanoplasty is a commonly performed procedure in children. There have been multiple studies evaluating the effect of age on success rate. However, controversy remains regarding the ideal age at which pediatric tympanoplasty should be performed. Despite the lack of definite evidence of an association between age and tympanoplasty success rate, many authors [1–3] have recommended delaying tympanoplasty until the child is older than 6 to 8 years old to allow time for Eustachian tube maturation and increase the odds of favorable outcome. In a survey by Lancaster et al. 70% of otolaryngologists reported a set age below which they would not perform a tympanoplasty, the most common age reported being 10 years old [4]. However, others have suggested adverse sequelae from persistent tympanic membrane perforations based on quality of life measures [5] and Friedman et al. [6] and Knapik et al. [7] have demonstrated excellent tympanic membrane closure rate in selected children under 7 years of age.

While multiple studies have evaluated the impact of age on success rate of tympanoplasty, studies have generally limited their analysis to children above 6 to 8 years old [8–10] or grouped a small number of preschool with older children [11–13]. Thus far, no study has specifically evaluated the success rate of tympanoplasty in preschool children. Anatomical success rate of tympanoplasty in studies having specifically evaluated children under 8 years old is presented in Table 1.

At our institution, child's age is not used to determine the timing of a tympanic membrane perforation repair. Rather, surgery will be offered after a period of observation of 6 months if the child exhibits evidence of good Eustachian tube function in the opposite ear or of the perforation is dry for at least 6 months in cases of bilateral perforations; if the perforation is large, causes significant hearing loss; or it is deemed to be high-risk for cholesteatoma formation due to a marginal location or epithelium ingrowth. The

* Corresponding author at: McGill University Department of Otolaryngology Head & Neck Surgery 2300 Tupper St, Room A-334 Montreal, QC, Canada H3H 1P3. Tel.: +1 438 825 6024.
E-mail address: melanie.duval@muhc.mcgill.ca (M. Duval).

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Table 1
Reported anatomical success rate of tympanoplasty in children below 8 years old.

Author (year)	*N*	Age (years)	Anatomical success rate (%)	Follow-up	Surgical technique
Berger (1983) [14]	26	4–8	96	>1 month	Temporalis fascia, perichondrium
Black (1995) [15]	14	2–7	56	>6 mos	Temporalis fascia
Buchwach (1980) [16]	25	3–8	64	>12 mos	Temporalis fascia
Chandrasekhar (1995) [17]	69	<7	94	>6 mos	Unknown
Charlett (2009) [18]	21	4–8	57	>2 months	Temporalis fascia, fat, perichondrium
Collins (2003) [19]	6	<6	83	>1 month	Temporalis fascia, cartilage
Denoyelle (1999) [20]	76	4–8	83	>12 mos	Temporalis fascia
Friedberg (1980) [21]	4	3–7	100	>2 months	Temporalis fascia
Friedman (2013) [6]	43	4–7	93	>1 month	Cartilage
Kessler (1994) [22]	37	2–6	81	>6 mos	Temporalis fascia
Knapik (2011) [7]	20	<6	100	>6 mos	Temporalis fascia, perichondrium
Koch (1989) [1]	10	2–7	30	>6 months	Unknown
Lau and Tos (1986) [23]	26	2–7	92	>3 months	Unknown
Te (1998) [24]	11	<8	91	>6 mos	Temporalis fascia
Umapathy (2003) [25]	23	4–8	87	>12 mos	Temporalis fascia
Cumulative data	411		84		

main arguments for early repair of tympanic membrane perforation in children include improved hearing for optimization of speech and language development, prevention of chronic ear disease and allowing children to enjoy water activities.

2. Objective

The objective of this study was to evaluate the success rate of primary tympanoplasty performed in pre-school children as compared to that of older children. The primary outcome measure evaluated was the status of the tympanic membrane at the end of the period of follow-up. Secondary outcome measures evaluated were need for tympanostomy tubes, cholesteatoma formation and improvement in hearing thresholds.

3. Methods

A retrospective review of children 13 years old or younger having undergone a primary tympanoplasty between 2002 and 2013 at a tertiary care pediatric hospital by four pediatric otolaryngologists was performed. Approval from the University of Utah and Primary Children's Hospital ethics review board was obtained. Four surgeons performed all tympanoplasties included in this study and all worked regularly with residents. Surgical technique, approach and graft material varied between the surgeons. Exclusion criteria included revision tympanoplasty, cholesteatoma, concomitant or previous ipsilateral mastoidectomy, concomitant ossiculoplasty, concomitant tympanostomy tube insertion and tympanic membrane retraction pocket without a perforation. Data collected included age at time of surgery, gender, etiology of perforation, status of the contralateral ear, prior adenoidectomy, characteristics of the perforation, type of graft used, surgical technique, complications and duration of follow-up. Hearing results were evaluated by reviewing pre- and post-operative speech reception thresholds (SRT) and pure-tone average air-bone gap (ABG). Air-bone gap was calculated according to the American Academy of Otolaryngology—Head and Neck Surgery guidelines published in 1995 [26]. Post-operative audiogram was usually performed at 6 to 12 weeks post-operatively.

Patients were separated into 3 age categories: 2–4 years old, 5–7 years old and 8–13 years old. These age groups were designed to compare the outcome in pre-school children to those older than 8 years of age.

3.1. Outcome

A satisfactory outcome was defined as an intact tympanic membrane at the end of the follow-up period. Status of the tympanic membrane was determined by the operating surgeon at follow-up visits using otoscopy and/or micro-otoscopy. A persistent perforation was defined as a perforation noted within 6 months post-operatively and a recurrent perforation was defined as any perforation noted more than 6 months post-operatively. Secondary outcomes evaluated included post-operative tympanic membrane or middle ear cholesteatoma, need for tympanostomy tube and audiologic responses (ABG and SRT).

3.2. Analysis

Data analysis was performed using Stata version 12. Chi-square test was used to analyze categorical data and *t*-test was used to analyze continuous data. A *p*-value less than 0.05 was considered significant on crude analysis for possible inclusion of the variable into the multivariate analysis. A paired *t*-test was used to evaluate the difference between pre-operative and post-operative hearing results. An analysis of variance (ANOVA) was used to determine whether hearing results were statistically different between the three different age groups. A logistic regression was performed to evaluate the association between age group and post-tympanoplasty perforation as well as determine which factors were associated with anatomical success. A subgroup logistic regression analysis was also performed including only children with 6 months or more of follow-up.

4. Results

A total of 284 tympanoplasties in 259 children were performed between 2002 and 2013 by four pediatric otolaryngologists. The median follow-up duration was 7.5 months (range 1 to 106 months). One hundred fifty-five children had 6 or more months of follow-up.

Distribution of patient's and surgical characteristics is presented in Table 2. The overall incidence of intact tympanic membrane for the whole duration of follow-up was 72.5% overall and 63.2% in patients with at least 6 months of follow-up. The incidence of an intact tympanic membrane by age group was 69.4% in children age 2–4, 68.5% in children age 5–7 and 79.1% in children age 8–13. There was no statistically significant evidence of a linear association between rate of perforation post-tympanoplasty and age (OR = 0.91, 95% CI 0.82–1.01). Mean prevalence of intact tympanic membrane at the end of the follow-up period by age is presented in Fig. 1. On crude analysis, factors that were most strongly associated with increased odds of post-tympanoplasty perforation were use of acellular dermis ($p = 0.004$), transcanal approach ($p < 0.001$) and surgeon ($p = 0.004$). There was no association between post-tympanoplasty perforation and season

Table 2
Patient and surgical characteristics per status of the tympanic membrane at the end of the follow-up period.

Characteristic	No perforation $n=206$, n (%)	Perforation $n=78$, n (%)	OR, (p-value)
Age group			(0.16)
2–4	34 (69.4)	15 (30.6)	1.66 (0.19)
5–7	89 (68.5)	41 (31.5)	1.74, (0.07)
8–13	83 (79.0)	22 (21.0)	1.0
Gender			
Male	111 (73.5)	40 (26.5)	0.89, (0.67)
Female	95 (71.4)	38 (28.6)	
Adenoidectomy			
Yes	98 (73.7)	35 (26.3)	0.89, (0.68)
No	107 (71.3)	43 (28.7)	
Craniofacial anomaly			
Yes	54 (79.4)	14 (20.6)	0.62, (0.15)
No	151 (70.2)	64 (29.8)	
Contralateral perforation			
Yes	53 (70.7)	22 (29.3)	1.14, (0.66)
No	153 (73.2)	56 (26.8)	
Middle ear inflammation			
Yes	16 (88.9)	2 (11.1)	0.31, (0.13)
No	188 (71.2)	76 (28.8)	
Etiology			(0.04)
Tubes	167 (70.2)	71 (29.8)	1.0
Chronic ear disease	17 (89.5)	2 (10.5)	0.28, (0.09)
Trauma	9 (90.0)	1 (10.0)	0.26, (0.21)
Surgeon			(0.005)
1	88 (84.6)	16 (15.4)	1.0,
2	70 (67.3)	34 (32.7)	2.67, (0.004)
3	40 (64.5)	22 (35.5)	3.03, (0.004)
4	8 (57.1)	6 (42.9)	4.13, (0.02)
Approach			
Transcanal	98 (64.1)	55 (35.9)	2.64, (<0.001)
Post-auricular	108 (82.4)	23 (17.6)	
Technique			
Overlay	24 (96.0)	1 (4.0)	0.10, (0.02)
Underlay	182 (70.3)	77 (29.7)	
Material			(0.01)
Temporalis fascia	118 (79.2)	31 (20.8)	1.0
Perichondrium	25 (69.4)	11 (30.6)	1.67, (0.21)
Acellular dermis	51 (60.0)	34 (40.0)	2.54, (0.002)
Cartilage	11 (84.6)	2 (15.4)	0.69, (0.64)
Size			
>50%	32 (64.0)	18 (36.0)	1.60, (0.16)
<50%	159 (74.0)	56 (26.0)	
Location			(0.39)
Anterior	86 (71.7)	34 (28.3)	1.0
Posterior	52 (70.3)	22 (29.7)	1.07, (0.84)
Central	30 (85.7)	5 (14.3)	0.42, (0.10)

($p = 0.35$), number of previous tympanostomy tubes ($p = 0.82$), otorrhea in the 6 months prior to surgery ($p = 0.27$), previous adenoidectomy ($p = 0.68$) or previous myringoplasty ($p = 0.77$). Pre-school children were more likely to have a contralateral perforation ($p = 0.02$).

There was a total of 69 children with craniofacial disorders including 36 children with cleft palate, 24 children with Down syndrome and 9 children with other craniofacial disorders such a craniosynostosis. The anatomical success rate in children with craniofacial disorders was between 70.8% and 88.9% and was not statistically different between the different subtypes of craniofacial disorders or compared to children without any craniofacial disorder. While children with craniofacial abnormalities did not have a decreased anatomical success rate, they were significantly more likely to develop serous otitis media and/or require tympanostomy tubes after tympanoplasty ($p = 0.02$). The number of children with other relevant comorbidities such as chronic sinusitis (1), environmental allergies (1) or asthma (1) was not sufficient in order to perform a subgroup analysis.

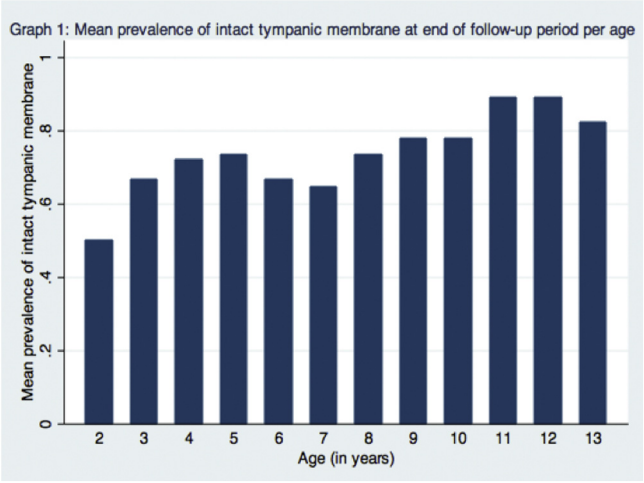

Fig. 1. Prevalence of intact tympanic membrane at the end of the follow-up period per age.

Results of the crude analysis with odds ratio of the different complications evaluated per age group and their associated odds ratio is presented in Table 3. There were no significant differences in the rate of any of the complications evaluated for the different age groups. There were 78 anatomical failures with a perforation noted at the end of the follow-up period of which 16 (20.5%) were recurrent perforations noted after more than 6 months of follow-up and 62 (79.5%) were persistent perforations. Of the 78 recurrent or persistent perforations, 20 were pinpoint (25.6%), 42 were <50% and 2 were >50% of the tympanic membrane area. 17.9% of perforations were the same size, 55.1% were smaller, 7.7% were larger and 19.2% were of unknown size. The two residual perforations >50% had been <50% at the initial surgery. Seventeen children (6.0%) underwent a tympanostomy tube insertion post-tympanoplasty and 17 children (6.4%) developed a tympanic membrane cholesteatoma pearl (12) or middle ear cholesteatoma (5). Fifty-six children underwent revision surgery for tympanic membrane perforation (42) or cholesteatoma (14). Five children undergoing revision surgery for a tympanic membrane perforation underwent a concomitant mastoidectomy due to chronic otorrhea. First revision tympanoplasty for tympanic membrane perforation was successful in 20/37 (54.1%) children, unsuccessful in 14/37 (37.8%) children and was unknown in 3/37 (8.1%) children.

Hearing results are shown in Tables 4 and 5. All age groups had significant improvement in their hearing thresholds post-tympanoplasty and the hearing thresholds were not significantly different between the three age groups. Children with an ongoing perforation after the initial tympanoplasty had poorer hearing outcomes than children with a successful tympanoplasty and had a post-operative SRT of 21.0 dB ($p = 0.25$) and a post-operative ABG of 13.5 dB ($p = 0.02$).

Logistic regression analysis revealed that covariates modifying the association between perforation post-tympanoplasty and age group were surgeon, surgical approach (transcanal vs postauricular) and etiology of perforation. Results may be found in Table 6. Multivariate analysis revealed that after adjusting for confounders there is a significant difference between the perforation rate post-tympanoplasty in preschool children (age 2–4) ($p = 0.04$) and children age 5–7 years old ($p = 0.03$) compared to

Table 3
Odds ratio of various complications per age group.

Outcome	Age 2–4 OR (95% CI)	Age 5–7 OR (95% CI)	Age 8–13 OR	*p*-Value (overall)
Persistent perforation	1.16 (0.49–2.73)	1.60 (0.85–3.02)	1.0	0.32
Recurrent perforation	3.86 (0.88–16.88)	1.93 (0.49–7.67)	1.0	0.19
Any perforation	1.66 (0.77–3.59)	1.74 (0.96–3.16)	1.0	0.16
Tubes	1.59 (0.48–5.29)	0.56 (0.17–1.82)	1.0	0.28
Cholesteatoma	2.27 (0.44–11.67)	3.46 (0.95–12.59)	1.0	0.12
Any failure	1.58 (0.78–3.23)	1.72 (0.99–2.98)	1.0	0.13
Revision surgery	2.01 (0.88–4.60)	1.47 (0.75–2.91)	1.0	0.24

children age 8–13 years old. When limiting the multivariate analysis to children with at least 6 months of follow-up the difference between the lowest and highest age group was significant with pre-school children having an incidence of perforation more than 5 times higher (95% CI 1.68–17.93, $p = 0.005$) than that of children aged 8–13 years old. The perforation rate in children aged 5–7 years old was not significantly different than that of children aged 8–13 years old ($p = 0.07$). Surgeon acted as a strong negative confounder and weakened the association between age and post-tympanoplasty perforation, thus increasing the odds of perforation in pre-school children after controlling for the effect of surgeon.

5. Discussion

This study represents the largest reported evaluation of pediatric tympanoplasty assessing specifically the outcome of pre-school children. After adjusting for confounding factors, the current study does suggest that pre-school children have a significantly higher rate of post-tympanoplasty perforation as compared to older children. The higher rate of failure in pre-school children seems to be mostly attributed to a high rate of re-perforation noted more than 6 months after tympanoplasty, with a third of failures due to reperforations after initial successful healing. This could be explained by an initially successful tympanoplasty and subsequent reperforation due to persistent Eustachian tube dysfunction or due to an acute otitis media. In addition, overall success rate of tympanoplasty in this study was lower than those previously reported in the literature for all age groups. This may be partially explained by the significant resident involvement in those cases and the fact that the procedures were performed at a tertiary referral centre and that some of these children may have been referred from other otolaryngologists that may have considered the repair too difficult for them to attempt. It may also be a reflection of the patient selection criteria by the surgeons at our centre.

Results of previous studies evaluating the association between age and success rate in pediatric tympanoplasty have been conflicting. A study by Black et al which included 14 children age 2–7 years old revealed a rate of intact graft of 56% in that age group as compared to 77% in children age 8–10 years old [15]. The difference in intact graft between the age groups was not statistically significant. Kessler et al. examined tympanoplasty outcome in 209 children and reported a lower long-term success rate in the 37 children under 6 years old ($p < 0.05$), but the short-term outcome was similar between the different age groups examined [22]. The late failure rate observed in that study and the current study suggest a high rate of recurrent perforation after initial successful healing possibly due to an immature Eustachian tube in younger children.

A meta-analysis evaluating the effect of age on pediatric tympanoplasty success included 19 articles evaluating the effect of age, with the lowest age limit being 6 years old [27]. Compilation of these articles revealed a linear association between success rate and increasing age ($p = 0.005$). Interestingly, only 5 out of the 30 articles included in the overall meta-analysis had reported an association between age and tympanoplasty success rate. While the literature does seem to indicate that the success rate in children is somewhat lower than that in adults, uncertainty remains as to what is the ideal age to repair tympanic membrane perforations in children [28]. The current results suggest that surgeons should exert caution when considering performing tympanoplasty on children less than 5 years of age since results from tympanoplasty in that age group seems to be associated with a lower success rate. Possible reasons for previous failure to identify an association between age and pediatric tympanoplasty success rate include exclusion of younger children (under 6 or 8 years old), lack of sufficient power to detect a significant difference as most studies published thus far had case series of less than 100 patients and lack of multivariate analysis to control for possible confounding factors.

While complete closure of the tympanic membrane is the desired goal, significant improvements in quality of life can also be achieved with a decreased perforation size. Sheahan et al. conducted a phone survey with parents of children who had previously undergone a tympanoplasty to evaluate parental satisfaction 8–60 months after surgery [5]. Seventy-nine percent of parents were satisfied with the outcome. For children with a persistent perforation, 40% of parents were satisfied, 56% reported fewer ear infections and 40% reported improvement in hearing.

The main confounding factor that modified the association between age and perforation post-tympanoplasty was the identity of the surgeon performing the surgical procedure. The fact that the association between the surgeon and the anatomical success rate was maintained in the multivariate analysis suggests that the surgeon's effect is likely attributable to criteria used for patient selection by each surgeon, surgical skills and variation in technique undetected by the chart review and not solely due to patient's age or choice of graft material. Individual surgeon's success rate did seem to indicate that surgeons with more than 20 years of experience (surgeons 1 and 2) had a higher success rate, which is a finding that has previously been reported when comparing senior

Table 4
Pre- and post-operative SRT per age group.

Age group	Pre-operative SRT	Post operative SRT	*p*-Value
2–4	23.3	16.7	0.02
5–7	21.7	16.7	<0.001
8–13	25.6	18.4	<0.001
ANOVA *p*-value	0.23	0.61	

Table 5
Pre- and post-operative ABG per age group.

Age group	Pre-operative ABG	Post operative ABG	*p*-Value
2–4	15.7	9.1	0.04
5–7	16.7	9.5	<0.001
8–13	21.5	11.3	<0.001
ANOVA *p*-value	0.16	0.24	

Table 6
Adjusted odds ratio of association between perforation and age group by logistic regression after controlling for confounding effect of surgeon, surgical approach and etiology of perforation.

Variable	Level	Adjusted OR of perforation OR (95% CI) $n = 267$	Adjusted OR of perforation if follow-up >6 mos OR (95% CI) $n = 146$
Age group	2–4 years old	2.46 (1.04–5.85)	5.48 (1.68–17.93)
	5–7 years old	2.06 (1.06–4.00)	2.27 (0.94–5.46)
	8–13 years old	1.0	1.0
Surgeon	1	1.0	1.0
	2	1.62 (0.71–3.73)	1.16 (0.40–3.33)
	3	3.48 (1.49–8.11)	5.07 (1.64–15.62)
	4	3.66 (0.95–14.15)	3.12 (0.61–15.80)
Approach	Post-auricular	1.0	1.0
	Trans-canal	2.37 (1.15–4.90)	2.76 (1.07–7.09)
Etiology	Tympanostomy tubes	1.0	1.0
	Chronic otitis media	0.32 (0.06––1.56)	0.13 (0.01–1.47)
	Trauma	0.25 (0.03–2.16)	0.57 (0.05–6.30)

surgeons to trainees [15,28] but no study has previously investigated specifically success rate of tympanoplasty in established surgeons. While the surgeons' choices of surgical approach, technique and graft material may have influenced their individual success rate, this study was not powered to detect factors to explain individual surgeon's success rate.

While there appeared to be a strong association between use of acellular dermis and success rate, the association between graft material, specifically acellular dermis, and success rate was not maintained on multivariate analysis. This may have been due to the fact that the association may have been explained by the surgeon's identity, as surgeons 2 and 3 were the main users of this material. It may also be due to a lack of power due to the small size of the study. Given some of the advantages of acellular dermis such as avoidance of a post-auricular incision in trans-canal tympanoplasty, further research is needed to determine whether acellular dermis is a acceptable graft material alternative for pediatric tympanoplasty.

Other factors that have been previously evaluated for their possible association with pediatric tympanoplasty success rate were evaluated as part of our study. On multivariate analysis, in addition to surgeon, surgical approach and etiology of perforation were found to be associated with success rate of tympanoplasty. The only study having directly evaluated the success rate of post-auricular compared to trans-canal tympanoplasty in children had not found any difference in the success rate between the two approaches [2]. However, given the narrower ear canal in young children, the post-auricular approach could be advantageous in providing better exposure to the tympanic membrane and thus lead to better success rate. With the increased use of the otologic endoscope and increased exposure associated with this technique, it would be interesting to evaluate whether this will lead to a decrease rate of perforation post-tympanoplasty in transcanal tympanoplasties.

In summary, the otolaryngologist should notify the caregivers of the pros and cons of early repair and inform the parents of the potential for an unsuccessful outcome in younger children undergoing tympanoplasty. Advantages of early repair include prevention of complications such as potential reduction of chronic otitis media, improved hearing and the ability to participate in water activities. Disadvantages include a potentially more technically difficult surgical procedure due to the smaller size of the external auditory canal and higher failure rate and possible need for a revision procedure or tympanostomy tubes.

5.1. Strengths and weaknesses

The major strength of this study is the large number of pre-school age children included in the analysis as well as the large size of our cohort. In addition, these results represent a "real life" situation with children with and without comorbidities having undergone surgery by multiple surgeons using different surgical techniques. Finally, this is one of few studies having performed multivariate analysis in order to determine the factors associated with failure of pediatric tympanoplasty.

The most important weakness of this study is the short duration of follow-up. One hundred twenty-nine children had less than 6 months of follow-up and the median duration of follow-up was only 7 months. This is partially attributed to the fact that the tympanoplasties were performed in a tertiary care institution with a large referral base and that some children may have had post-operative care performed by an otolaryngologist closer to home. It is possible that the results obtained would have differed if follow-up had been longer. The differences in results between all children and children with 6 or more months of follow-up could be due to the fact that children with an intact tympanic membrane at the first follow-up visit may be less likely to return for follow-up. Conversely, it is possible that children who did not have a minimum of 6 months of follow-up may have developed a recurrent or residual perforation that went undiagnosed due to their failure to return for a follow-up visit thus lowering the recurrent or persistent perforation rate when including children with less than 6 months of follow-up in the current analysis.

6. Conclusion

This is the first study evaluating the success rate of tympanoplasty in pre-school children and the study with the largest number of children under 6 years old. After adjusting for confounders, pre-school children appear to have a significantly higher odd of perforation post-tympanoplasty. While it remains uncertain whether the possible improvement in quality of life and small improvement in hearing thresholds associated with tympanoplasty outweighs the risk of tympanoplasty failure in young children, the 26% rate of revision tympanoplasty in children age 2–4 years old suggest that surgery may be best delayed in that age group.

Prospective studies with a longer follow-up period, large sample size and quality of life measures are needed to elucidate some of the key questions generated from this and prior studies.

Conflict of interest statement

No conflict of interest to disclose.

Disclosure

No financial support or financial interest to disclose.

References

[1] W.M. Koch, E.M. Friedman, T.J.I. McGill, G.B. Healy, Tympanoplasty in children: the Boston Children's Hospital experience, Arch. Otolaryngol. Head Neck Surg. 116 (1990) 35–40.
[2] A. Halim, J. Borgstein, Pediatric myringoplasty: postaural versus transmeatal approach, Int. J. Pediatr. Otorhinolaryngol. 73 (2009) 1580–1583.
[3] R.R. MacDonald, R.P. Lusk, H.R. Muntz, Fasciaform myringoplasty in children, Arch. Otolaryngol. Head Neck Surg. 120 (1994) 138–143.
[4] J.L. Lancaster, Z.G.G. Makura, G. Porter, M. McCormick, Paediatric tympanoplasty, J. Laryngol. Otol. 133 (1999) 628–632.
[5] P. Sheahan, T. O'Dwyer, A. Blayney, Results of type 1 tympanoplasty in children and parental perceptions of outcome of surgery, J. Laryngol. Otol. 116 (2002) 430–434.
[6] A.B. Friedman, M.B. Gluth, P.C. Moore, J.L. Dornhoffer, Outcomes in cartilage tympanoplasty in the pediatric population, Otolaryngol.–Head Neck Surg. 148 (2013) 297–301.
[7] M. Knapik, I. Saliba, Pediatric myringoplasty: a study of factors affecting outcome, Int. J. Pediatr. Otorhinolaryngol. 75 (2001) 818–823.
[8] S. Kumar, A. Acharya, E. Hadjihanas, C. Panagamuwa, A.L. McDermott, Pediatric myringoplasty: definition of success and factors affecting outcome, Otol. Neurotol. 31 (2010) 1417–1420.
[9] L. Shih, T. de Tar, J.A. Crabtree, Myringoplasty in children, Otolaryngol. Head Neck Surg. 105 (1991) 74–77.
[10] Y. Uyar, B. Keles, S. Koc, K. Ozturk, H. Arbag, Tympanoplasty in pediatric patients, Int. J. Pediatr. Otorhinolaryngol. 70 (2006) 1805–1809.
[11] M.M. Carr, C.P. Poje, M.L. Nagy, M.P. Pizzuto, L.S. Brodsky, Success rates in pediatric tympanoplasty, J. Otolaryngol. 30 (4) (2001) 199–201.
[12] C.A.J. Prescott, W.J. Robartes, Tympanoplasty surgery at the Red Cross War Memorial Children's Hospital 1986–1988, In. J. Pediatr. Otorhinolaryngol. 21 (1991) 227–234.
[13] M. Tos, Tympanoplasty and age, Arch. Otolaryngol. 96 (1972) 493–498.
[14] G. Berger, S. Berger, Paediatric revision myringoplasty: outcomes and prospects, J. Laryngol. Otol. 116 (2002) 690–694.
[15] J.H. Black, S.A. Hickey, P.J. Wormald, An analysis of the results of myringoplasty in children, Int. J. Pediatr. Otorhinolaryngol. 31 (1995) 95–100.
[16] K.A. Buchwach, H.G. Birck, Serous otitis media and type 1 tympanoplasties in children, Ann. Otol. Rhinol. Laryngol. Suppl. 39 (1980) 324–325.
[17] S.S. Chandrrasekhar, J.W. House, U. Devgan, Pediatric tympanoplasty: a 10-year experience, Arch. Otolaryngol. Head Neck Surg. 121 (1995) 873–878.
[18] S.D. Charlett, L.C. Knight, Pediatric myringoplasty: does previous adenoidectomy improve the likelihood of perforation closure, Otol. Neurotol. 30 (2009) 939–942.
[19] W.O. Collins, F.F. Telischi, T.J. Balkany, C.A. Buchman, Pediatric tympanoplasty: effect of contralateral ear status on outcome, Arch. Otolaryngol. Head Neck Surg. 129 (2003) 646–651.
[20] F. Denoyelle, G. Roger, P. Chauvin, E-N. Garabedian, Myringoplasty in children: predictive factors of outcome, Laryngoscope. 109 (1) (1999) 47–51.
[21] J. Friedberg, T. Gillis, Tympanoplasty in childhood, J. Otolaryngol. 9 (2) (1980) 165–168.
[22] A. Kessler, W.P. Potsic, R.R. Marsh, Type 1 tympanoplasty in children, Arch. Otolaryngol. Head Neck Surg. 120 (1994) 487–490.
[23] T. Lau, M. Tos, Tympanoplasty in children: an analysis of late results, Am. J. Otol. 7 (1) (1986) 55–59.
[24] G.O. Te, F.M. Rizer, A.G. Schuring, Pediatric tympanoplasty of iatrogenic perforations from ventilation tube therapy, Am. J. Otol. 19 (1998) 301–305.
[25] N. Umapathy, P.J. Dekker, Myringoplasty: is it worth performing in children? Arch. Otolaryngol. Head Neck Surg. 129 (2003) 1053–1055.
[26] E.M. Monsell, T.A. Balkany, G.A. Gates, R.A. Goldenberg, W.L. Meyerhoff, J.W. House, Committee on Hearing and Equilibrium guidelines for the evaluation of results of treatment of conductive hearing loss. American Academy of Otolaryngology– Head and Neck Surgery Foundation, Inc, Otolaryngol. Head. Neck. Surg. 113 (1995) 186–187.
[27] J.T. Vrabec, R.W. Deskin, J.J. Grady, Meta-analysis of pediatric tympanoplasty, Arch. Otolaryngol. Head Neck Surg. 125 (1999) 530–534.
[28] H. Emir, K. Ceylan, Z. Kizilkaya, H. Gocmen, H. Uzunkulaoglu, E. Samim, Success is a matter of experience: type 1 tympanoplasty, Eur. Arch. Otorhinolaryngol. 264 (2007) 595–599.

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Single-sided Deafness Cochlear Implantation: Candidacy, Evaluation, and Outcomes in Children and Adults

David R. Friedmann, Omar H. Ahmed, Sean O. McMenomey, William H. Shapiro, Susan B. Waltzman, and J. Thomas Roland Jr.

Department of Otolaryngology–Head and Neck Surgery, NYU School of Medicine, New York, NY, U.S.A.

Objectives: Although there are various available treatment options for unilateral severe-to-profound hearing loss, these options do not provide the benefits of binaural hearing since sound is directed from the poorer ear to the better ear. The purpose of this investigation was to review our center's experience with cochlear implantation in such patients in providing improved auditory benefits and useful binaural hearing.
Study Design: Retrospective chart review.
Methods: Twelve adult patients and four pediatric patients with unilateral severe-to-profound hearing loss received an implant in the poorer ear. Outcome measures performed preoperatively on each ear and binaurally included consonant–nucleus–consonant (CNC) monosyllabic words and sentences in noise. The mean pure-tune average in the better ear was within normal range.
Results: Test scores revealed a significant improvement in CNC and sentence in noise test scores from the preoperative to most recent postoperative evaluation in the isolated implant ear. All adult subjects use the device full-time.
Conclusions: The data reveal significant improvement in speech perception performance in quiet and in noise in patients with single-sided deafness after implantation. Performance might depend on factors including length of hearing loss, age at implantation, and device usage. **Key Words:** Pediatric and adult cochlear implantation—Single-sided deafness.
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Single-sided deafness (SSD) refers to an asymmetric condition in which a patient has one ear with severe-profound sensorineural hearing loss with normal hearing in the contralateral ear. The impact of unilateral hearing loss may be variable and considerations in children are different from those in adults. Nevertheless, they experience a substantial hearing deficit.

In typical listening situations, sound reaching one ear differs from the sound that reaches the opposite ear in two ways: because of the head shadow effect, there is a difference in the intensity of the sound at each ear and there is a variance between the times when the sound reaches each ear. One of the most important uses of these differences is to allow the listener to know the direction from which a sound, including speech, originates. Moreover, these abilities allow the listener to separate speech from background noise. Since the lack of ability to discriminate and understand speech in the presence of competing sounds reduces an individual's competence and effectiveness in personal and professional interactions, the loss of binaural hearing can significantly affect socioeconomic and quality-of-life functions.

Studies in children reveal that unilateral hearing impairment may negatively affect language development, social interactions, and academic performance (1,2). Some adults with postlingual SSD seem only minimally bothered by the loss and do not pursue further treatment, whereas others possibly related to occupational or social considerations seek assistive listening technologies.

Still the benefits of binaural hearing, especially in aiding with difficult listening situations, are clear and have been well described elsewhere for both normal hearing listeners (3) and those with bilateral cochlear implants (4). These include improved speech understanding in quiet and in noise, better localization, and the ability to hear at greater distances. In addition to the objective benefits of binaural hearing there are numerous subjective advantages including a more ''balanced'' and less tiring listening experience.

Most rehabilitative options for SSD route sound to the contralateral cochlea resulting in only unilateral auditory stimulation either with transmission via cross-routing of

Address correspondence and reprint requests to David R. Friedmann, M.D., NYU Langone Medical Center, New York, NY 10016, U.S.A.; E-mail: drf249@nyumc.org

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S.O.M., J.T.R., and W.H.S. are on the advisory boards for Cochlear Corp. J.T.R. is also on the advisory board for AB Corp. The remaining authors disclose no conflicts of interest.

sound (CROS) amplification devices or osseointegrated devices such as bone anchored hearing aids (BAHA). Although both of these approaches provide the patients with some access to sound, the configurations do not restore hearing to the deaf ear but rather route the signals so that the benefits of binaural hearing are not maximally achieved as previously demonstrated (5). Even with such technology, improved hearing in difficult listening situations and the ability to localize sound remain elusive to most patients with SSD (6) and may actually make listening more difficult with certain signal-to-noise ratios incident on the unaffected ear. Cochlear implants for SSD were first introduced in the setting of intractable tinnitus (7), but have since been shown to have benefits far beyond tinnitus suppression (8,9).

Our purpose in this article was to review our institutional experience with selecting appropriate SSD pediatric and adult patients to receive a cochlear implant for various indications and their subjective and objective outcomes to date to determine if 1) there is a functional increase in word and sentence recognition in quiet and in noise and 2) the binaural advantage can be restored by placing a cochlear implant in the poorer ear.

METHODS

Subjects

This retrospective chart review was approved by our institutional review board (IRB) and included 12 adult patients and 4 children with SSD. All patients had unaidable hearing in the affected ear. There were no strict hearing criteria in the better and all patients were evaluated on an individual basis but the average PTA in the better hearing ear was 12.7 (SD 7.0). All patients contributing data had at least 1 year of CI use.

See Table 1 for adult demographic factors. Most subjects were deaf as a result of sudden sensorineural hearing loss (SSNHL) (67%), and did not have any pathology in their normal hearing ear (83%). The PTA of the deaf ear among all subjects was 87.0 (SD 8.3). The mean age at diagnosis among adult patients with SSD was 47.3 years (SD 12.4) and on average they were implanted 3.1 years (SD 5.7) later. Eleven adult patients received Cochlear Nucleus (Englewood, CO, U.S.A.) devices and one received Advanced Bionics (Valencia, CA, U.S.A.) devices. All four children received Cochlear Nucleus devices. Intraoperatively, all patients had full insertions of the electrode array without perioperative or postoperative complications.

Speech Perception

Patients were evaluated according to our institutional SSD protocol (Table 2). Before the availability of direct connect, a ''plug and muff'' technique was used to minimize/eliminate the role of better hearing ear (n = 4) in a sound-proof booth using recorded material. To ensure that the poor ear was completely isolated from the ''good'' ear on the nonimplanted side, the good ear was plugged and muffed using E.A.R. foam earplugs (3 M Co., St. Paul, MN, U.S.A.) and TASCO sound shield over-the-head earmuff Model #2900. (TASCO Corp, Riverside, RI, U.S.A.). For the plug, the mean attenuation for frequencies 125 to 8000 Hz was 42.3 dB with a noise reduction rating (NRR) of 29. The muff had a mean attenuation of 33.9 dB for frequencies 125 to 8000 Hz with an NRR of 29.

TABLE 1. *Demographics*

Category	n (%)
Sex	
Male	6 (50)
SSD ear	
Left	7 (58)
Etiology of SSD	
SSNHL	8 (67)
Other	4 (33)
Pathology in normal ear	
Yes	2 (17)
	Mean (SD)
Age at implantation	50.5 (13.4)
Age at deafness	47.3 (12.4)
Pure-tone average (PTA); 0.5, 1, 2 kHz	
Normal ear	12.7 (7.0)
SSD ear	87.0 (8.3)
Duration of deafness to CI (yr)	3.1 (5.7)
Length postoperative follow-up (yr)	3.4 (1.8)

Demographics of adult SSD patients who underwent cochlear implantation at our institution (n = 12).

PTA was calculated using air conduction lines. Other etiologies of SSD in the data set include Ménière's, chronic otitis media, and sequela from CPA meningioma resection. SD indicates standard deviation.

Later in our experience, a manufacturer-specific direct connect system to the cochlear implant sound processor was used to allow isolation of the CI ear for testing with an insert earphone in the unaffected ear. Direct connect (DC) audiometric testing (Cochlear Americas), via electrical cable connection, to the cochlear implant processor allows testing of each ear in isolation or together (binaurally) using tones or speech. This allows elimination of the inadvertent role of the better hearing ear in sound field testing and allows for hearing in noise testing with spatially separated competing signal and sound localization without the need for multispeaker arrays. The generalizability of this system has been validated elsewhere including precise timing and level cues (10–12). The signals are processed via a head-related transfer function (HRTF) so that it is equivalent to sound field presentation and the software provides calibration to ensure that the signals are delivered at the desired presentation levels.

TABLE 2. *Institutional protocol for cochlear implantation in SSD patients*

Pure-tone air and bone conduction thresholds
Imittance measures including tympanometry and acoustic reflexes and otoacoustic emissions
MRI or CT imaging confirmation of a cochlea and cochlear nerve and to detect inner ear malformations or evidence of ossification
Speech reception thresholds and speech discrimination where age appropriate (CNC, HINT)
Adaptive HINT is also done with sound field using CROS amplification and/or the BAHA soft band
Localization testing using a manufacturer-specific ''direct connect'' system
Vertigo and tinnitus questionnaires are included in the evaluation
All postimplantation testing is performed using a manufacturer-specific direct connect system

Institutional protocol for cochlear implantation in SSD patients.

Speech perception both pre- and postoperatively was measured in quiet using consonant–nucleus–consonant (CNC) words as well as AzBio sentences and administered at 60 dB A.

Hearing in Noise

Hearing in background noise with various signal-to-noise ratios (SNR) was also tested with speech from the front and noise incident from the front, the better hearing ear, and the CI ear. Bamford–Kowal–Bench sentence-in-noise (BKB-SIN) (Etymotic Research 2005, Elk Glove Village, IL, U.S.A.) testing was administered for four adult subjects, whereas adaptive hearing in noise test (HINT) testing was administered for the remaining six adult subjects.

BKB-SIN is designed to assess sentence recognition in noise and consists of 36 lists of sentences presented in 4-talker babble noise. The sentences are presented at 65-dB SPL and the level of the noise is varied in 3 dB steps at fixed SNR beginning at +21 dB SNR (easy) descending to −6 dB SNR (hard) to obtain a speech reception threshold where the subjects can repeat key words 50% of the time (SNR-50); therefore, a lower score is indicative of better performance. The test was performed in the sound field in each ear individually and in the sound field in three conditions: speech front/noise front, speech front/noise right, speech front/noise left (n = 4) or using Direct Connect (n = 6) as noted above. Scores are indicated as dB SNR. In those patients tested in both sound field and using Direct Connect, results were found to be equivalent.

As DC was integrated into our evaluations, we began using adaptive HINT testing in place of BKB-SIN for evaluating hearing in noise sentences on all new patients as well as for subsequent evaluations of previously implanted patients.

Localization

Localization testing was performed with the Direct Connect system as described above for five adult patients. A broadband noise from 1 of 12 virtual locations in the rear hemifield with locations numbered 1 through 12 on a response sheet, from right to left, and positioned to represent an arc from 97.5 degrees (on the right) to 262.5 degrees (on the left) with 15 degrees separations between source locations. The task involves a verbal response corresponding to the perceived location of the sound. Localization testing is reported as the degrees root mean squared (RMS) error.

RESULTS

Adult Subjects, n = 12

Postoperative data were available for 10 adult patients (Table 3) as one transitioned care to another center whereas another was not a native English speaker. Data from most recent postoperative evaluation (3.4 yr ± 1.8) were used for performance comparison relative to preoperative data. Table 4 demonstrates individual subject outcomes data.

Speech Perception

There was significant improvement in CNC word scores in the implanted ear with an average benefit of 54% (SE ± 8.4), $p = 0.001$ in seven adult patients who underwent this test. Improvement in sentence scores on AzBio in quiet relative to the SSD ear was on average 82.5% (SE ± 14.5); however, this was not statistically significant ($p = 0.11$) as there were only two matched pairs. Sound field and direct connect results were equivalent in all patients.

Hearing in Noise

Speech-in-noise using binaural hearing BKB-SIN or adaptive HINT tests demonstrated that when noise was presented to the SSD/CI ear (speech front), the signal-to-noise ratio significantly decreased with an average reduction of 2.0 dB SNR (SE ± 0.8), $p = 0.047$ in nine

TABLE 3. *Outcomes across clinical time points*

Category	n	Preop (SD)	n	1 year Postop (SD)	n	Most recent Postop	Preop vs Most Recent Postop *p* Value
CNC words (% score)							
CI ear	9	2.9 (5.6)	8	55.4 (16.9)	7	57.7 (21.1)	0.001
Bilateral	4	98.0 (2.3)	8	98.0 (1.4)	7	95.7 (4.1)	0.594
AZ BIO (quiet)							
CI ear	5	6.6 (9.2)	3	95.0 (4.6)	2	92.0 (7.1)	0.111
Bilateral	5	100 (0)	3	100.0 (0)	2	100.0 (0)	—
HINT/BKB-SIN-noise front (SNR)							
Bilateral	10	−1.8 (1.9)	8	−2.4 (1.0)	7	−2.1 (1.3)	0.960
HINT/BKB-SIN-noise CI ear (SNR)							
Bilateral	10	−2.4 (2.7)	8	−6.6 (2.5)	7	−5.3 (3.0)	0.047
HINT/BKB-SIN-noise better ear (SNR)							
Bilateral	10	−0.3 (3.1)	8	−2.5 (2.0)	7	−3.7 (1.5)	0.005
Localization (degrees RMS)							
CI ear	0	—	5	54.0 (11.6)	5	67.0 (15.1)	—
Bilateral	4	42.5 (7.7)	5	47.2 (9.4)	5	45.0 (16.6)	0.205

Speech perception of adult SSD patients who underwent cochlear implantation.

p values calculated using dependent *T* test. ''—'' indicates measurement could not be calculated secondary to lack of matched pairs or the standard error of the difference being zero. As given in Table 1, the average time from surgery to the most recent post-op visit (>1 yr post-op) is 3.4 years (SD 1.8). AzBio (quiet) indicates Arizona biomedical sentences in quiet condition; BKB-SIN, Bamford–Kowal–bench sentence-in-noise test; CI, cochlear implant; CNC words, consonant–vowel nucleus–consonant words; HINT, hearing in noise test; RMS, root mean square; SNR, signal-to-noise ratio.

TABLE 4. *Individual subject data*

ID	Age at Implantation	Duration of Deafness (yr)	Etiology	PTA of Normal Ear	PTA of SSD Ear	CNC Words Score (% score)		HINT/BKB-SIN, Noise Front (SNR)		HINT/ BKB-SIN, Noise CI Ear (SNR)		HINT/ BKB-SIN, Noise Better Ear (SNR)		Localization (degrees RMS)		Device
						Preop, CI Ear	One Year Postop, CI Ear	Preop, Bilateral	One Year Postop, Bilateral	Preop, Bilateral	1 Year Postop, Bilateral	Preop, Bilateral	1 Year Postop, Bilateral	Preop, Bilateral	1 Year Postop, Bilateral	
1	58	0.92	SSNHL	17	95	0	69	−0.6	−4.0	1.4	−7.4	−4.8	−3.1	46	60	Nucleus
2	64	21	Ménière's	18	83	0	24	−6.5	−3.3	−3.5	−8.6	0.3	−3.1	48	44	Nucleus
3	65	1.75	SSNHL	5	78	8	63	−0.5	−1.9	−5.5	−7.8	2.3	−1.0	45	35	Nucleus
4	27	1.08	SSNHL	0	100	0	49	−1.9	−2.9	0.4	−8.3	−5.5	−4.3	31	45	Nucleus
5	30	1	SSNHL	20	85	0	76	−3.0	−1.3	−5.5	−4.5	−3.5	−3.8	—	—	Nucleus
6	62	0.75	SSNHL	23	85	2	76	−0.1	−4.0	−1.5	−5.5	1.5	−4.5	—	—	Nucleus
7	36	0.42	COM	10	112	0	66	−1.5	−3.0	−6.0	−6.3	3.5	0.8	—	—	Nucleus
8	56	3.42	SSNHL	17	90	0	84	−0.5	−1.6	−0.5	−1.5	0.8	−4.5	—	—	Nucleus
9	47	2.42	CPA lesion	7	73	16	54	−2.0	−1.0	−0.5	−1.3	1.0	−0.3	—	—	AB
10	62	1.58	SSNHL	10	98	—	42	−1.5	−2.0	−2.8	−8.3	1.4	−4.8	—	52	Nucleus

Individual adult subject outcomes data after SSD cochlear implantation.
Pure-tone average (PTA) was calculated using air conduction lines at 0.5, 1, and 2 kHz. "—" indicates that data were unavailable. For subjects 6 and 8 in table ("ID" column), data from 3 years post-op were used as 1 year post-op data were unavailable.
AB indicates Advanced Bionics; COM, chronic otitis media; RMS, root mean square; SD, standard deviation; SNR, signal-to-noise ratio; SSNHL, sudden sensorineural hearing loss.

adult patients tested. When noise was presented to the better hearing ear (speech front), the signal-to-noise ratio significantly decreased with an average reduction of 4.6 dB (SE ± 1.0), $p = 0.005$.

Localization

No significant difference in sound localization was found when comparing preoperative data to 1-year postoperative data with regards to root mean square (RMS) error values (n = 4 matched pairs, $p = 0.61$). Furthermore, no difference was found when comparing preoperative data to postoperative data from more than 1 year after surgery (n = 2 matched pairs, $p = 0.21$).

Subjective Assessment

All adult subjects were able to integrate the signal from the implanted ear (electrical) with the acoustic signal, without deterioration in speech understanding in their better hearing ear. All patients with tinnitus reported suppression since device activation.

Pediatric Subjects (n = 4)

Our institutional experience consists of four pediatric SSD patients implanted to date. The first child was implanted at the age of 10, and is now 14 years old. She has enlarged vestibular aqueduct (EVA) and a long duration of deafness in her left ear. Preoperatively, she obtained 0% on CNC words in the effected ear alone. Her score at the 1-year post-op interval was 18% but has since dropped to 6% by year three. Concurrently, there has been a progressive decline in the nonimplanted ear alone from 98 to 80% at her most recent evaluation. At 3 months and 1 year, BKB-SIN scores were significantly improved in all three conditions compared with preoperative values, but have since declined to poorer than preimplant scores. Although she initially wore the device regularly, she now wears it only in school—though she does report subjective benefit during use as duly noted by her parents and teachers. Evidence from our experience with SSD patients after cochlear implantation is that although the quality of the auditory percept may not be acceptable, as they lose hearing in the nonimplanted hearing ear (as expected in patients of EVA, for example), they begin to better integrate and interpret the CI signal. This has not been the case to date with this patient as she has been wearing her device with less regularity over time. When questioned, she seems too focused over concern for her declining acoustic hearing to recognize the long-term benefit of using her implant more regularly.

The second pediatric impatient was implanted at the age of six and had PBK-word scores of 20%, HINT-Q was 76% and HINT-N was 49% in implant only condition at 3-months poststimulation. Bimodal scores were 100% showing that the signal was not being degraded by the addition of an electrical stimulus to the normal hearing ear. Interestingly, despite the apparent increase in performance, he only wears the CI in school and sometimes complains that it "bothers" the good ear.

More recently, his father reports he has not worn his implant at all over the last few months. Of note, family dynamics seem to play a role in this patient's device use.

The third pediatric patient was 3 years old at the time of implantation. As of the 3-month postoperative evaluation, PBK-word scores were 96% with the nonimplanted ear alone and 32% with the implant alone. In the bimodal condition the word score was 96% attributable to the ceiling effect from having one normal hearing ear. Importantly, the combined signal did not cause a decrement in performance. On the sentence test, with noise-front she scored 100% in the nonimplanted ear, 70% with the CI alone, and 100% in the bimodal condition. Her father reports that the patient no longer asks where sound is coming from and responds better to sound in general.

Overall, the children demonstrated varying degrees of open-set speech perception in the implanted ear and bilateral improvement in the presence of background noise. However, these few children introduce some of the issues related to expectations after a prolonged duration of deafness and the impact of device use on performance.

Most recently, a family presented with their 6-month old who was diagnosed with sensorineural hearing loss. The family had done extensive research and asked many appropriate questions. At their request, the child underwent a cochlear implant evaluation at our center. After extensive counseling, the family elected to proceed with cochlear implantation, at the age of 11 months. There are not yet any postoperative data available.

DISCUSSION

Perhaps the least understood aspect of unilateral hearing loss is determining if and when treatment is indicated. Some patients have to the ability to adapt well without any intervention. Although adults who have experienced postlingual SSD can endorse certain deficits or listening difficulties, the same cannot be assumed of children. Experience suggests that some children benefit from noninvasive interventions; however, determining optimal treatment and timing for a given patient remains a challenge. Some children and adults also overcome such deficits without intervention.

The other available treatment options for SSD do not restore hearing to the affected ear and hence, lack the advantages of binaural hearing that require sound to arrive at each ear independently for the processing of timing and pitch differences to be integrated by the brain. It should be noted that both the CROS and bone-anchored hearing aids may have undesirable effects in certain listening situations including hearing in noise, especially when noise is present on the side with the implant and may be routed to the better hearing ear, worsening the signal-to-noise ratio and making listening more difficult. Cochlear implants may overcome these issues, but should not be expected to restore all of the benefits of binaural hearing.

Studies such as our own on SSD CI are hampered by our inability to fully measure the efficacy of the treatment. Subjective improvement of localization and speech understanding in difficult listening situations in real-life situations with the addition of the second ear after implantation may actually be more important than our ability to quantify this with currently available tools and methods. It is possible that the tests currently being used are not sensitive enough to accurately reflect subjective patient reports until a certain level of competence is reached. As we move forward with evaluating SSD candidacy for cochlear implantation, it will be important to devise measurement tools that can better reflect the binaural advantage in the sound field in the presence of a normal or near-normal ear. Next we consider the factors that we use to consider candidacy for SSD CI on the basis of our experience so far.

Candidacy Considerations

As observed in Table 1, our patients were diverse in their baseline characteristics including both demographics and audiometric characteristics. In some patients, the better hearing ear was in the normal range, but threatened in some way as in the case of an inner ear malformation predisposing to progressive hearing loss or as yet minimally symptomatic retrocochlear pathology in an only-hearing ear. Patients differed significantly in their motivating factors for pursuing cochlear implantation be it tinnitus suppression, trouble in difficult listening situations, or anticipated hearing loss in an only-hearing ear. Many more patients with SSD have been evaluated for cochlear implantation at our center and this experience has allowed us to define the following parameters for SSD CI candidacy.

Absolute Indication: Late Stage Unilateral Ménière's Disease

Patients with late stage Ménière's disease may struggle with intractable vertigo from an ear essentially nonfunctional from an auditory perspective. With a simultaneous labyrnthectomy and ipsilateral cochlear implant, patients can have definitive treatment of their vertigo while bringing their ''ear back to life'' all during an outpatient ambulatory procedure. In 2013, Hansen et al. reported on the results of cochlear implantation in patients with Ménière's disease who progressed to profound sensorineural hearing loss with one ear. They reported significant improvement in word and sentence scores, though ability to localize sound in this cohort showed much more modest improvement (13). We have had similar experience with our cohort and we think this provides a hopeful option for patients who have often had years of suffering with their disease to both alleviate their vertigo and rehabilitate their hearing.

Absolute Indication: An ''At Risk'' Only Hearing Ear

Though rare, a threatened only hearing ear, for example, an acoustic neuroma or other retrocochlear pathology, is an important consideration for a cochlear implant. These patients live in fear of the possibility of 1 day waking up suddenly deaf ill equipped to handle the

communication challenges that arise and not having previous experience or need to comprehend manual communication. Depending on the etiology, these patients may still be candidates for CI after bilateral hearing loss, but pre-emptive implantation at an early age can limit the duration of deafness in the worse hearing ear and hence improve likely outcomes if the threatened ear is not viable for implantation.

Additionally, a cochlear implant can provide assurance that if and when the patient loses hearing in the threatened only hearing ear that they will not be completely ''off line'' with their cochlear implant. We have found this to be important in patients even in cases where the electric signal is not well integrated during the interval of persistent acoustic hearing as these patients quickly adapt to electric only hearing once further loss occurs.

Absolute Indication: Pediatric Progressive Hearing Loss

Although criteria continue to be defined, cochlear implant candidacy for SSD is most favored in younger patients with progressive conditions such as enlarged vestibular aqueduct (EVA), genetic conditions, autoimmune inner ear disease, ototoxicity, and certain metabolic diseases. Since the good ear is likely to decline eventually, re-establishing hearing in the poorer ear avoids the untoward sequelae of long duration of deafness and total auditory deprivation.

Counseling and Other Considerations

Just as in any family with children undergoing evaluation for a cochlear implant, an important part of the preoperative counseling includes ensuring patients and their families understand the range of possible outcomes as well as the considerable time and effort required for optimal performance with the device. Additionally, particular consideration should include discussion about subjective performance and progress over time, in addition to objective testing. An assessment of functional impairments may be more important than objective audiologic testing, most of which may be relatively normal with one hearing ear. For those children who are school age, one should inquire of the family whether they have noted difficulty in particular listening conditions, in social interactions, or in reports from teachers.

Another consideration is the very young child with SSD. With acknowledgement that some children with SSD grow up to be well-functioning adults and adapt well, these outcomes are difficult to predict. The developing brain is at maximal neuroplasticity at a young age and so a prolonged period of auditory deprivation may compromise ultimate auditory performance with treatment. By analogy to adults, there are some adults who have lived with SSD without perceived difficulty, whereas others have found it challenging and no factors have yet been identified to know which patients fall into which group. Unfortunately, attempting to clarify these unknowns introduces a paradox. Waiting until a child gets older may allow a better determination of the impact of the hearing loss on functioning and learning, but this wait introduces a longer duration of deafness, a negative relationship in predicting CI outcomes. A recent review of the experience in Freiburg, Germany, with pediatric SSD indicates that children with acquired hearing loss and a shorter duration of hearing loss outperformed those with a longer duration of SSD (14). It is important that the family understands all of these considerations when making the decision with the cochlear implant team.

Additionally, at this early stage of investigation, successfully obtaining financial reimbursement surrounding the surgery, the device and associated visits to the implant center represent an important obstacle to its wider adoption.

Relative Contraindications

After a certain period of time, as yet undefined, one might expect the length of deafness to be too long for the benefits of cochlear implants to be realized. Until data clarify such a cut-off, implantation with proper counseling may be considered.

CONCLUSIONS

SSD can have a significant impact on developmental spheres and various aspects of quality of life. An informed discussion to include all available therapies and their respective advantages and disadvantages with the family and CI team is essential to the decision-making process. Early experience with SSD CI recipients suggests that cochlear implantation, with appropriate preoperative assessment and counseling and postoperative management, may offer these patients the best opportunity to realize the benefits of binaural hearing. Although in our center, certain conditions seem like clear indications, further data will be necessary before this treatment modality is advocated more widely.

REFERENCES

1. Lieu JE, Tye-Murray N, Fu Q. Longitudinal study of children with unilateral hearing loss. *Laryngoscope* 2012;122:2088–95.
2. Bess FH, Tharpe AM. Performance and management of children with unilateral sensorineural hearing loss. *Scand Audiol Suppl* 1988;30:75–9.
3. Hawley ML, Litovsky RY, Culling JF. The benefit of binaural hearing in a cocktail party: Effect of location and type of interferer. *J Acoust Soc Am* 2004;115:833–43.
4. Brown KD, Balkany TJ. Benefits of bilateral cochlear implantation: a review. *Curr Opin Otolaryngol Head Neck Surg* 2007;15:315–8.
5. Arndt S, Aschendorff A, Laszig R, et al. Comparison of pseudobinaural hearing to real binaural hearing rehabilitation after cochlear implantation in patients with unilateral deafness and tinnitus. *Otol Neurotol* 2011;32:39–47.
6. Wazen JJ, Ghossaini SN, Spitzer JB, Kuller M. Localization by unilateral BAHA users. *Otolaryngol Head Neck Surg* 2005;132:928–32.
7. Van de Heyning P, Vermeire K, Diebl M, et al. Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Ann Otol Rhinol Laryngol* 2008;117:645–52.
8. Vermeire K, Van de Heyning P. Binaural hearing after cochlear implantation in subjects with unilateral sensorineural deafness and tinnitus. *Audiol Neurootol* 2009;14:163–71.

9. Roland JT Jr, Shapiro WH, Waltzman SB. Cochlear implantation as a treatment option for single-sided deafness: Speech perception benefit. *Audiol Neurotol* 2011;16 (Suppl 1): 8–9.
10. Aronoff JM, Freed DJ, Fisher LM, et al. The effect of different cochlear implant microphones on acoustic hearing individuals' binaural benefits for speech perception in noise. *Ear Hear* 2011;32:468–84.
11. Aronoff JM, Freed DJ, Fisher LM, et al. Cochlear implant patients' localization using interaural level differences exceeds that of untrained normal hearing listeners. *J Acoust Soc Am* 2012;131: EL382–7.
12. Chan JC, et al. Evaluation of binaural functions in bilateral cochlear implant users. *Int J Audiol* 2008;47:296–310.
13. Hansen MR, Gantz BJ, Dunn C. Outcomes after cochlear implantation for patients with single-sided deafness, including those with recalcitrant Ménière 's disease. *Otol Neurotol* 2013;34:1681–7.
14. Arndt S, et al. Cochlear implantation in children with single-sided deafness: Does aetiology and duration of deafness matter? *Audiol Neurootol* 2015;20 (Suppl 1):21–30.

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Significance of Unilateral Enlarged Vestibular Aqueduct

John Greinwald, MD; Alessandro deAlarcon, MD; Aliza Cohen, MA; Trina Uwiera, MD; Keijan Zhang, PhD; Corning Benton, MD; Mark Halstead, MD; Jareen Meinzen-Derr, PhD

Objectives/Hypothesis: To describe the clinical phenotype of pediatric patients with unilateral enlarged vestibular aqueduct (EVA) and then to compare the findings to two clinically related phenotypes: bilateral EVA and unilateral hearing loss without EVA. In view of clinical observations and previously published data, we hypothesized that patients with unilateral EVA would have a much higher rate of contralateral hearing loss than patients with unilateral hearing loss without EVA.

Study Design: Retrospective cohort study.

Methods: Patients with unilateral or bilateral EVA were identified from a database of children with sensorineural hearing loss who were seen at a tertiary care institution between 1998 and 2010. Those with imaging findings consistent with well-established EVA criteria were identified. A comparative group of patients with unilateral hearing loss without EVA was also identified. The following specific outcome measurements were analyzed: 1) hearing loss phenotype, 2) laterality of EVA and hearing loss, 3) midpoint and operculum vestibular aqueduct measurements, and 4) genetic test results.

Results: Of the 144 patients who met our inclusion criteria, 74 (51.4%) had unilateral EVA. There was a strong correlation between the presence of hearing loss and ears with EVA. Fifty-five percent of patients with unilateral EVA had hearing loss in the contralateral ear; in most of these patients, the hearing loss was bilateral. Contralateral hearing loss occurred in only 6% of patients with unilateral hearing loss without EVA. No significant differences were found in temporal bone measurements between the ears of patients with unilateral EVA and ipsilateral hearing loss and all ears with EVA and normal hearing ($P = .4$). There was no difference in the rate of hearing loss progression in patients with unilateral EVA between ears with or without EVA (16 of 48 [33.3%] vs. 9 of 27 [33.3%], respectively; $P = 1.0$). There was no difference in the rate of hearing loss progression in patients with bilateral and unilateral EVA (41 of 89 ears [46.1%] vs. 25 of 75 ears [33.3%], respectively; $P = .1$); however, both EVA groups had higher rates of progression compared to patients with unilateral hearing loss without EVA. There was a strong correlation between the presence of hearing loss at 250 Hz and the risk of more severe hearing loss and progressive hearing loss. Patients with bilateral EVA and *SLC26A4* mutations had a higher rate of progression than patients who had no mutations ($P = .02$). No patients with unilateral EVA had Pendred syndrome.

Conclusions: Children with unilateral EVA have a significant risk of hearing loss progression. Hearing loss in the ear contralateral to the EVA is common, suggesting that unilateral EVA is a bilateral process despite an initial unilateral imaging finding. In contrast to bilateral EVA, unilateral EVA is not associated with Pendred syndrome and may have a different etiology. Temporal bone measurements, hearing loss severity, and hearing loss at 250 Hz were all correlated with the risk of progressive hearing loss. Clinicians should become knowledgeable regarding the implications of this disease process so that families can be counseled appropriately.

Key Words: Hearing loss, genetics, molecular biology.

Level of Evidence: 2b.

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INTRODUCTION

Over the past two decades, abnormalities of the temporal bone have increasingly been recognized as an important etiology of sensorineural hearing loss (SNHL).[1–4] Given that high-resolution computed tomography (CT) and magnetic resonance imaging have identified these abnormalities in up to 37% of children with previously unexplained SNHL, imaging has become an integral component of the standard evaluation of children with SNHL.[3,4] The most common finding revealed by imaging is an enlarged vestibular aqueduct (EVA); this is followed by abnormalities of the cochlea and the vestibular system.[5]

Valvassori and Clemis were the first to describe a group of children with SNHL and concomitant EVA.[6] In a cohort of 3,700 patients who had undergone polytomographic studies, these authors identified 50 patients with

From the Ear and Hearing Center, Division of Pediatric Otolaryngology, Cincinnati Children's Hospital Medical Center (J.G., A.D., A.C., T.U., J.M.-D.); Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati College of Medicine (J.G., A.D., J.M.-D.); Division of Human Genetics, Cincinnati Children's Hospital Medical Center (J.G., K.Z.); Department of Radiology, Cincinnati Children's Hospital Medical Center (C.B., M.H.); and Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center (J.M.-D.), Cincinnati, Ohio, U.S.A.

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Send correspondence to John Greinwald, MD, FAAP, Ear and Hearing Center, Division of Pediatric Otolaryngology–Head and Neck Surgery, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229. E-mail: John.Greinwald@cchmc.org

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EVA and proposed that EVA was a congenital malformation of the temporal bone that predisposes affected individuals to the early onset of hearing loss and vestibular disturbance. Valvassori and Clemis, as well as other authors, maintained that enlargement of the endolymphatic sac and duct is the underlying process causing the bony change of the vestibular aqueduct.[7–9] Spiegel and Lalwani proposed that the underlying pathophysiology of EVA is similar to that of endolymphatic hydrops.[10]

EVA was initially defined as a vestibular aqueduct >1.5 mm at the midpoint.[6] This measurement was based on polytomographic studies, which are somewhat crude in comparison to our current technology. Although early generation CT scans allowed for a clearer view of the vestibular aqueduct, the advent of high-resolution CT permitted more accurate and quantifiable aqueduct assessment; this enabled researchers to distinguish between normal and enlarged aqueducts. In view of this technological advancement, Vijayasekaran et al. were able to specifically define EVA.[11] Using a standardized measurement algorithm, they studied 73 children with normal hearing and determined a normal vestibular aqueduct midpoint to be at $\leq$0.9 mm and a normal vestibular aqueduct operculum to be $\leq$1.9 mm. These measurements have since been used as the radiographic standard for defining EVA.

The otologic phenotype of EVA is exceedingly variable. This phenotype can be associated with fluctuating and progressive hearing loss[12,13] as well as disequilibrium and vertigo.[14] The age at diagnosis of the hearing loss ranges from infancy to adulthood. The reported severity of hearing loss ranges from normal hearing (rare) to profound hearing loss, which is usually bilateral.[15,16] Although unilateral hearing loss in patients with EVA has been reported,[12,17,18] it is not well described. Preciado et al.[19] found that the diagnostic yield of imaging studies in children with EVA was significantly higher in those with unilateral vs. bilateral SNHL. In patients with bilateral SNHL, there was a statistically significant trend toward a higher prevalence of EVA with increasing severity of the hearing loss. No specific analysis was performed on patients with unilateral EVA in this study.

A conductive component of the hearing loss has been observed at 250 Hz, despite a clinically normal middle ear and tympanogram.[9,12,20] The prevalence of an accompanying low-frequency conductive or mixed hearing loss ranges from 28% to 80% of ears with EVA.[7,12,20] Although the clinical significance of the conductive component is unknown, some investigators have proposed that it may represent the audiologic effect of a third inner ear window.[20] Others have suggested that it may represent an inherent increased stiffness of the ossicles due to the inner ear fluid disturbance.[5,20]

The prevalence of progressive SNHL in patients with EVA varies from 12% to 65%.[9,12,13,16,21] Hearing loss progression can occur in a stepwise fashion over a prolonged period of time, or suddenly, after minor head trauma, barotrauma, or in idiopathic SNHL. In a seminal study, Boston et al.[9] found a linear relationship between the size of the aqueduct and the likelihood of hearing loss progression. Additionally, these authors found that the presence of a low-frequency conductive hearing loss was associated with an increased risk of hearing loss progression.

The most common genetic etiology for EVA is mutations in the *SLC26A4* gene (also known as *PDS*).[22] This gene produces a protein called pendrin, which is responsible for iodine and chloride ion transport in the inner ear and thyroid gland. Biallelic mutations in *SLC26A4* cause Pendred syndrome and are present in 10% to 20% of patients with EVA.[23,24] Patients with this syndrome typically have severe to profound hearing loss and inner ear anomalies such as EVA; they can also develop a thyroid goiter and hypothyroidism. Single *SLC26A4* mutations have been found in 15% to 20% of patients with EVA. These patients typically have a less severe hearing phenotype than patients with Pendred syndrome, have less severe abnormalities of the vestibular aqueduct, and have no thyroid dysfunction. It has been proposed that sequence changes in other gene(s) interact with the single mutations in *SLC26A4*.[23–25] Recently, mutations have been identified in *FOXI1*, which reduce the transcription of *SLC26A4*, resulting in an EVA phenotype.[26] Mutations in the *KCNJ10* gene have also been implicated in EVA when present in combination with *SLC26A4* heterozygotes.[27] Additionally, EVA has been associated with disorders such as CHARGE syndrome,[28] Waardenburg syndrome,[29] and branchio-otorenal syndrome.[30]

Children with bilateral EVA and any *SLC26A4* mutations are more likely to have greater aqueduct enlargement and are more likely to experience progression of hearing loss.[25] Data pertaining to the prevalence of *SLC26A4* mutations in patients with unilateral EVA is scant. Berrettini et al.[18] reported on two patients with unilateral EVA who did not have mutations in *SLC26A4*. Consistent with this finding, Madden et al.[25] observed a lower prevalence of these mutations in a clinical population of patients with unilateral EVA than in those with bilateral EVA.

In a review of studies investigating patients with EVA, Zalzal et al.[12] found that reported prevalence rates of unilateral EVA ranged from 6% to 40%.[7,31] Although unilateral EVA is not uncommon, its audiometric and temporal bone phenotype, natural history, and genetic etiology are not well understood. This gap in knowledge creates several problematic clinical questions: 1) How should families be counseled in regard to their child's hearing loss and imaging findings?; 2) How should patients be monitored in regard to their hearing loss and the potential risk of disease progression?; and 3) What is the positive predictive value of genetic testing?

In light of these issues, the purpose of the current study was to describe the clinical phenotype of patients with unilateral EVA and then to compare the findings to two clinically related phenotypes: bilateral EVA and unilateral hearing loss without EVA. Taking into account our clinical observations and the aforementioned data, we hypothesized that patients with unilateral EVA would have a much higher rate of contralateral hearing loss than patients with unilateral hearing loss without EVA.

MATERIALS AND METHODS

Enlarged Vestibular Aqueduct Population

We performed a database search of all children seen at our center who were diagnosed with EVA or unilateral hearing

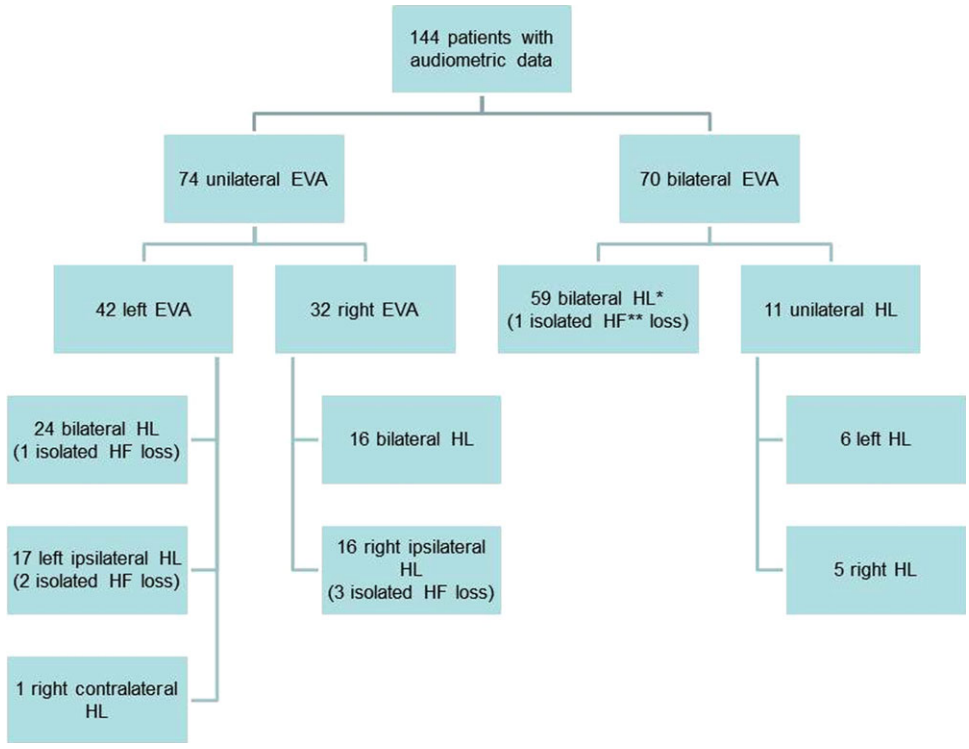


Fig. 1. Flow diagram of enlarged vestibular aqueduct (EVA) study population. *HL = hearing loss; **HF = high frequency. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

loss without EVA from 1998 to 2010. Patients included in the study were required to meet the following criteria: 1) diagnosis of EVA was consistent with the previously published and well-established criteria;[9,11] 2) a complete audiometric assessment was performed and at least 3 months of audiometric follow-up data were available; and 3) genetic testing (*GJB2, SLC26A4*) was performed if offered at our institution at the time of the hearing loss evaluation (Fig. 1). Exclusion criteria included temporal bone dysmorphology that would prevent measurements, aural atresia, known syndromic hearing loss, documented ototoxicity, or a history of temporal bone fractures, meningitis, hydrocephalus with a shunt, autoimmune inner ear disease, or auditory neuropathy. Demographic data, audiometric data, temporal bone measurements, and genetic test results were obtained for study patients. This study was approved by the institutional review board and was in compliance with Health Insurance Portability and Accountability Act of 1996 regulations.

Audiometric Data

A pure tone average (PTA) for each ear was derived by averaging the audiometric findings at 500, 1,000, 2,000, and 4,000 Hz at the initial and most recent audiometric evaluation. A PTA for each ear was also derived for the high frequencies (high-frequency PTA [HFPTA]) by averaging the audiometric findings at 4,000, 6,000, and 8,000 Hz. An additional subanalysis was performed on the individual 250-Hz pure tone frequency.

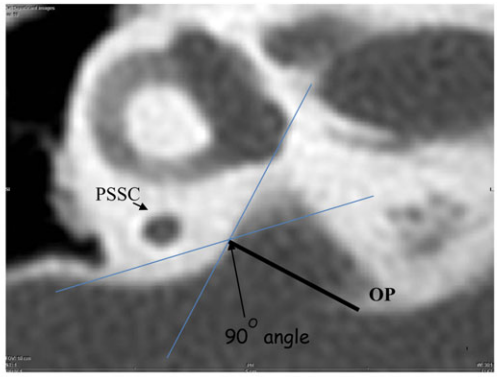
Progressive hearing loss was defined as a 10 dB or greater increase in PTA over a follow-up period of at least 3 months. Patients with an initial PTA $\geq$90 dB were eliminated from further analysis with regard to progressive SNHL. Progressive hearing loss was evaluated as absolute change in PTA values as well as a rate of change in PTA (in decibel loss per year), which takes into account the time between audiologic visits. When reporting PTA values for patients with asymmetric bilateral hearing loss, the better-hearing ear was used for describing the hearing phenotype for that patient. The levels of hearing loss were defined within the following framework: mild loss (20–39 dB), moderate loss (40–54 dB), moderately severe loss (55–69 dB), severe loss (70–89 dB), and profound loss (>90 dB).

Temporal Bone CT Analysis

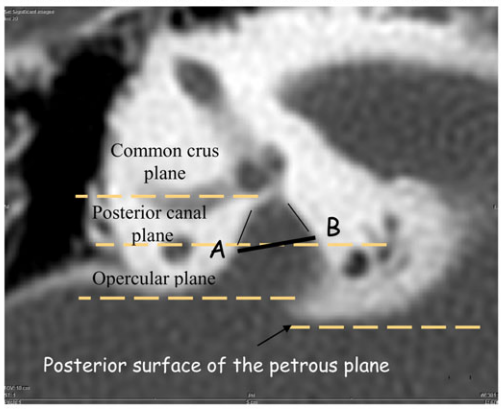
Measurement of the various structures of the temporal bone seen on CT scans was carried out according to a previously published algorithm.[9,11] All patients in the study had CT scans available for review. Briefly, the width of the aqueduct was measured at both the operculum (a line perpendicular to the posterior surface of the petrous pyramid going to the most lateral or posterolateral pixel in the medial wall of the operculum) and at the midpoint between the coronal plane of the operculum and the coronal plane of the posterior wall of the crus commune or upper vestibule. The vestibular aqueduct was considered enlarged when its width exceeded the 95th percentile of normal temporal bones at either the operculum or the midpoint (1.9 mm and 0.9 mm, respectively; Fig. 2). All measurements were performed by two neuroradiologists (C.B. and M.H.). When there was a discrepancy between the measurements performed by these two physicians, the mean of the two measurements was used.

Methodology for GJB2, GJB6, MTRNR1, *and* SLC26A4 *Genetic Testing*

Genomic DNA was isolated from blood and buccal swab tissues using the Puregene DNA purification Kit (Gentra Systems, Minneapolis, MN) or the Roche MagNA Pure Compact system (Roche Diagnostics Corporation, Indianapolis, IN) according to the manufacturers' instructions. Coding exons and at least 50 base pairs of the adjacent intronic regions of the *GJB2* (NC_000013 and NM_86849), MTRNR1 (NC_001807) and *SLC26A* (NC_000007.13 and NM_000441) genes were amplified by polymerase chain reaction (PCR), followed by bidirectional sequencing using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems by Life Technologies, Foster City, CA).



A. Operculum measurement; PSSC- Posterior semicircular canal; OP-Operculum



B. Midpoint measurements- half of the distance between the opercular and crus plane (A to B)

Fig. 2. Schema for acquiring vestibular aqueduct measurements. (A) Operculum measurement. (B) Midpoint measurements: half of the distance between the opercular and crus plane (A to B). OP = operculum; PSSC = posterior semicircular canal. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Sequencing products were analyzed using the ABI Prism 3730 Capillary Sequence Detection System, and raw data were obtained and compared to the published consensus sequences using Sequencher 4.8 (Gene Codes Corporation, Ann Arbor, MI) sequencing analysis software. The 342-kb deletion in the genetic region of D13S1830 (*GJB6*-D13S1830) locus on chromosome 13q12 was analyzed by PCR and gel electrophoresis. Detailed methodologies have previously been published.[19,25] Mutation nomenclature is based on the recommendations of the American College of Medical Genetics and the Human Genome Variation Society.

Several in silico analysis methods for the prediction of functional consequences of sequence variants were utilized to provide initial classification. All sequence variants were verified by the Human Gene Mutation Database, the National Center for Biotechnology Information Single Nucleotide Polymorphism database, and locus-specific mutation databases, such as Connexin Deafness Homepage (http://davinci.crg.es/deafness/index.php?seccion = mut_db&db = nonsynd&nonsynd = cx26mut). For novel mutations, we used SIFT (http://blocks.fhcrc.org/sift/SIFT.html), which utilizes evolutionary information from homologous proteins,[16] and PolyPhen (http://www.bork.embl-heidelberg.de/PolyPhen/), which incorporates structural information into classification rules.[17] The Grantham Scale[18] was also used to evaluate the significance of amino acid substitutions, and a determination of the likelihood of the sequence change being pathogenic was made by the Molecular Genetics laboratory.

Statistical Analyses

Data distributions were reported as medians with ranges or interquartile ranges for continuous variables and frequencies with proportions for categorical variables. Comparisons were made among subjects who had ipsilateral hearing loss, contralateral hearing loss, and bilateral hearing loss relative to the ear with the identified EVA. Due to the non-normal distribution of the majority of the data, nonparametric statistics were used in the analyses. Continuous data were compared using the Kruskal–Wallis test or the Wilcoxon rank sums test, as appropriate. Categorical data were compared among groups using χ^2 analysis or the Fisher exact test, as appropriate. Correlations between vestibular measurements and continuous variables such as PTA values were conducted using the Spearman rank correlation coefficient. For assessing which factors may be independently related (independent predictors) to having a progressive hearing loss in an ear, multivariate analysis was conducted using generalized estimating equations (GEE). GEE allows for the clustering of ears in the analysis (two ears belonging to the same individual). GEE was used for both modeling of odds or risk progression as a dichotomous variable and modeling the rate of progression (as a decibel loss per year). For all analyses, a P value of .05 or less was considered statistically significant. All analyses were performed using SAS for Windows, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Our database search identified 144 patients (67 males, 77 females) who met our inclusion criteria. Unilateral EVA was identified in 74 (51.4%) of these patients (Fig. 1); 42 (56.8%) had left-sided EVA, and 32 had right-sided EVA. The median age at which the hearing loss was identified was 59.5 months (range, 0–324.5 months). The median follow-up time was 37.8 months (range, 0–812.5 months), and 116 (80.5%) patients were followed for at least 3 months. As shown in Table I, patients with unilateral EVA were identified at a later age than patients with bilateral EVA (70 vs. 54.5 months; $P = .01$). They also had a shorter period of audiometric follow-up (32.8 vs. 56.3 months; $P = .02$) and were more likely to have unilateral hearing loss (46% vs. 15.7%; $P < .0001$).

Unilateral Versus Bilateral Hearing Loss

Forty-five patients (31.3%) with EVA had unilateral hearing loss. In 23 (51%) of these patients, the hearing loss was left-sided. Among the 74 patients with unilateral EVA, 34 (46%) had unilateral hearing loss; in 1 patient, the unilateral loss was in the contralateral ear. The remaining 39 patients had bilateral hearing loss. More than 55% of patients with unilateral EVA presented with hearing loss in the contralateral ear (Fig. 1). Among the 70 patients with bilateral EVA, only 11 (15.7%) had unilateral hearing loss. The median age at which hearing loss was identified in all EVA patients (n = 144) was significantly higher among those with unilateral hearing loss as compared to those with bilateral loss (78.5 vs. 45.5 months; range, 16.5–158 vs. 0–324.5 months; $P < .0001$). This finding was consistent when patients were stratified into a unilateral EVA group (80.5 vs. 42.8 months; range, 16.5–158 vs. 0–324.5

TABLE I.
Data Pertaining to Patients With EVA.

Characteristic	Unilateral, n = 74	Bilateral, n = 70	*P*
Male	38 (51%)	29 (41%)	.26
Age at identification of hearing loss, mo*	70 (0–324.5) [39.5–106]	54.5 (0–208) [32.5–69.5]	.01
Follow-up time, mo†	32.8 (0.5–164) [13.5–69.5]	56.3 (0.5–812.5) [33.8–76.8]	.02
≥3 months of follow-up	55 (74.3%)	61 (87.1)	.05
Unilateral hearing loss at initial assessment	34 (46.0%)	11 (15.7%)	<.0001
Pure tone average in better-hearing ear, dB	37.9 (10–130) [27.5–65]	50 (6.25–130) [32.5–70]	.19
Hearing loss severity in better-hearing ear			.48
Mild	30 (40.5%)	21 (30.0%)	
Moderate	11 (14.9%)	15 (21.4%)	
Moderately severe	11 (14.9%)	12 (17.1%)	
Severe	3 (4.1%)	7 (10%)	
Profound	11 (14.9%)	10 (14.3%)	
Normal/borderline‡	8 (10.8%)	5 (7.1%)	

*Range in parentheses and interquartile range (25th and 75th percentile) in brackets.
†Among 126 patients with follow-up.
‡High-frequency loss in 6 of 8 patients with unilateral EVA and 1 of 5 with bilateral EVA.
EVA = enlarged vestibular aqueduct.

months; $P = .02$) and a bilateral EVA group (75.0 vs. 48 months; range, 38–102.5 vs. 0–208 months; $P = .008$).

Hearing Loss Severity

The median PTAs at the initial and final audiometric assessments for all ears with hearing loss (n = 243) were 50 (range, 10–130) and 57 (range, 7.5–122.5), respectively. Nine ears had an isolated HFPTA (median HFPTA was 35.8; range, 20–57.5). Patients with hearing loss and unilateral EVA had slightly better hearing than those with bilateral EVA, although this difference was not statistically significant (47.5 [range, 10–130] vs. 55.6 [range, 12–130], respectively; $P = .075$). This finding was consistent when analyzing the better-hearing ear in both groups.

At initial audiometric assessment, there was no statistical difference between the median PTA of patients with unilateral hearing loss (n = 45) and the better-hearing ear of patients with bilateral loss (n = 99; 48.75 vs. 41.25; $P = .4$). This finding was consistent when our cohort was stratified into unilateral and bilateral EVA groups. Among the 74 patients with unilateral EVA (n = 114 ears with hearing loss), there was no significant difference in the median PTA at the initial audiometric assessment between ipsilateral ears (n = 73) and contralateral ears (n = 41; 47.5 [range, 10–130] vs. 41 [range, 14–130], respectively; $P = .9$). This finding was consistent with the final audiometric assessment of ipsilateral and contralateral PTA values (52.5 [range, 7.5–121.25] vs. 50 [range, 12.5–130], respectively; $P = .6$).

The severity of hearing loss at the initial assessment was categorized as borderline to mild in 37.4% of ears with hearing loss, moderate to severe in 45.3% of affected ears, and profound in the remaining 17.3% of affected ears. There was no difference in hearing loss severity between patients with bilateral vs. unilateral EVA ($P = .48$; Table I). There was no statistical relationship ($P = .21$) between levels of hearing loss severity and whether the loss was ipsilateral or contralateral to the EVA at either the initial or the final audiometric assessment.

Vestibular Aqueduct Measurements

Hearing loss and vestibular aqueduct phenotypes were compared regarding temporal bone measurements at the midpoint and the operculum (Table II). No significant differences were found in the temporal bone measurements between the ears of patients with unilateral EVA and ipsilateral hearing loss and all ears with EVA and normal hearing ($P = .4$). Operculum measurements were significantly greater in the ears of patients with bilateral EVA than in those with unilateral EVA ($P = .025$).

TABLE II.
Vestibular Measurements of Ears With Hearing Loss.

	Bilateral EVA, 129 Ears*	Unilateral EVA and Ipsilateral Hearing Loss, 73 Ears†	Non-EVA Ears and Contralateral Hearing Loss, 41 Ears	EVA Ears With Normal Hearing, 12 Ears‡
Midpoint, mm (range)	1.7 (0.1–4.1)	1.5 (0.1–3.5)	0.41 (0.1–0.9)	1.25 (0.1–3.8)
Operculum, mm (range)	2.7 (0.68–7.6)	2.3 (0.1–7.5)	1.37 (0.1–1.9)	2.0 (0.8–4.2)

* versus †: midpoint $P = .069$, operculum $P = .025$
† versus ‡: midpoint $P = .4$, operculum $P = .4$.
EVA = enlarged vestibular aqueduct.

TABLE III.
Median (Range) [IQR] Aqueduct Measurements by the Side of the Hearing Loss Relative to the Side of the EVA.

Hearing Loss With EVA	Ipsilateral Opercular Width, mm*	Ipsilateral Midpoint Width, mm†	Contralateral Opercular Width, mm	Contralateral Midpoint Width, mm
Ipsilateral hearing loss	2.7 (0.1–7.6) [2.1–3.5]	2.05 (0.1–4.1) [1.6–2.55]	1.25 (0.1–4.2) [0.85–1.85]	0.4 (0.1–3.8) [0.2–0.9]
Contralateral hearing loss‡	1.1	0.7	2	1.4
Bilateral hearing loss	2.5 (0.4–7.5) [1.95–3.0]	1.5 (0.1–3.6) [1.0–1.9]	1.4 (0.1–1.9) [0.9–1.6]	0.4 (0.1–0.9) [0.1–0.7]

*Comparison between ipsilateral and bilateral hearing loss groups: not significantly different ($P = .09$).
†Comparison between ipsilateral and bilateral hearing loss groups: significantly different ($P < .0001$).
‡Only 1 subject with unilateral EVA had contralateral hearing loss.
IQR = interquartile range (25th and 75th percentile); EVA = enlarged vestibular aqueduct.

In the 144 patients with EVA, there were 243 ears with hearing loss. The midpoint and operculum measurements of these ears correlated with the PTA of the final audiogram (Spearman rho = 0.20 [$P = .002$] and 0.17 [$P = .007$], respectively). This was consistent when correlating midpoint and operculum measurements with the HFPTA at the final audiogram (Spearman rho = 0.28 [$P = .003$] and 0.23 [$P = .01$], respectively). When analyzing only ears with hearing loss and EVA (n = 202), similarly significant correlations were found for PTA measurements (Spearman rho = 0.18 [$P = .01$] and 0.14 [$P = .05$], respectively). For HFPTA, the correlations were slightly stronger (Spearman rho = 0.30 [$P = .004$] and 0.25 [$P = .018$], respectively). In the ears of patients with EVA who had hearing loss at their initial evaluation (n = 164), significant correlations were found between the PTA and the size of the midpoint and operculum (Spearman rho = 0.22 [$P = .006$] and 0.26 [$P = .0009$], respectively). For HFPTA, similarly significant correlations were found (Spearman rho = 0.32 [$P = .005$] and 0.24 [$P = .04$], respectively).

Vestibular aqueduct measurements were compared among audiometric phenotypes (Table III). Only 1 patient with unilateral EVA had contralateral hearing loss (midpoint, 1.4; operculum, 2.0). The median midpoint measurement in patients with ipsilateral hearing loss (2.05; range, 0.1–4.1) was greater than this measurement in patients with bilateral hearing loss (1.5; range, 0.1–3.6; $P < .0001$). Also, the median operculum measurement in patients with ipsilateral hearing loss was greater (2.45; range, 0.1–5.2) than this measurement in patients with bilateral hearing loss (2.05; range, 0.4–7.5; $P = .09$); however, this difference was not statistically significant.

Hearing Loss Progression

There were 232 ears in children with ≥3 months of audiometric follow-up that were included in the analysis of hearing loss progression; 31 ears were excluded from analysis, as they had profound hearing loss (n = 201). At the initial audiometric evaluation, 164 ears had hearing loss, and 37 had normal hearing. Overall, 65 of 201 (39.6%) ears had progression. The initial median PTA in the progressive hearing loss group was 53.3 (range, 15–90), and the final median PTA was 78.7 (range, 27.5–120). The proportion of ears with progressive hearing loss was slightly higher among ears of patients with bilateral EVA compared to ears of patients with unilateral EVA, although this difference was not statistically significant (41 of 89 ears [46.1%] vs. 25 of 75 ears [33.3%], respectively; $P = .1$). No difference in hearing loss progression was found when we compared patients with bilateral vs. unilateral hearing loss (55 of 134 [41%] vs. 11 of 30 [36.7%], respectively; $P = .7$).

Additionally, in analyzing patients with unilateral hearing loss, we found a trend toward a higher prevalence of progression in patients with bilateral vs. unilateral EVA, although this trend was not statistically significant (5 of 8 [62.5%] vs. 6 of 22 [27.3%], respectively; $P = .1$). In the patients with unilateral EVA and normal hearing, 3 of 37 (8.1%) demonstrated hearing loss progression. However, the rate of progression in these patients was lower than in patients with EVA and hearing loss at initial presentation (65 of 164 [39.6%]; $P = .0003$) and in the ears of patients with unilateral EVA (25 of 75 [33%]; $P = .002$). Among the 75 ears in patients with unilateral EVA and hearing loss, there was no difference in the likelihood of hearing loss progression between ears with and without EVA (16 of 48 [33.3%] vs. 9 of 27 [33.3%], respectively; $P = 1.0$, Fisher exact test).

For all 201 ears analyzed for progression, the median change in PTA between the initial and final audiogram was 5.0 dB (range, −38.75 to 77.5 dB). For the ears that progressed (n = 68), the annual rate of progression was 4.5 (range, 1.0–63 dB). For all 164 ears with initial hearing loss, the median change in PTA between the initial and final audiogram was 6.25 dB (range, −38.75 to 77.5); among the ears with progression (n = 65), the annual rate of hearing loss progression was 4 (range, 1.0–63 dB). The rate of progression was significantly correlated with the midpoint (Spearman rho = 0.41; $P = .001$), but not with the operculum (Spearman rho = 0.18; $P = .16$). The midpoint measurement was highly predictive of how fast an individual would progress (taking into account the clustering of ears or that two ears can belong to the same individual; $\beta = .37$; standard error = .07; $P < .0001$). For every 0.37-U increase in the midpoint measurement, the rate of progression per year increased by a factor of 1 dB. The change in PTA was not correlated with either the midpoint (Spearman rho = 0.18; $P = .16$) or the operculum (Spearman rho = 0.08; $P = .5$).

During our study period, 100 patients with unilateral SNHL without EVA who had at least 3 months of follow-up audiometric data were identified. A portion of these patients have been previously described.[32] Twenty-

seven (27%) of these patients had progression in at least one ear, and 2 patients had progression in both ears. Twenty-three of the 100 (23%) patients had ipsilateral progression, whereas 6 of 100 (6%) had contralateral progression. As compared to patients with EVA and ipsilateral hearing loss (65 of 164 [39.6%]), patients with unilateral hearing loss without EVA had a significantly lower rate of progression (27 of 100 [27%]; $P = .037$). There was no difference in the rate of progression in patients with normal hearing and EVA (3 of 37 [8.1%]) and patients with unilateral hearing loss without EVA (6 of 100 [6%]; $P = .9$).

Low-Frequency Hearing Loss Progression

Of the 144 patients with EVA, 237 ears had pure tone audiometric data at 250 Hz (PT250); 194 of these ears had hearing loss at 250 Hz. PT250 strongly correlated with midpoint and operculum measurements (Spearman rho = 0.43, $P < .001$ and 0.42, $P < .0001$, respectively). The PT250 also strongly correlated with the final PTA and HFPTA (Spearman rho = 0.79, $P < .0001$ and 0.64; $P < .0001$, respectively). Controlling for temporal bone measurements, the PT250 was still highly correlated with the final PTA (Spearman rho = 0.7; $P < .0001$). There was no association between the PT250 and a positive *SLC26A4* test result.

One hundred seventy-six patients met our study criteria for determining hearing loss progression. In these patients, 57 ears showed progression (median, 40 dB hearing loss at 250 Hz), and 119 ears showed no progression (median, 25 dB hearing loss at 250 Hz; $P = .003$). A mixed hearing loss at 250 Hz was seen in 117 ears. There was a significantly higher rate of progression in ears with a hearing loss at 250 Hz than in ears with normal hearing thresholds (46 of 117 [39.3%] vs. 11 of 59 [18.6%], respectively; $P = .0003$).

Among all ears that had PT250 values and were analyzed for progression (n = 176 ears) using GEE to account for clustered data by ear, the odds for progression increased with increasing PT250 (Table IV). This relationship weakened when midpoint measurements and initial PTA were controlled for in the analysis. Both the hearing level at 250 Hz and the initial PTA were strongly correlated with the likelihood of progression (Table IV).

TABLE IV.
Risk Analysis of Hearing Loss Progression.

Variable	Odds Ratio	95% CI	*P*
PTT @ 250 Hz	1.10*	1.03-1.19	.009
PTT @ 250 Hz†	1.08*	0.996-1.17	.06
PTT @ 250 Hz‡	1.04*	0.93-1.16	.5
Initial PTA4	1.12*	1.04-1.20	.003
Initial PTA4§	1.10*	1.02-1.19	.018

*For every 5-dB increase in initial value.
†Controlling for midpoint.
‡Controlling for initial PTA4 value.
§Controlling for midpoint. CI = confidence interval; PTA = pure tone average; PTT = pure tone threshold.

TABLE V.
Genetic Test Results.

	Unilateral EVA, n = 74	Bilateral EVA, n = 70	*P*
Number of patients who received genetic testing			
GJB2	51 (68.9%)	50 (71.4%)	.74
GJB6	4 (5.4%)	5 (7.1%)	.74*
SLC26A4	39 (52.7%)	46 (65.7%)	.11
MTRNR1	4 (5.4%)	3 (4.3%)	1.0*
Positive results among those tested			
GJB2	3 (5.9%)	3 (6.0%)	1.0*
GJB6	0	1 (20%)	1.0*
SLC26A4	4 (10.3%)	20 (43.5%)	0.0007
MTRNR1	0	0	—

*Fisher exact test.
EVA = enlarged vestibular aqueduct.

Genetics

A summary of genetic test results is shown in Tables V and VI. *SLC26A4* testing was positive for a significantly higher number of patients with bilateral EVA than with unilateral EVA (43.5% vs. 10.3%; $P = .007$). Of patients with positive *SLC26A4* results, 7 of 24 (29%) had biallelic mutations (i.e., Pendred syndrome), and 17 of 24 (71%) had a single mutation. No unilateral EVA patients had biallelic mutations compatible with Pendred syndrome. Very few patients had mutations in the *GJB2*, *GJB6*, or *MTRNR1* genes. Only 1 patient had biallelic *GJB2* mutations.

Overall, the rate of hearing loss progression in patients with *SLC26A4* mutations was similar to the rate in patients without *SLC26A4* mutations (Table VII). Analysis of hearing loss phenotypes indicated that the rate of progression was significantly related to positive results in ears with hearing loss in patients with bilateral EVA (Table VIII). Additionally, of patients with positive genetic test results and progressive hearing loss, significantly more had bilateral EVA (14 of 35 [40%]) than unilateral EVA (3 of 30 [10%]; $P = .006$).

DISCUSSION

Although unilateral EVA is not an uncommon otologic finding, its audiometric and temporal bone

TABLE VI.
SLC26A4 Genotypes.

3 –2 A>G	682–698del17	L445W
M1T	N322D (2)	1614 +1 G>A
P10T (2)	N324Y	Y530H
L50R (2)	F335L	L597S
G209V	F335S	L729P
T410M	1001 +1 G>A (2)	G740S
V138F	T416P (3)	G740V
L236P (2)	L441P	

Amino acid changes shown for missense mutations. Numbers in parentheses denote the number of alleles found.

phenotype, natural history, and genetic etiology remain unclear. The underlying goal of the present study was to shed light on these areas of uncertainty and to determine the clinical significance of unilateral EVA in pediatric patients.

Overall, the patients in this study demonstrated an extremely heterogeneous audiometric phenotype. Patients with unilateral EVA as well as those with bilateral EVA had unilateral and bilateral hearing loss and varying levels of hearing loss severity. Interestingly, we found no difference in hearing loss severity between the unilateral and bilateral EVA cohorts. This finding implies that the inner ear dysfunction in patients with bilateral EVA is not necessarily more severe than the dysfunction in patients with unilateral EVA.

In patients with unilateral EVA, there was no correlation between the side of the hearing loss and the side of the EVA, as >50% of patients with unilateral EVA had contralateral hearing loss. Furthermore, these patients showed no difference in hearing loss severity between the contralateral and ipsilateral ears. These findings suggest that unilateral EVA may be a phenotypic expression of bilateral alterations in the membranous labyrinth and that unilateral EVA is likely not a unilateral disease process. The latter conclusion can perhaps be explained by events that occur during embryogenesis. Specifically, perturbation of the inner ear labyrinth, which causes endolymphatic duct dilatation, can occur after embryonic temporal bone mesenchyme condenses into bone; hence, imaging would not reveal enlargement of the vestibular aqueduct. Alternatively, if endolymphatic duct dilatation occurs earlier in embryogenesis, imaging studies would reveal the enlargement of the vestibular aqueduct.

Data pertaining to temporal bone phenotypes show a correlation between the final PTA and midpoint and operculum measurements and the HFPTA and midpoint and operculum measurements. This correlation has not been previously established. Studies conducted by Zalzal et al.[12] and Colvin et al.[21] reported no relationship between the absolute level of hearing or hearing loss progression and temporal bone measurements; however, both studies used more restrictive criteria for EVA (i.e., a midpoint measurement ≥1.5 mm) and had small study populations.

TABLE VII.
Rate of Progression Based on Audiometric Phenotype and *SLC26A4* Testing Results by Patient.

Progression in	Unilateral EVA, n = 54	Bilateral EVA, n = 54	*P*
Both ears	6 (11%)	11 (20.4%)	.18
Only one ear	15 (27.8%)	19 (35.2%)	
No ears	33 (61.1%)	24 (44.4%)	

Rate of Progression	*SLC26A4* Positive	*SLC26A4* Negative	
All patients with EVA	10/17 (58.8%)	22/48 (45.8%)	.36
Patients with unilateral EVA	0/3	13/27 (48.2%)	.24*
Patients with bilateral EVA	10/14 (71.4%)	9/21 (42.9%)	.10

*Fisher exact test.
EVA = enlarged vestibular aqueduct.

TABLE VIII.
Rate of Progression Based on Audiometric Phenotype and *SLC26A4* Testing Results by Ears.

	SLC26A4 Positive	*SLC26A4* Negative	*P*
Ears with HL	14/27 (51.9%)	26/73 (35.6%)	.14
Ears with HL + EVA	14/26 (53.9%)	20/59 (33.9%)	.08
Ears with HL + unilateral EVA	0/2	10/24 (41.7%)	.51*
Ears with HL + bilateral EVA	14/24 (58.3%)	10/35 (28.6%)	.02

*Fisher exact test.
EVA = enlarged vestibular aqueduct; HL = hearing loss.

Reporting on 77 patients, Madden et al.[5] found a relationship between the midpoint and operculum measurements and the rate of progression, but not with the initial PTA. The disparity between historical findings and the present study may be attributed to our use of a final PTA measurement, which may have been affected by the presence of progressive hearing loss.

Patients with unilateral EVA had slightly better hearing compared to those with bilateral EVA, although this difference was not statistically significant. The difference may be related to the relatively high prevalence of isolated high-frequency hearing loss in patients with unilateral EVA. Overall, a comparison of temporal bone measurements in patients with unilateral and bilateral EVA revealed no critical differences. Nevertheless, subtle differences were evident. Specifically, although operculum measurements were larger in patients with unilateral EVA, there was no difference in midpoint measurements between patients with unilateral and bilateral EVA. Also, patients with unilateral EVA and ipsilateral hearing loss had larger vestibular aqueduct measurements than patients with bilateral EVA, suggesting the possibility of a different underlying etiology between the two groups.

Hearing loss progression was seen both in patients with unilateral EVA and in patients with bilateral EVA. Although it was more commonly seen in patients with bilateral EVA, this difference was not statistically significant. This lack of significance remained constant when analyzing ears with unilateral and bilateral hearing loss.

Interestingly, patients with unilateral EVA had a similar rate of progression in both the ipsilateral and contralateral ears. When compared to the ears in patients with unilateral hearing loss without EVA, the ears of patients with unilateral EVA had a higher likelihood of progression. In patients with unilateral hearing loss without EVA, only 6% had involvement of the contralateral ear. In sharp contrast, 55% of patients with unilateral EVA had involvement of the contralateral ear. Collectively, these data support our study hypothesis that patients with unilateral EVA would have a much higher rate of contralateral hearing loss than patients with unilateral hearing loss without EVA.

In patients with EVA, hearing loss at 250 Hz is strongly correlated with the severity of the PTA and the likelihood of progression. Additionally, the hearing loss

at 250 Hz is related to larger temporal bone measurements. When controlling for PTA and midpoint temporal bone measurements, the correlation between hearing loss at 250 Hz and the likelihood of progression is weakened, thus showing that the strength of temporal bone measurements is an indicator of progression. Overall, our data indicate that hearing levels at 250 Hz alone may be a sensitive clinical indicator in patients with EVA. Our data support the findings of Boston et al.,[9] which showed a similar correlation in ears with a mixed hearing loss between 250 and 1,000 Hz.

As discussed by Zhou et al.,[20] the etiology of low-frequency, predominantly mixed hearing loss is uncertain. Increased intralabyrinthine fluid pressure or a possible third inner ear window phenomenon has been proposed as an etiology for this hearing loss. The relationships shown in the current study between temporal bone measurements, hearing loss progression, and hearing loss at 250 Hz may support the abovementioned etiologic theory that larger vestibular aqueducts cause increased inner ear fluid pressure; in turn, fluid pressure may lead to a high rate of progression and the presence of hearing loss at 250 Hz.

Patients with bilateral EVA had a significantly higher likelihood of having *SLC26A4* mutations and of having Pendred syndrome than did patients with unilateral EVA. Our analysis of the ears of patients with hearing loss revealed that mutations were present at a higher rate in patients with bilateral EVA than in those with unilateral EVA. The presence of mutations overall did not increase the likelihood of progressive hearing loss or the severity of hearing loss in either EVA group. Specifically, in the ears of patients with bilateral EVA and hearing loss, the presence of mutations increased the likelihood of hearing loss progression. These findings support previously published data[25] indicating that single mutations contribute to the EVA phenotype. These single mutations, together with other as yet undetermined mutations, are thought to be responsible for the hearing loss phenotype.[23,25]

The audiometric phenotype was similar in patients with unilateral and bilateral EVA. Because of the relatively high rate of hearing loss progression in patients with unilateral EVA, we feel that it is prudent to recommend close audiometric monitoring. Families and patients should be made aware of the possibility that a unilateral imaging finding does not necessarily signify that the process occurring within the membranous labyrinth is a unilateral process and that the development of bilateral hearing loss is quite common. Additionally, they should be advised that *SLC26A4* testing is a valuable diagnostic adjunct in the evaluation of all patients with EVA.

Our study has several limitations. Given that all of our data were based on previously collected imaging and audiometric results, biases may have been introduced regarding how data were entered into the database and which patients were included in the database. Children who did not receive an imaging study of the inner ear did not meet our inclusion criteria, thus making the true prevalence of unilateral EVA in the total population of children with SNHL difficult to assess. Also, we examined only EVA and did not investigate other less common temporal bone anomalies. Further study may thus be warranted to determine the possible role of such anomalies in the hearing loss phenotype of patients with EVA.

CONCLUSION

Children with unilateral EVA have a significant risk of hearing loss progression. Hearing loss in the ear contralateral to the EVA is common, suggesting that unilateral EVA is a bilateral process despite an initial unilateral imaging finding. In contrast to bilateral EVA, unilateral EVA is not associated with Pendred syndrome, but may have a different etiology. Clinicians should become knowledgeable regarding the implications of this disease process so that families can be counseled appropriately.

BIBLIOGRAPHY

1. Jackler RK, Luxford WM, House WF. Congenital malformations of the inner ear: a classification based on embryogenesis. *Laryngoscope* 1987; 97:2–14.
2. Mafong DD, Shin EJ, Lalwani AK. Use of laboratory evaluation and radiologic imaging in the diagnostic evaluation of children with sensorineural hearing loss. *Laryngoscope* 2002;112:1–7.
3. Antonelli PJ, Varela AE, Mancuso AA. Diagnostic yield of high-resolution computed tomography for pediatric sensorineural hearing loss. *Laryngoscope* 1999;109:1642–1647.
4. Preciado DA, Lim LHY, Cohen AP, et al. A diagnostic paradigm for childhood idiopathic sensorineural hearing loss. *Otolaryngol Head Neck Surg* 2004;131:804–809.
5. Madden C, Halsted M, Benton C, Greinwald JH, Choo DI. Enlarged vestibular aqueduct syndrome in the pediatric population. *Otol Neurotol* 2003;24:625–632.
6. Valvassori GE, Clemis JD. The large vestibular aqueduct syndrome. *Laryngoscope* 1978;88:723–728.
7. Jackler RJ, De La Cruz A. The large vestibular aqueduct syndrome. *Laryngoscope* 1989;99:1238–1243.
8. Antonelli PJ, Nall AV, Lemmerling MM, Mancuso AA, Kubilis PS. Hearing loss in children with cochlear modiolar defects and large vestibular aqueducts. *Am J Otol* 1998;19:306–312.
9. Boston M, Halsted M, Meinzen-Derr J, et al. The large vestibular aqueduct: a new definition based on audiologic and computed tomography correlation. *Otolaryngol Head Neck Surg* 2007:136:972–977.
10. Spiegel JH, Lalwani AK. Large vestibular aqueduct syndrome and endolymphatic hydrops: two presentations of a common primary inner-ear dysfunction? *J Laryngol Otol* 2009;123:919–922.
11. Vijayasekaran S, Halsted MJ, Boston M, et al. When is the vestibular aqueduct enlarged? A statistical analysis of the normative distribution of vestibular aqueduct size. *Am J Neuroradiol* 2007;28:1133–1138.
12. Zalzal GH, Tomaski SM, Gilbert Vezina L, Bjornsti P, Grundfast KM. Enlarged vestibular aqueduct and sensorineural hearing loss in childhood. *Arch Otolaryngol Head Neck Surg* 1995;121:23–28.
13. Mori T, Westerberg BD, Atashband S, Kozak FK. Natural history of hearing loss in children with enlarged vestibular aqueduct syndrome. *J Otolaryngol Head Neck Surg* 2008;37:112–118.
14. Grimmer JF, Hedlund G. Vestibular symptoms in children with enlarged vestibular aqueduct anomaly. *Int J Pediatr Otorhinolaryngol* 2007;1: 275–282.
15. Levenson MJ, Parisier SC, Jacobs M, Edelstein DR. The large vestibular aqueduct syndrome in children. *Arch Otolaryngol Head Neck Surg* 1989;115:54–58.
16. Lai CC, Shiao AS. Chronological changes of hearing in pediatric patients with large vestibular aqueduct syndrome. *Laryngoscope* 2004;114: 832–838.
17. Dewan K, Wippold J II, Lieu JE. Enlarged vestibular aqueduct in pediatric sensorineural hearing loss. *Otolaryngol Head Neck Surg* 2009;140: 552–558.
18. Berrettini S, Forli F, Neri E, Salvatori L, Casani AP, Franceschini SS. Large vestibular aqueduct syndrome: audiological, radiological, clinical, and genetic features. *Am J Otolaryngol* 2005;26:363–371.
19. Preciado DA, Lawson L, Madden C, et al. Improved diagnostic effectiveness with a sequential diagnostic paradigm in idiopathic pediatric sensorineural hearing loss. *Otol Neurotol* 2005;26:610–615.
20. Zhou G, Gopen Q, Kenna MA. Delineating the hearing loss in children with enlarged vestibular aqueduct. *Laryngoscope* 2008;118:2062–2066.
21. Colvin IB, Beale T, Harrop-Griffiths K. Long-term follow-up of hearing loss in children and young adults with enlarged vestibular aqueducts: relationship to radiologic findings and Pendred syndrome diagnosis. *Laryngoscope* 2006;116:2027–2036.

22. Van Camp G, Smith RJH. Hereditary hearing loss homepage. Available at: http://hereditaryhearingloss.org. Accessed July 29, 2011.
23. Pryor SP, Madeo AC, Reynolds JC, et al. SLC26A4/PDS genotype-phenotype correlation in hearing loss with enlargement of the vestibular aqueduct (EVA): evidence that Pendred syndrome and non-syndromic EVA are distinct clinical and genetic entities. *J Med Genet* 2005;42: 159–165.
24. Campbell C, Cucci RA, Prasad S et al. Pendred syndrome, DFNB4, and PDS/SLC26A4: identification of eight novel mutations and possible genotype-phenotype correlations. *Hum Mutat* 2001;17:403–411.
25. Madden C, Halsted M, Meinzen-Derr J, et al. The influence of mutations in the SLC26A4 gene on the temporal bone in a population with enlarged vestibular aqueduct. *Arch Otolaryngol Head Neck Surg* 2007; 133:162–168.
26. Yang T, Vidarsson H, Rodrigo-Blomqvist S, Rosengren SS, Enerback S, Smith RJ. Transcriptional control of SLC26A4 is involved in Pendred syndrome and nonsyndromic enlargement of vestibular aqueduct (DFNB4). *Am J Hum Genet* 2007;80:1055–1063.
27. Yang T, Gurrola JG II, Wu H, et al. Mutations of KCNJ10 together with mutations of SLC26A4 cause digenic nonsyndromic hearing loss associated with enlarged vestibular aqueduct syndrome. *Am J Hum Genet* 2009;84:651–657.
28. Murofishi T, Ouvrier RA, Parker GD, et al. Vestibular abnormalities in CHARGE association. *Ann Otol Rhinol Laryngol* 1997;106: 129–134.
29. Madden C, Halsted M, Hopkin R, Choo DI, Benton C, Greinwald JH. Temporal bone abnormalities associated with hearing loss in Waardenburg syndrome. *Laryngoscope* 2003;113;2035–2041.
30. Chen A, Francis M, Ni L, et al. Phenotypic manifestations of branchio-otorenal syndrome. *Am J Med Genet* 1995;58:365–370.
31. Valvassori GE. The large vestibular aqueduct and associated anomalies of the ear. *Otolaryngol Clin North Am* 1983;16:95–101.
32. Uwiera TK, deAlarcon A, Meinzen-Derr J, et al. Hearing loss progression and contralateral involvement in children with unilateral sensorineural hearing loss. *Ann Otolaryngol Head Neck Surg* 2009;118: 781–785.

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ORIGINAL INVESTIGATION

Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss

Christina M. Sloan-Heggen[1,2] · Amanda O. Bierer[1] · A. Eliot Shearer[1] · Diana L. Kolbe[1] · Carla J. Nishimura[1] · Kathy L. Frees[1] · Sean S. Ephraim[1] · Seiji B. Shibata[1] · Kevin T. Booth[1] · Colleen A. Campbell[1] · Paul T. Ranum[1] · Amy E. Weaver[1] · E. Ann Black-Ziegelbein[1] · Donghong Wang[1] · Hela Azaiez[1] · Richard J. H. Smith[1,2,3]

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Abstract Hearing loss is the most common sensory deficit in humans, affecting 1 in 500 newborns. Due to its genetic heterogeneity, comprehensive diagnostic testing has not previously been completed in a large multiethnic cohort. To determine the aggregate contribution inheritance makes to non-syndromic hearing loss, we performed comprehensive clinical genetic testing with targeted genomic enrichment and massively parallel sequencing on 1119 sequentially accrued patients. No patient was excluded based on phenotype, inheritance or previous testing. Testing resulted in identification of the underlying genetic cause for hearing loss in 440 patients (39 %). Pathogenic variants were found in 49 genes and included missense variants (49 %), large copy number changes (18 %), small insertions and deletions (18 %), nonsense variants (8 %), splice-site alterations (6 %), and promoter variants (<1 %). The diagnostic rate varied considerably based on phenotype and was highest for patients with a positive family history of hearing loss or when the loss was congenital and symmetric. The spectrum of implicated genes showed wide ethnic variability. These findings support the more efficient utilization of medical resources through the development of evidence-based algorithms for the diagnosis of hearing loss.

Introduction

Hearing loss is the most common sensory deficit in humans. It is diagnosed in 1 in 500 newborns and affects half of all octogenarians (Fortnum et al. 2001; Morton and Nance 2006). Although causality is multifactorial, in developed countries, a large fraction of hearing loss is genetic and non-syndromic, i.e., not associated with other phenotypes (Marazita et al. 1993). Non-syndromic hearing loss (NSHL) mimics are syndromic forms of hearing loss that present as NSHL early in life with syndromic features developing later. Type 1 Usher syndrome, for example, is an NSHL mimic presenting as congenital profound hearing loss with delayed motor milestones. The associated progressive vision loss begins in late childhood (Smith et al. 1994).

Genetic diagnosis of NSHL and NSHL mimics is valuable. It provides prognostic information on possible progression of hearing loss, permits meaningful genetic counseling, and impacts treatment decisions (Kimberling et al. 2010). A positive diagnosis also saves healthcare dollars by directing the clinical evaluation and obviating unnecessary testing such as the routine use of imaging. The challenge, however, is in providing comprehensive genetic testing. Hearing loss is extremely heterogeneous, with over 90 genes causally implicated in NSHL (Van Camp and Smith 2015). Although

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✉ Richard J. H. Smith
richard-smith@uiowa.edu

[1] Molecular Otolaryngology and Renal Research Laboratories, Department of Otolaryngology—Head and Neck Surgery, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242, USA

[2] Department of Molecular Physiology and Biophysics, University of Iowa Carver College of Medicine, Iowa City 52242, IA, USA

[3] Interdepartmental PhD Program in Genetics, University of Iowa, Iowa City 52242, IA, USA

historically this heterogeneity restricted genetic testing to just a few genes (Hilgert et al. 2009), the advent of targeted genomic enrichment and massively parallel sequencing (TGE + MPS) has revolutionized the clinical care of the patient with hearing loss by making comprehensive genetic testing possible (Shearer and Smith 2015).

TGE + MPS have been used in several small cohorts with positive diagnostic rates that range from 10 to 83 % [reviewed in (Shearer and Smith 2015)]. This variability reflects selection bias (i.e., including only a select ethnicity or only patients with a positive family history for hearing loss), platform bias (i.e., including only a limited number of genes), and analytic bias (i.e., neglecting to consider copy number variations in the analysis) (Hoppman et al. 2013; Ji et al. 2014; Shearer et al. 2013, 2014b). Herein, we report the analysis of the largest patient cohort to date that has undergone comprehensive clinical genetic testing for hearing loss. Of the 1119 patients presenting for testing in our clinical diagnostic laboratory, we were able to diagnose a genetic cause of deafness in 440 persons (39 %). We show that the diagnostic rate reflects ethnicity and clinical phenotype, and ranges from 1 % in patients with unilateral hearing loss to 72 % in patients of Middle Eastern ethnicity. These results provide a foundation from which to make appropriate recommendations for the use of comprehensive genetic testing in the evaluation of patients with hearing loss.

Materials and methods

Patients

Patients included in this study were sequentially referred to the Molecular Otolaryngology and Renal Research Laboratories (MORL) for clinical genetic testing from January 2012 to September 2014. All genetic screenings were done on a custom-designed TGE + MPS panel called OtoSCOPE® (Shearer et al. 2010). Relatives of patients were not included in this analysis (each nuclear and/or extended family was represented by only the proband), but no exclusions were otherwise made based upon age, age of onset, phenotype or previous testing. All available phenotype, family history, and ethnicity data were recorded. Abnormal physical exam features were classified as described in Table S1. The Institutional Review Board of the University of Iowa approved this study, and the described research was performed in accordance with the Declaration of Helsinki.

Library preparation, sequencing and bioinformatics

TGE + MPS were completed on DNA prepared from whole blood using a Sciclone NGS workstation (PerkinElmer, Waltham, MA) for sample preparation. The testing platform was either OtoSCOPE® v4 (408 individuals) or v5 (711 individuals) which targets 66 or 89 deafness-associated genes, respectively (Table S2) using custom-designed SureDesign capture technology (Agilent Technologies, Santa Clara, CA). Each platform included all known NSHL and NSHL mimic genes at the time of design (May 2011 and November 2012, respectively). Samples were analyzed in pools of 48 samples sequenced on an Illumina HiSeq (Illumina, Inc., San Diego, CA, USA) flow cell using 100-bp paired-end reads. If pre-determined quality control values were not met, the sample was rerun, as previously described (Shearer et al. 2014b).

Data were analyzed using a local installation of the open-source Galaxy software (Blankenberg et al. 2010; Goecks et al. 2010) and a combination of several other open-source tools, including read mapping with Burrows–Wheeler Alignment (BWA) (Li and Durbin 2009), duplicate removal with Picard, local re-alignment and variant calling with GATK Unified Genotyper (McKenna et al. 2010), enrichment statistics with NGSRich (Frommolt et al. 2012), and variant reporting and annotation with custom-produced software. Copy number variant analysis was performed as described (Nord et al. 2011; Shearer et al. 2014b).

Variant interpretation

On a patient-by-patient basis, all variants were discussed in the context of phenotypic data at a weekly interdisciplinary Hearing Group Meeting that included clinicians, scientists, geneticists, genetic counselors, and bioinformaticians. Each variant's interpretation included consideration of quality/coverage depth (QD $\geq$ 5), minor allele frequency (MAF) from 1000 Genomes Project Database and the National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project Exome Variant Server [thresholds for recessive and dominant NSHL were <0.005 (excluding *GJB2* variants) and <0.0005, respectively] (Shearer et al. 2014a) conservation (GERP and PhyloP) and pathogenicity prediction annotation (including PolyPhen2, SIFT, MutationTaster and LRT), and annotation within the Deafness Variation Database (deafnessvariationdatabase.org), an in-house curated, open-access database. Based upon the decision reached at Hearing Group Meeting, result letters were generated for all patients, reporting all variants with MAF <1 % to the ordering physician. In the case of positive results [variant(s) reported as 'pathogenic' or 'likely pathogenic' based on criteria defined by the American College of Medical Genetics and Genomics (ACMG) and further refined by the MORL for NSHL] (Richards et al. 2015; Shearer et al. 2014a), clinical correlation and segregation analysis were recommended. Positive results were confirmed via Sanger sequencing prior to reporting. The

majority of rare variants deemed unlikely to cause hearing loss and not previously reported to be pathogenic were categorized as Variants of Unknown Significance (VUSs).

Statistical analysis

All provided clinical and phenotypic data were recorded. Diagnostic rates were compared using the Fisher exact test (comparing a specified group to all other members of the cohort) or Chi-square test (comparing more than 2 groups), with $p < 0.05$ considered significant. Data were compiled using Microsoft Excel and analyzed using Prism 6 (GraphPad).

Results

Patients

1119 unrelated patients were sequentially accrued during the study period. Relations were not included; otherwise, there were no exclusionary criteria. Patient demographics were binned into broad key categories: inheritance, onset, severity, laterality, physical exam and previous genetic testing (Fig. 1; Table 1). No clinical information was provided

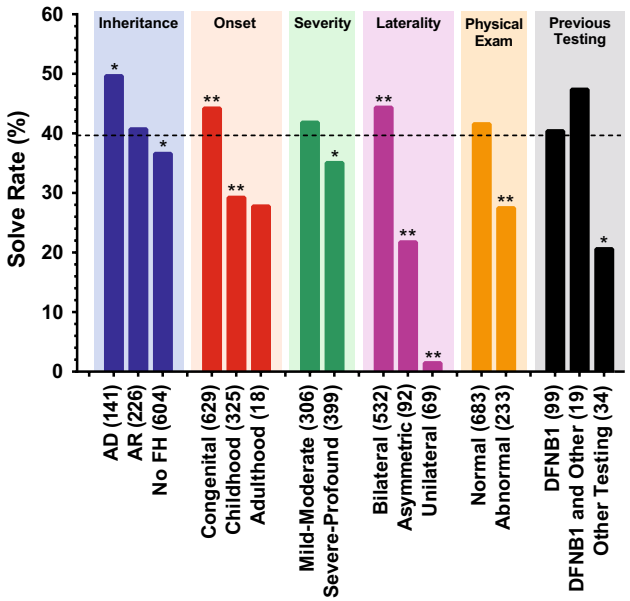

Fig. 1 Diagnostic rates are dependent on patient-specific clinical and phenotypic characteristics and are shown as the percentage of patients with the noted characteristic. *Background shading* separates categories. *N* for each characteristic is listed after the label. *Dashed line* indicates the overall diagnostic rate for this study (39.3 %). Fisher exact test used to determine statistical significance with $*p < 0.05$ and $**p < 0.005$

Table 1 Reported ethnic and phenotypic characteristics of patients evaluated in this study

Characteristic	Number	%
Sex		
Male	561	50.1
Female	550	49.2
NP	8	0.7
Age when ordered (years)		
Age ≤2	415	37.1
Age 3–17	607	54.2
Age ≥18	82	7.3
Ethnicity		
Caucasian	549	49.1
Hispanic	128	11.4
African American	51	4.6
Asian	40	3.6
Mixed ethnicity	57	5.1
Middle Eastern	25	2.2
Ashkenazi Jewish	8	0.7
Other	7	0.6
NP	254	22.7
Family history		
Autosomal recessive	226	20.2
Autosomal dominant	141	12.6
X-linked	1	0.1
Ambiguous	8	0.7
No family history	604	54.0
NP	139	12.4
Onset		
Congenital	629	56.2
Childhood	325	29.0
Adult	18	1.6
NP	147	13.1
Severity		
Normal	1	0.1
Mild-moderate	306	27.3
Severe-profound	399	35.7
NP	413	36.9
Laterality		
Bilaterally symmetric	532	47.5
Unilateral	69	6.2
Asymmetric	92	8.2
NP	426	38.1
Not SNHL		
Conductive	6	0.5
Mixed	24	2.1
Physical exam		
Normal	683	61.0
Any abnormality	233	20.8
NP	203	18.1

Table 1 continued

Characteristic	Number	%
Previous testing		
Any	147	13.1
DFNB1	99	8.8
DFNB1 and other genes	19	1.7
Other genes	24	2.1

NP not provided, *SNHL* sensorineural hearing loss

on 72 patients. For all other individuals, the available clinical information was considered during Hearing Group Meeting and discussed in the context of the genetic data. The most common characteristics included: Caucasian ethnicity (49 %); young age (93 % were <18 years of age); congenital hearing loss (56 %); severe-to-profound hearing loss (36 %); and symmetric impairment (48 %). Patients most commonly had no family history of hearing loss (54 %) and a normal physical exam (61 %).

Genetic diagnoses

We identified a genetic cause of hearing loss in 440 patients (39 %) (Table S3). Of these patients, 101 (23 %) received a genetic diagnosis implicating an NSHL mimic, which included Usher syndrome (59 patients), Pendred syndrome (29 patients), Deafness-infertility syndrome (6 males and 1 female with NSHL), Alström syndrome (1 patient), autosomal dominant non-ocular Stickler syndrome (1 patient), branchiootorenal syndrome (BOR) (2 patients), MYH9-associated disease (1 patient), and Wolfram syndrome (1 patient) (Table S4).

Panel versioning

During the course of this study, the TGE + MPS platform was updated from v4 to v5 as part of our standard operating procedure, increasing the number of genes screened from 66 to 89. Of the 711 patients analyzed on v5, 11 patients carried causative variants in genes not included in v4, thus increasing the diagnostic rate by 2 % in all patients screened with V5 and accounting for 4 % of all positive diagnoses (11 of 263 positive diagnoses). Read metrics for V4 and V5 are shown in Table S5. Although patients sequenced with v5 had a lower average number of reads and lower average target coverage, the percentage of reads overlapping target was higher, as was the coverage at 1, 20, and 30×.

Variant identification

Our analysis of 1119 patients identified 5900 variants, which we reported to healthcare providers. 14 % of variants were considered causally related to the hearing loss phenotype and reported as pathogenic or likely pathogenic; 4 % were previously reported pathogenic variants for recessive hearing loss, with a second variant not identified (carrier status); and 82 % of variants were reported as VUSs. The median number of reported variants was 4 (range = 0–14) and 5 (0–19) for v4 and v5, respectively (Fig. S1).

Diagnostic rate and phenotype

There was considerable phenotypic diversity that impacted the overall diagnostic rate of 39 % (Fig. 1). In patients with a family history of dominant hearing loss, for example, the diagnostic rate was 50 % ($p < 0.05$), while in patients with a family history of recessive hearing loss it was only 41 % (not significant—n.s.). In patients with no family history of hearing loss, the diagnostic rate was 37 % ($p < 0.05$).

When age of onset is considered, patients with congenital hearing loss had a diagnostic rate of 44 %, which was significantly greater than the diagnostic rate in patients with childhood (29 %)- or adult (28 %)-onset hearing loss ($p < 0.005$ in both cases). Patients with bilateral hearing loss were significantly more likely to receive a diagnosis than patients with asymmetric or unilateral hearing loss (44, 22 and 1 %, respectively; $p < 0.005$). Patients with conductive or mixed hearing loss had a decreased likelihood of receiving a genetic diagnosis (17 and 21 %, respectively), but the difference was not significant.

Any kind of abnormality on physical exam decreased the likelihood of a genetic diagnosis using this panel (27 %, $p < 0.005$), as compared to patients with NSHL (42 %, n.s.). In patients with a clinical diagnosis of Usher or BOR syndromes, the diagnostic rate was 31 and 37 %, respectively. In none of the 15 patients with neurological findings (seizures or severe mental retardation) and hearing loss was a non-syndromic genetic cause for deafness identified (Table S6).

Combining demographic characteristics provided a more realistic assessment of the diagnostic rate (Figs. 1, 2). Patients with dominant, recessive or no family history of hearing loss had diagnostic rates of 50, 41, and 37 %, respectively. If the hearing loss was also congenital, the diagnostic rate increased to 55, 43, and 44 %. Additional phenotypic characteristics further improved the diagnostic rate (Fig. S2). For example, a patient with a negative family history for hearing loss had a lower-than-average diagnostic rate (37 %); however, if the hearing loss was congenital, the diagnostic rate increased to 44 % ($p < 0.005$ as compared to patients with non-congenital hearing loss and a negative family history for hearing loss). With congenital onset and symmetric hearing loss, the rate increased to 48 % ($p < 0.005$), and if the physical examination was normal, it increased further to 51 % ($p < 0.005$). The same trend was true for patients with family histories of dominant and

recessive hearing loss—their diagnostic rates jumped to 67 and 55 %, respectively, when the hearing loss was congenital and symmetric and the physical examination was otherwise normal.

For adult-onset hearing loss, the diagnostic rate was 28 %, however, if the family history was positive, the diagnostic rate climbed to 50 %, and if the patient also had symmetric hearing loss, the diagnostic rate jumped again to 67 %.

Only when the hearing loss was unilateral was there a marked negative impact on diagnostic rate (1 % of patients). This finding, when combined with any other characteristic, decreased diagnostic success (Fig. 2).

Diagnostic rate by ethnicity

Ethnic differences impacted the diagnostic rate ($p < 0.005$). In the cohort self-identified as Caucasian (549, 49 %), the diagnostic rate was 38 %. However, in cohorts self-identified as Asian (40, 4 %) and Middle Eastern (25, 2 %), the diagnostic rate was 63 and 72 %, respectively ($p < 0.005$). The diagnostic rate was lowest in African Americans (51, 5 %), at 26 %, $p < 0.05$ (Fig. 3).

Genetic spectrum

In total, 49 genes were causally implicated in hearing loss (Table 2). However, nearly three-fourths of all diagnoses (317 of 440, 72 %) were attributable to 10 genes. The four genes most frequently implicated were *GJB2* (22 %), *STRC* (16 %), *SLC26A4*, (7 %) and *TECTA* (5 %), although this list varied based on degree of hearing loss. For example, while variants in *GJB2* were the most common cause of severe-to-profound hearing loss (20 %), *STRC* accounted for 30 % of diagnoses in persons with mild-to-moderate hearing loss, followed closely by *GJB2* (25 %) and then *TECTA* (7 %). *SLC26A4* pathogenic variants were identified in 7 % of patients with positive diagnoses; however, all of these patients had severe-to-profound hearing loss (10 % of severe-to-profound hearing loss).

Frequency of causative genes also varied by ethnicity (Fig. 3, S4). For example, amongst self-identified Caucasian and Hispanics, *STRC*-related deafness was just as likely to be diagnosed as *GJB2*-related deafness (21 vs. 20 % and 16 vs. 14 %, respectively), but in Middle Eastern or Asian patients, *GJB2* diagnoses were more common than *STRC* diagnoses (17 vs. 6 % and 36 vs. 4 %, respectively). No African American patients were diagnosed with *GJB2*-related hearing loss (Fig. 3, S4).

Causal variants

The profile of causal variant type differed with inheritance pattern. Amongst all 440 diagnoses, 49 % were due to missense variants (Table S7); however, if the hearing loss was dominantly inherited, missense variants were diagnosed 85 % of the time, as compared to 46 % with recessive inheritance. Variants predicting null alleles were much more common with recessive diagnoses—CNVs, indels, nonsense variants, and splice variants made up 20, 19, 9, and 6 % of recessive and 2, 3, 5, and 5 % of dominant diagnoses. 146 CNV alleles in 9 different genes were identified as causative in 88 patients (*GJB2, MYH9, OTOA, PCDH15, SLC26A4, STRC, TMC1, TMPRSS3, USH2A*). These genes contributed to 20 % of all 440 diagnoses, including one dominant diagnosis.

Discussion

Amongst studies of genetic hearing loss, this report is unique as no restrictive criteria were imposed on patient selection. Comprehensive genetic testing was completed on 1119 sequentially accrued and unrelated patients. Following a collaborative diagnostic meeting (Hearing Group) at which identified genetic variants in each patient were discussed in the context of the patient-specific phenotype, a genetic cause of hearing loss was identified in 440 patients (39 %) (Table S3). Several smaller studies have reported similar diagnostic rates (Shearer and Smith 2015).

Our data show that a focused history and physical examination can guide the expected outcome when genetic testing is ordered. The phenotypic correlations that improve or decrease the diagnostic utility of genetic testing are intuitive and logical. For example, we found that a family history positive for hearing loss improved diagnosis (44 % for dominant or recessive family history compared to 37 % for no family history).

Symmetry of hearing loss also impacted diagnosis. In patients with an otherwise normal physical exam, if the hearing loss was symmetric, the diagnostic rate was 48 %. However, a genetic cause was never identified in patients with ‘presumed’ unilateral NSHL suggesting that this condition does not exist (Figs. 1, 2). In fact, the only instance of a positive genetic diagnosis associated with unilateral hearing loss was in a patient with a family history of BOR syndrome caused by a truncating variant in *EYA1*, a well-recognized phenotype–genotype association (Chang et al. 2004; Chen et al. 1995).

Ethnicity impacted diagnostic rate. Nearly half (49 %) of the patients in this study self-identified as Caucasian and had a diagnostic rate of 38 %. In patients of Middle Eastern ethnicity, the diagnostic rate was higher (72 %), an increase that reflects the higher coefficient of inbreeding in this population (Najmabadi and Kahrizi 2014). Coefficient of inbreeding is known to vary across populations, ranging from 0.0365 in Bedouins to 0.0026 in Japanese and

a

	Male	Female	Caucasian	Hispanic	African American	Asian	Middle Eastern	Ashkenazi Jewish	Mixed Ethnicity	Other	AD	AR	No family history	Congenital	Childhood	Adult	Mild-moderate	Severe-profound	Symmetric	Asymmetric	Unilateral	Conductive	Mixed	Normal PE	Abnormal PE	DFNB1	DFNB1 & other	Other testing	% of cohrt
Male	561		281	69	23	16	11	2	25	3	58	123	299	326	153	9	154	194	258	52	38	2	11	333	117	43	11	21	50.1
Female		550	268	59	28	23	14	6	32	4	83	101	305	302	172	9	151	204	273	40	31	4	13	349	116	56	8	13	49.2
Caucasian	281	268	549								80	113	305	326	161	14	170	213	302	50	36	3	15	350	128	57	10	21	49.1
Hispanic	69	59		128							11	35	70	74	39	1	32	52	60	12	9	0	2	86	25	11	3	6	11.4
African American	23	28			51						5	11	30	23	23	0	10	23	22	5	7	0	0	32	10	2	1	1	4.6
Asian	16	23				40					1	6	26	17	12	0	13	16	25	3	1	0	1	26	13	5	2	2	3.6
Middle Eastern	11	14					25				2	8	12	19	5	0	4	16	19	0	0	0	0	19	3	1	1	0	2.2
Ashkenazi Jewish	2	6						8			4	2	2	6	2	0	4	4	5	1	1	0	0	8	0	2	0	0	0.7
Mixed Ethnicity	25	32							57		12	16	29	34	21	0	21	22	27	5	6	0	0	42	10	7	1	0	5.1
Other	3	4								7	1	3	3	3	4	0	3	4	5	2	0	0	0	5	2	0	0	0	0.6
AD	58	83	80	11	5	1	2	4	12	1	141			75	45	8	53	40	70	16	8	1	3	87	30	2	2	1	12.6
AR	123	101	113	35	11	6	8	2	16	3		226		147	65	2	68	93	123	18	15	2	0	160	45	25	8	6	20.2
No family history	299	305	305	70	30	26	12	2	29	3			604	372	197	7	165	243	309	50	43	2	17	399	140	64	6	23	54
Congenital	326	302	326	74	23	17	19	6	34	3	75	147	372	629			158	258	325	50	35	3	11	412	149	67	12	23	56.2
Childhood	153	172	161	39	23	12	5	2	21	4	45	65	197		325		122	117	163	35	27	2	10	220	64	28	7	8	29
Adult	9	9	14	1	0	0	0	0	0	0	8	2	7			18	5	9	11	2	1	0	0	14	3	0	0	0	1.6
Mild-moderate	154	151	170	32	10	13	4	4	21	3	53	68	165	158	122	5	306		208	52	14	4	15	201	71	29	5	6	27.3
Severe-profound	194	204	213	52	23	16	16	4	22	4	40	93	243	258	117	9		399	286	36	38	1	6	263	93	50	12	23	35.7
Symmetric	258	273	302	60	22	25	19	5	27	5	70	123	309	325	163	11	208	286	532			2	9	357	126	66	15	25	47.5
Asymmetric	52	40	50	12	5	3	0	1	5	2	16	18	50	50	35	2	52	36		92		1	9	54	26	8	2	1	6.2
Unilateral	38	31	36	9	7	1	0	1	6	0	8	15	43	35	27	1	14	38			69	2	6	45	13	4	1	2	8.2
Conductive	2	4	3	0	0	0	0	0	0	0	1	2	2	3	2	0	4	1	2	1	2	6		3	3	0	0	0	0.5
Mixed	11	13	15	2	0	1	0	0	0	0	3	0	17	11	10	0	15	6	9	9	6		24	10	8	3	1	1	2.1
Normal PE	333	349	350	86	32	26	19	8	42	5	87	160	399	412	220	14	201	263	357	54	45	3	10	683		66	15	13	61
Abnormal PE	117	116	128	25	10	13	3	0	10	2	30	45	140	149	64	3	71	93	126	26	13	3	8		233	20	3	19	20.8
DFNB1	43	56	57	11	2	5	1	2	7	0	2	25	64	67	28	0	29	50	66	8	4	0	3	66	20	99		4	8.8
DFNB1 & other	11	8	10	3	1	2	1	0	1	0	2	8	6	12	7	0	5	12	15	2	1	0	1	15	3		19	1	1.7
Other testing	21	13	21	6	1	2	0	0	0	0	1	6	23	23	8	0	6	23	25	1	2	0	1	13	19	4	1	34	2.1
	0	10	25	50	75	100	200	300	400	500	600	683																	

b

	Male	Female	Caucasian	Hispanic	African American	Asian	Middle Eastern	Ashkenazi Jewish	Mixed Ethnicity	Other	AD	AR	No family history	Congenital	Childhood	Adult	Mild-moderate	Severe-profound	Symmetric	Asymmetric	Unilateral	Conductive	Mixed	Normal PE	Abnormal PE	DFNB1	DFNB1 & other	Other testing
Male	38.7		37.0	37.7	26.1	81.3	45.5		32.0		55.2	36.6	36.5	43.3	28.1		38.3	34.5	44.2	19.2	0.0		0.0	40.5	30.8	34.9	63.6	23.8
Female		39.6	38.1	30.5	25.0	47.8	92.9		46.9		45.8	44.6	36.7	45.0	30.2		45.0	35.3	44.3	25.0	3.2		38.5	42.4	24.1	44.6		15.4
Caucasian	37.0	38.1	37.5								45.0	44.2	34.1	40.8	31.7	35.7	44.1	33.3	43.4	18.0	0.0		20.0	40.0	27.3	38.6	40.0	19.0
Hispanic	37.7	30.5		34.4							54.5	25.7	34.3	39.2	23.1		43.8	21.2	33.3	33.3				34.9	20.0	45.5		
African American	26.1	25.0			25.5							27.3	26.7	39.1	13.0		30.0	17.4	36.4					37.5	10.0			
Asian	81.3	47.8				62.5							53.8	76.5	58.3		61.5	56.3	56.0					69.2	46.2			
Middle Eastern	45.5	92.9					72.0						75.0	73.7				81.3	78.9					73.7				
Ashkenazi Jewish																												
Mixed Ethnicity	32.0	46.9							40.4		50.0	37.5	37.9	47.1	28.6		47.6	40.9	63.0					42.9	30.0			
Other																												
AD	55.2	45.8	45.0	54.5					50.0		49.6			54.7	37.8		49.1	40.0	54.3	25.0				50.6	33.3			
AR	36.6	44.6	44.2	25.7	27.3				37.5			40.7		42.9	32.3		50.0	33.3	45.5	22.2	0.0			45.0	15.6	48.0		
No family history	36.5	36.7	34.1	34.3	26.7	53.8	75.0		37.9				36.6	43.5	26.4		38.2	34.6	42.1	22.0	0.0		17.6	38.6	30.0	40.6		21.7
Congenital	43.3	45.0	40.8	39.2	39.1	76.5	73.7		47.1		54.7	42.9	43.5	44.2			47.5	39.9	49.2	24.0	2.9		18.2	46.8	30.9	44.8	58.3	30.4
Childhood	28.1	30.2	31.7	23.1	13.0	58.3			28.6		37.8	32.3	26.4		29.2		35.2	25.6	34.4	20.0	0.0		20.0	32.3	21.9	32.1		
Adult			35.7													27.8			36.4					35.7				
Mild-moderate	38.3	45.0	44.1	43.8	30.0	61.5			47.6		49.1	50.0	38.2	47.5	35.2		41.8		49.5	19.2	0.0		13.3	49.8	22.5	48.3		
Severe-profound	34.5	35.3	33.3	21.2	17.4	56.3	81.3		40.9		40.0	33.3	34.6	39.9	25.6			35.1	40.6	25.0	0.0			34.2	30.1	38.0	50.0	21.7
Symmetric	44.2	44.3	43.4	33.3	36.4	56.0	78.9		63.0		54.3	45.5	42.1	49.2	34.4	36.4	49.5	40.6	44.4					47.6	31.0	42.4	46.7	20.0
Asymmetric	19.2	25.0	18.0	33.3							25.0	22.2	22.0	24.0	20.0		19.2	25.0		21.7				27.8	11.5			
Unilateral	0.0	3.2	0.0									0.0	0.0	2.9	0.0		0.0	0.0			1.4			0.0	7.7			
Conductive																												
Mixed	0.0	38.5	20.0										17.6	18.2	20.0		13.3						20.8	20.0				
Normal PE	40.5	42.4	40.0	34.9	37.5	69.2	73.7		42.9		50.6	45.0	38.6	46.8	32.3	35.7	49.8	34.2	47.6	27.8	0.0		20.0	41.6		45.5	40.0	15.4
Abnormal PE	30.8	24.1	27.3	20.0	10.0	46.2			30.0		33.3	15.6	30.0	30.9	21.9		22.5	30.1	31.0	11.5	7.7				27.5	25.0		15.8
DFNB1	34.9	44.6	38.6	45.5								48.0	40.6	44.8	32.1		48.3	38.0	42.4					45.5	25.0	40.4		
DFNB1 & other	63.6		40.0											58.3				50.0	46.7					40.0			47.4	
Other testing	23.8	15.4	19.0										21.7	30.4				21.7	20.0					15.4	15.8			20.6
	0	10	20	30	40	50	60	70	80	90	100																	

◀**Fig. 2** Diagnostic rate is influenced by ethnic, clinical and phenotypic characteristics. **a** *N* for each combination of two reported characteristics for all combinations. *Color/shading* reflects the number of patients with the paired criteria, up to the maximum of $n = 683$. **b** Diagnostic success for each corresponding category in **a**. *Coloring/shading* indicative of diagnosis: *light orange* indicates below average diagnostic rate, *yellow indicates* close to average diagnostic rate (39.3 %), and *dark green* indicates above average diagnostic rate. *Empty squares* had fewer than 10 individuals. *AD* autosomal dominant, *AR* autosomal recessive, *PE* physical exam, *DFNB1* prior genetic DFNB1 (*GJB2*) testing, *DFNB1 & other* prior genetic testing including DFNB1 and other tests, *other testing* prior genetic testing excluding DFNB1 testing

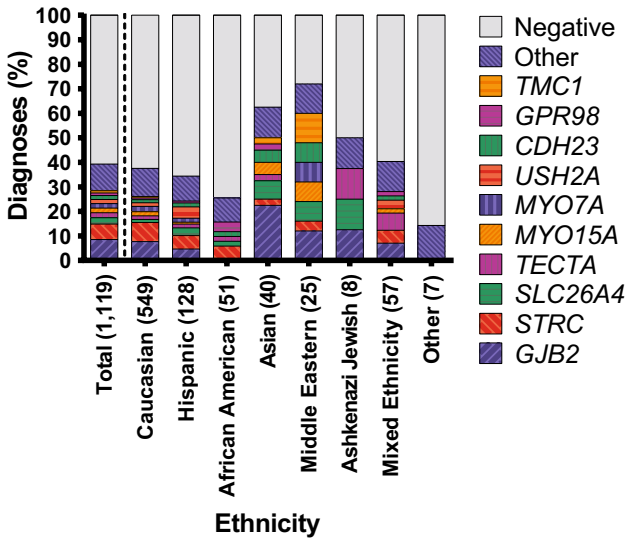

Fig. 3 Solve rate and implicated genes across ethnicities. The 10 genes with ≥10 diagnosis for the entire cohort are plotted individually; all other genes diagnosed are grouped as "other". Ethnic-specific differences are readily apparent

5.96E−8 in an Afro-European admixed population of Chicago (Pemberton and Rosenberg 2014).

That the diagnostic rate was lowest in African Americans and the 'Other' group (which included patients of African, Bahaman or Native American heritage) suggests that there is a 'discovery gap' to fill in these ethnic groups (Gasmelseed et al. 2004; Shan et al. 2010). Nevertheless, in all ethnic groups, a relatively large number of less frequently implicated genes accounted for 10–15 % of diagnoses (Fig. 3), implying that across populations a similar proportion of hearing loss is due to multiple, rare, ethnic-specific variants that arise randomly and independently.

In many of the world's populations, variants in *GJB2* are the predominant cause of congenital severe-to-profound ARNSHL (Kenneson et al. 2002). In this study, they accounted for 22 % of all diagnoses and 26 % of diagnoses in the congenital severe-to-profound ARNSHL cohort. The ethnic-specific breakdown of *GJB2*-related hearing loss in Caucasian, Hispanic, African American, Asian, and Middle Eastern patients was 20, 14, 0, 36 and 17 %, respectively (Fig. 3, S2). When corrected for *GJB2* pre-screening, the percentages increased slightly (22, 16, 0, 45, and 17 %, respectively), which is in agreement with other reports (Bazazzadegan et al. 2012; Dai et al. 2009; Du et al. 2014; Pandya et al. 2003; Usami et al. 2012).

STRC causative variants accounted for 30 % of diagnoses in patients with mild-moderate hearing loss, providing the most common diagnosis among those with this degree of hearing loss. In aggregate, 16 % of diagnoses implicated *STRC*. It is noteworthy that the majority of causative mutations in *STRC* involved large CNVs (99 %), underscoring the requirement that all comprehensive genetic testing panels for hearing loss include CNV detection.

Of variants with a MAF of <0.01, the largest majority were of unknown significance (VUSs, Fig. S1). In addition, however, we identified several known or likely pathogenic variants associated with ARNSHL in genes without a second causal variant. For example, 151 of the 679 patients, in whom a genetic diagnosis was not made, carried reported ARNSHL-causal variants without having a second variant in the coding sequence of that gene. This carrier rate of 22 % is roughly 8 times higher than that reported in hearing control populations and suggests that many of these patients have yet-to-be-identified non-coding mutations (Green et al. 1999).

Variant annotation is a dynamic process. Interpretation of variants as pathogenic, likely pathogenic, VUS, likely benign and benign is continuously refined based on increasingly robust data. The Deafness Variation Database (deafnessvariationdatabase.org) captures this area of active study in an open-source, continuously updated, interpretational database that we maintain on all variant positions interrogated on the OtoSCOPE platform.

In summary, we believe that comprehensive genetic testing is a foundational diagnostic test that allows healthcare providers to make evidence-based decisions in the evaluation of hearing loss thereby providing better and more cost-effective patient care (Fig. 4, Table S8). While only 10 genes accounted for 72 % of diagnoses, 49 genes were identified as causative and 20 % of diagnoses involved at least one CNV (Table 2 and Shearer et al. (2014b)), mandating comprehensive TGE + MPS and thorough data analysis. While whole exome sequencing (WES) is becoming cheaper and for many indications more practical, a focused deafness-specific panel continues to offer the advantages of better coverage of targeted regions, greater facility to detect multiple variant types (including CNVs and complicated genomic rearrangements), substantially lower costs, higher throughput, simpler bioinformatics analysis, and focused testing, obviating the need to deal with secondary/incidental findings that otherwise inevitably arise with WES.

Table 2 Diagnoses and inheritance patterns in 440 patients with genetic hearing loss

Gene	Total diagnoses		Autosomal dominant		Autosomal recessive		Mitochondrial or X-linked	
	Diagnoses	%	Diagnoses	%	Diagnoses	%	Diagnoses	%
GJB2	95	21.6	1	1.6	94	25.3		
STRC	71	16.1			71	19.1		
SLC26A4	29	6.6			29	7.8		
TECTA	23	5.2	15	23.8	8	2.2		
MYO15A	21	4.8			21	5.6		
MYO7A	20	4.5	1	1.6	19	5.1		
USH2A	19	4.3			19	5.1		
CDH23	18	4.1			18	4.8		
ADCRV1	12	2.7			12	3.2		
TMC1	10	2.3	2	3.2	8	2.2		
PCDH15	9	2.0			9	2.4		
OTOF					9	2.4		
TMPRSS3					9	2.4		
LOXHD1	8	1.8			8	2.2		
OTOA					8	2.2		
WFS1	7	1.6	5	7.9	2	0.5		
COL11A2	6	1.4	5	7.9	1	0.3		
KCNQ4			6	9.5				
MYH14	5	1.1	5	7.9				
MYO6			4	6.3	1	0.3		
ACTG1	4	0.9	4	6.3				
PTPRQ					4	1.1		
MYH9	3	0.7	3	4.8				
OTOGL					3	0.8		
TRIOBP					3	0.8		
CLDN14	2	0.5			2	0.5		
COCH			2	3.2				
ESPN			2	3.2				
EYA4			2	3.2				
LRTOMT					2	0.5		
POU3F4							2	40.0
SMPX							2	40.0
TPRN			1	1.6	1	0.3		
WHRN					2	0.5		
ALMS1	1	0.2			1	0.3		
DFNB59					1	0.3		
DIABLO			1	1.6				
DIAPH1			1	1.6				
EYA1			1	1.6				
GRXCR1					1	0.3		
ILDR1					1	0.3		
LHFPL5					1	0.3		
MTRNR1							1	20.0
MYO1A			1	1.6				
SLC17A8			1	1.6				
SLC26A5					1	0.3		
TSPEAR					1	0.3		
USH1C					1	0.3		
USH1G					1	0.3		

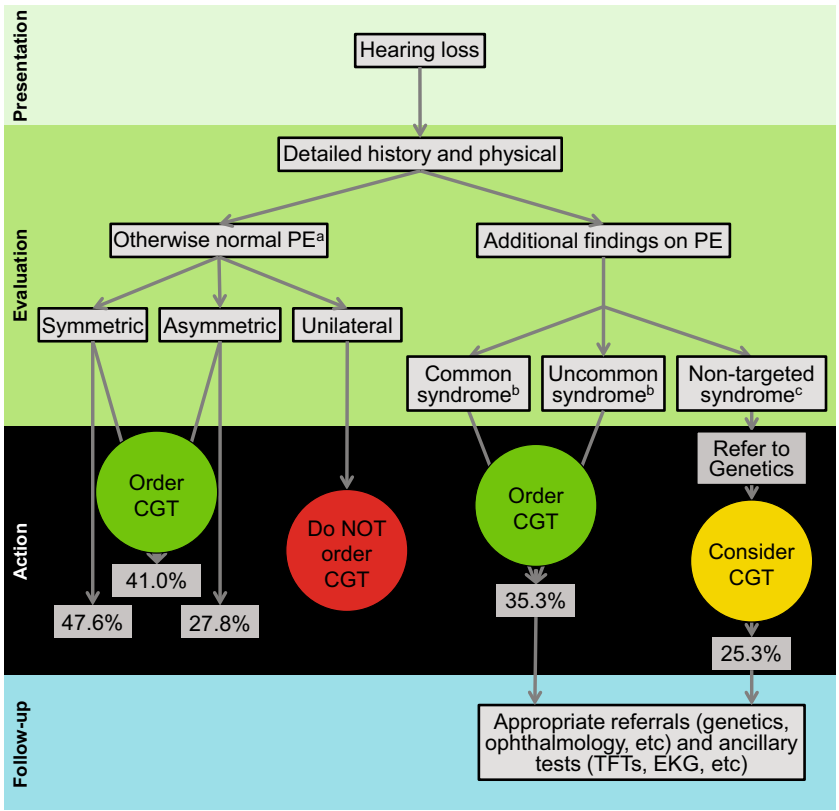

Fig. 4 Recommended diagnostic workflow of a patient with hearing loss showing the value of comprehensive genetic testing (CGT) with TGE and the expected diagnostic rate in percentage. A thorough physical and history is essential and determine the expected outcome of CGT. Patients with complex phenotypes may require referral to specialists. Additional phenotypic information on select syndromes is presented in Table S6. Questions regarding the appropriateness of testing can be sent to morl@uiowa.edu. *PE* physical exam, *CGT* comprehensive genetic testing, *NSHL* non-syndromic hearing loss, *TFT* thyroid function test. [a]Several forms of syndromic hearing loss may present as NSHL and are referred to as 'NSHL mimics'. CGT includes the diagnosis of these NSHL mimics. [b]Common syndromes that can be detected by an otolaryngologist and are targeted by this CGT include Usher syndrome, Pendred syndrome and BOR syndrome. For a complete list of syndromes included on the current CGT panel see Table S8. [c]Some individuals will present with extremely rare/private syndromes or phenotypes that reflect the co-occurrence of two (or rarely more) syndromes. CGT should be considered for the latter cohort of patients. CGT with the OtoSCOPE panel is not indicated in patients with neurological findings such as epilepsy, intellectual delay and autism, and in patients with complex multisystem syndromes that include hearing loss caused by genes NOT targeted for capture by OtoSCOPE

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Compliances with ethical standards

Conflict of interest CMSH, AOB, AES, DLK, CJN, KLF, SSE, SBS, KTB, CAC, PTR, AEW, EABZ, DW, and HA disclose no conflict of interest. RJHS directs the MORL, which offers TGE + MPS as a clinical diagnostic test for hearing loss.

References

Bazazzadegan N et al (2012) The spectrum of GJB2 mutations in the Iranian population with non-syndromic hearing loss–a twelve year study. Int J Pediatr Otorhinolaryngol 76:1164–1174. doi:10.1016/j.ijporl.2012.04.026

Blankenberg D et al. (2010) Galaxy: a web-based genome analysis tool for experimentalists. Curr Protoc Mol Biol 10:11–21. doi:10.1002/0471142727.mb1910s89 **(Chapter 19:Unit 19)**

Chang EH, Menezes M, Meyer NC, Cucci RA, Vervoort VS, Schwartz CE, Smith RJ (2004) Branchio-oto-renal syndrome: the mutation spectrum in EYA1 and its phenotypic consequences. Hum Mutat 23:582–589. doi:10.1002/humu.20048

Chen A et al (1995) Phenotypic manifestations of branchio-oto-renal syndrome. Am J Med Genet 58:365–370. doi:10.1002/ajmg.1320580413

Dai P et al (2009) GJB2 mutation spectrum in 2,063 Chinese patients with nonsyndromic hearing impairment. J Transl Med 7:26. doi:10.1186/1479-5876-7-26

Du W, Wang Q, Zhu Y, Wang Y, Guo Y (2014) Associations between GJB2, mitochondrial 12S rRNA, SLC26A4 mutations, and hearing loss among three ethnicities. Biomed Res Int 2014:746838. doi:10.1155/2014/746838

Fortnum HM, Summerfield AQ, Marshall DH, Davis AC, Bamford JM (2001) Prevalence of permanent childhood hearing impairment in the United Kingdom and implications for universal neonatal hearing screening: questionnaire based ascertainment study. BMJ 323:536–540

Frommolt P et al (2012) Assessing the enrichment performance in targeted resequencing experiments. Hum Mutat 33:635–641. doi:10.1002/humu.22036

Gasmelseed NM et al (2004) Low frequency of deafness-associated GJB2 variants in Kenya and Sudan and novel GJB2 variants. Hum Mutat 23:206–207. doi:10.1002/humu.9216

Goecks J, Nekrutenko A, Taylor J, Galaxy T (2010) Galaxy: a comprehensive approach for supporting accessible, reproducible, and transparent computational research in the life sciences. Genome Biol 11:R86. doi:10.1186/gb-2010-11-8-r86

Green GE, Scott DA, McDonald JM, Woodworth GG, Sheffield VC, Smith RJ (1999) Carrier rates in the midwestern United States for GJB2 mutations causing inherited deafness. JAMA 281:2211–2216

Hilgert N, Smith RJ, Van Camp G (2009) Forty-six genes causing nonsyndromic hearing impairment: which ones should be analyzed in DNA diagnostics? Mutat Res 681:189–196. doi:10.1016/j.mrrev.2008.08.002

Hoppman N, Aypar U, Brodersen P, Brown N, Wilson J, Babovic-Vuksanovic D (2013) Genetic testing for hearing loss in the United States should include deletion/duplication analysis for the deafness/infertility locus at 15q15.3. Mol Cytogenet 6:19. doi:10.1186/1755-8166-6-19

Ji H, Lu J, Wang J, Li H, Lin X (2014) Combined examination of sequence and copy number variations in human deafness genes improves diagnosis for cases of genetic deafness. BMC Ear Nose Throat Disord 14:9. doi:10.1186/1472-6815-14-9

Kenneson A, Van Naarden Braun K, Boyle C (2002) GJB2 (connexin 26) variants and nonsyndromic sensorineural hearing loss: a HuGE review. Genet Med 4:258–274. doi:10.1097/00125817-200207000-00004

Kimberling WJ et al (2010) Frequency of Usher syndrome in two pediatric populations: implications for genetic screening of deaf and hard of hearing children. Genet Med 12:512–516. doi:10.1097/GIM.0b013e3181e5afb8

Li H, Durbin R (2009) Fast and accurate short read alignment with Burrows–Wheeler transform. Bioinformatics 25:1754–1760. doi:10.1093/bioinformatics/btp324

Marazita ML, Ploughman LM, Rawlings B, Remington E, Arnos KS, Nance WE (1993) Genetic epidemiological studies of early-onset deafness in the U.S. school-age population. Am J Med Genet 46:486–491. doi:10.1002/ajmg.1320460504

McKenna A et al (2010) The genome analysis toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome Res 20:1297–1303. doi:10.1101/gr.107524.110

Morton CC, Nance WE (2006) Newborn hearing screening–a silent revolution. N Engl J Med 354:2151–2164. doi:10.1056/NEJMra050700

Najmabadi H, Kahrizi K (2014) Genetics of non-syndromic hearing loss in the Middle East. Int J Pediatr Otorhinolaryngol 78:2026–2036. doi:10.1016/j.ijporl.2014.08.036

Nord AS, Lee M, King MC, Walsh T (2011) Accurate and exact CNV identification from targeted high-throughput sequence data. BMC Genom 12:184. doi:10.1186/1471-2164-12-184

Pandya A et al (2003) Frequency and distribution of GJB2 (connexin 26) and GJB6 (connexin 30) mutations in a large North American repository of deaf probands. Genet Med 5:295–303. doi:10.1097/01.GIM.0000078026.01140.68

Pemberton TJ, Rosenberg NA (2014) Population-genetic influences on genomic estimates of the inbreeding coefficient: a global perspective. Hum Hered 77:37–48. doi:10.1159/000362878

Richards S et al (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405–424. doi:10.1038/gim.2015.30

Shan J et al (2010) GJB2 mutation spectrum in 209 hearing impaired individuals of predominantly Caribbean Hispanic and African descent. Int J Pediatr Otorhinolaryngol 74:611–618. doi:10.1016/j.ijporl.2010.03.004

Shearer AE et al (2010) Comprehensive genetic testing for hereditary hearing loss using massively parallel sequencing. Proc Natl Acad Sci 107:21104–21109. doi:10.1073/pnas.1012989107

Shearer AE et al (2013) Advancing genetic testing for deafness with genomic technology. J Med Genet 50:627–634. doi:10.1136/jmedgenet-2013-101749

Shearer AE et al (2014a) Utilizing ethnic-specific differences in minor allele frequency to recategorize reported pathogenic deafness variants. Am J Hum Genet 95:445–453. doi:10.1016/j.ajhg.2014.09.001

Shearer AE et al (2014b) Copy number variants are a common cause of non-syndromic hearing loss. Genome Med 6:37. doi:10.1186/gm554

Shearer AE, Smith RJ (2015) Massively parallel sequencing for genetic diagnosis of hearing loss: the new standard of care. Otolaryngol Head Neck Surg 153:175–182. doi:10.1177/0194599815591156

Smith RJ et al (1994) Clinical diagnosis of the Usher syndromes. Usher Syndrome Consortium. Am J Med Genet 50:32–38. doi:10.1002/ajmg.1320500107

Usami S, Nishio SY, Nagano M, Abe S, Yamaguchi T, Deafness Gene Study C (2012) Simultaneous screening of multiple mutations by invader assay improves molecular diagnosis of hereditary hearing loss: a multicenter study. PLoS One 7:e31276. doi:10.1371/journal.pone.0031276

Van Camp G, Smith, RJH (2015) Hereditary hearing loss homepage. http://hereditaryhearingloss.org. Accessed 15 June 2015

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The Protective Effect of Adenoidectomy on Pediatric Tympanostomy Tube Re-Insertions: A Population-Based Birth Cohort Study

Mao-Che Wang[1,2], Ying-Piao Wang[2,3], Chia-Huei Chu[1], Tzong-Yang Tu[1], An-Suey Shiao[1], Pesus Chou[2]*

1 Department of Otolaryngology Head Neck Surgery, Taipei Veterans General Hospital, Taipei, Taiwan and School of Medicine, National Yang-Ming University, Taipei, Taiwan, **2** Institute of Public Health and Community Medicine Research Center, National Yang-Ming University, Taipei, Taiwan, **3** Department of Otolaryngology Head Neck Surgery, Mackay Memorial Hospital, Taipei, Taiwan and Department of Audiology and Speech Language Pathology and School of Medicine, Mackay Medical College, New Taipei City, Taiwan

Abstract

Objectives: Adenoidectomy in conjunction with tympanostomy tube insertion for treating pediatric otitis media with effusion and recurrent acute otitis media has been debated for decades. Practice differed surgeon from surgeon. This study used population-based data to determine the protective effect of adenoidectomy in preventing tympanostomy tube re-insertion and tried to provide more evidence based information for surgeons when they do decision making.

Study Design: Retrospective birth cohort study.

Methods: This study used the National Health Insurance Research Database for the period 2000–2009 in Taiwan. The tube reinsertion rate and time to tube re-insertion among children who received tympanostomy tubes with or without adenoidectomy were compared. Age stratification analysis was also done to explore the effects of age.

Results: Adenoidectomy showed protective effects on preventing tube re-insertion compared to tympanostomy tubes alone in children who needed tubes for the first time (tube re-insertion rate 9% versus 5.1%, $p = 0.002$ and longer time to re-insertions, $p = 0.01$), especially those aged over 4 years when they had their first tube surgery. After controlling the effect of age, adenoidectomy reduced the rate of re-insertion by 40% compared to tympanostomy tubes alone (aHR: 0.60; 95% CI: 0.41–0.89). However, the protective effect of conjunction adenoidectomy was not obvious among children with a second tympanostomy tube insertion. Children who needed their first tube surgery at the age 2–4 years were most prone to have tube re-insertions, followed by the age group of 4–6 years.

Conclusions: Adenoidectomy has protective effect in preventing tympanostomy tube re-insertions compared to tympanostomy tubes alone, especially for children older than 4 years old and who needed tubes for the first time. Nonetheless, clinicians should still weigh the pros and cons of the procedure for their pediatric patients.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files. The claim data of the study subjects we retrieved from the Taiwan National Health Insurance Research Database for the analysis in this study is included as a supplemental file. This file can be opened and read with the statistical software ''SAS''. The identification of the subjects was censored.

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* Email: pschou@ym.edu.tw

Introduction

Acute otitis media (AOM) and otitis media with effusion (OME) are very common otologic problems in children. The middle ear cavity is filled with infected fluid and the mucosa is inflamed. Ninety percent of children experience AOM and OME before school age, most often between 6 months and 4 years of age [1,2]. Most OME resolve spontaneously within three months, but 30–40% may have recurrent OME and 5–10% of episodes may last for a year or longer [1,3,4]. Diagnosis of OME depends on history, including previous rhino-sinusitis or AOM, decreased hearing noted by the care giver, inattention at school, and aural fullness sensation as stated by the child. Physical examination is based mainly on pneumatic otoscopy, which is an inexpensive, accessible, and easily used diagnostic tool [3,5]. Diagnosis may be confirmed by telescopy, pure tone audiometry, and tympanometry [6]. Management includes conservative treatment and surgical intervention. The American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) set the clinical practice guidelines for OME in 2004. Based on the self-limiting nature of most OME,

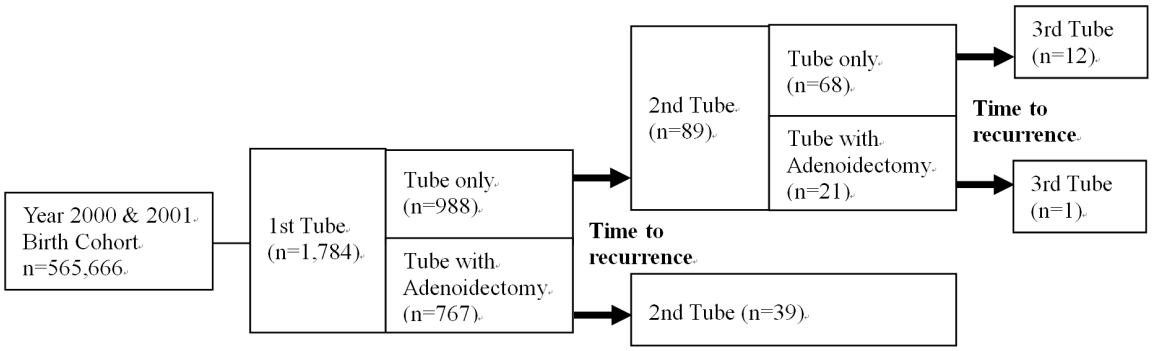

Figure 1. Study flow chart.
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clinicians should manage children who are not at risk by watchful waiting for three months from the date of effusion onset (if known) or from the date of diagnosis (if onset is unknown). If a child becomes a surgical candidate, tympanostomy tube insertion is the preferred initial procedure. Adenoidectomy should only be performed when there is nasal obstruction or chronic adenoiditis, or in repeated tympanostomy tube insertions. Tonsillectomy or myringotomy alone should not be used [5]. The AAO-HNS also set clinical practice guidelines for tympanostomy tubes in children in 2013, recommending that clinicians offer bilateral tympanostomy tubes to children with bilateral chronic OME (OME last for 3 months or longer), and recurrent AOM with middle ear effusion. The guideline also recommended that clinicians should not offer tympanostomy tubes to children with single episode of OME lasting less than 3 months, and recurrent AOM without middle ear effusion [7].

For children with tympanostomy tubes, 20–50% may require repeated tympanostomy tubes after their initial tubes extruded [8–10]. Adenoidectomy has been proved to be effective in preventing recurrence of OME, recurrent AOM, or the need for repeated tympanostomy tubes in many studies in the past 30 years [11–20], and only a few demonstrated contrary data [21–24]. Adenoidectomy may reduce repeated tympanostomy tubes by 50% [15–19]. Why is adenoidectomy effective in preventing pediatric middle ear infection? The adenoids are considered an important factor in pediatric middle ear infection since it may be a reservoir of pathogens [25], while its size effect may block the Eustachian tube orifice [26,27]. Thus, it may play a role in middle ear inflammation or decreased ciliated mucosa [28–30]. However, it is not suggested as a regular procedure in treating chronic OME or recurrent AOM or in conjunction with primary tympanostomy tube insertions [5,31], for the possible complications of general anesthesia and the procedure itself like bleeding, nasopharyngeal stenosis, and injury to the orifice of Eustachian tubes [32–34]. Although the AAO-HNS practice guidelines for OME suggested adenoidectomy only for children requiring repeated tympanostomy tubes [5], many surgeons performed adenoidectomy in conjunction with tympanostomy tubes insertion as the initial treatment for chronic OME or recurrent AOM in recent years after the release of AAO-HNS practice guidelines [16,18,19]. When to perform adenoidectomy for children with chronic OME remains a major debatable issue. Another controversial issue is the age at which adenoidectomy will be beneficial to children with chronic OME. Many studies show that adenoidectomy is only beneficial to children of certain age groups. In three studies, Gates et al. and Maw showed that adenoidectomy was beneficial in children with OME older than 4 years [11,12,14], and one most recent systemic review and metanalysis also concluded that adenoidectomy with primary tube insertion appears to provide a protective effect against repeated surgery in children older than 4 years [35], while Hammaren-Malmi et al. demonstrated that adenoidectomy did not reduce OME in children younger than 4 years old [21]. However, Coyte et al. found that adenoidectomy was beneficial to children older than 2 years old and that the benefits were more obvious among children older than 3 years old [15]. Thus, the results of these studies are not consistent. This population-based retrospective birth cohort study aimed to examine the protective effect of adenoidectomy for tube re-insertion using the National Health Insurance Research Database (NHIRD) in Taiwan. Specifically, this study examined the efficacy of adenoidectomy in conjunction with tympanostomy tube insertion for reducing the repeated tympanostomy tubes compared to tympanostomy tubes alone. We used Tympanostomy tube insertion as a surrogate for chronic OME and recurrent AOM because surgical procedures were usually for most serious and retractable cases. Besides, the reduction of tube insertion also means the reduction of the risk of general anesthesia and the procedure itself which were really burdens for both pediatric patients and their parents. The National Health Insurance (NHI) in Taiwan, established since 1995, has a nationwide coverage of more than 99% of legal residents. It is well known for its low fees and low reimbursement but high quality of service. All of the medical services and medication in Taiwan are paid for by NHI, which is also characterized by easy accessibility without a regulated referral system. Patients may go to any doctor or any hospital on their own will, with or without the referral of primary care physicians. All of the medical procedures and claims are recorded in the NHI database, which is the only buyer of medical service in Taiwan. The NHIRD is released for academic use yearly by the National Health Institute of Taiwan.

Materials and Methods

The study was reviewed and approved by the Institutional Review Board of Taipei Veterans General Hospital. (IRB number: 2013-02-019B) No inform consent was given because this study analyzed government released secondary data. The identification of every individual in the database was censored. This ten-year study (2000–2009) used the Taiwan NHIRD, a population-based data on approximately 23 million people covered by the NHI. Every admission and outpatient visit record was included in this database without sampling. All children born in the year 2000 and 2001 who had tympanostomy tube insertion before the end of the study period (end of the year 2009) were included. They were divided into two groups based on whether or not adenoidectomy

Table 1. Descriptions of 2000–2001 birth cohort who had undergone tympanostomy tubes before 9 years of age.

Characteristics	n	%
Total subjects	1755	100.0
Gender*		
Male	1065	60.7
Female	689	39.3
Age at 1st tube insertion*		
0–2 years	183	10.4
2–4 years	222	12.7
4–6 years	856	48.8
6–9 years	494	28.2
Number of chronic OME episodes		
1	1627	92.7
2	111	6.3
3	12	0.7
4+	5	0.3
Surgical operation		
Tube only	988	56.3
Tube + Adenoidectomy	767	43.7
Age at tube insertion†		
1st tube insertion	5.0	1.8
2nd tube insertion	5.9	1.5
3rd tube insertion	6.9	1.3
Age at adenoidectomy‡		
0–2 years	5	0.6
2–4 years	82	10.1
4–6 years	450	55.5
6–9 years	274	33.8

*One missing value.
†Shown by mean and standard deviation.
‡Only those who had undergone adenoidectomy were included (n = 767).
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was done together with their first tympanostomy tube insertion. Data on these children was examined to determine if they received repeated tube insertions before the end of the study period.

Those with repeated tube insertions without adenoidectomy on their first tympanostomy tube insertion were further divided into two groups based on whether or not adenoidectomy was done together with their second tympanostomy tube insertion. Data on these children was further examined to determine if they received a third tube insertion before the end of the study period (Fig. 1). The repeat tube insertion rate and time to repeated tubes were compared between children who received adenoidectomy with tympanostomy tubes and those who received tube insertion alone.

The study population was obtained by retrieving all of the patients with the procedure code for myringotomy with ventilation tube insertion under a microscope from 2000 to 2009 from the claims data of the NHIRD, with a birthday between January 1, 2000 and December 31, 2001. That is a population-based data without any sampling. As such, a population based year 2000 and 2001 birth cohort for tympanostomy tube insertion was obtained and followed-up to 8 or 9 years old. Children with cleft palate with diagnosis codes in International Classification of Disease, 9th Revision (ICD-9) 749.00~749.04 were excluded because they tended to have multiple tympanostomy tube insertions [36–38]. Adenoidectomy was also relatively contraindicated for children with cleft palate as it might lead to velo-pharyngeal incompetence [39]. Concurrent tympanostomy tube insertion and adenoidectomy was defined by identifying two procedure codes for myringotomy with ventilation tube insertion under a microscope, and for adenoidectomy on the same day in the claims data. Adenoidectomy done with tonsillectomy at the same time was also identified and was not included in this study.

The children were also stratified into four age groups in years in order to examine the effect of age ($0 \leqq age < 2$, $2 \leqq age < 4$, $4 \leqq age < 6$, and $6 \leqq age < 9$). The rate of repeated tympanostomy tube insertion and time to recurrence were examined in each age group to explore the protective effect of adenoidectomy on tube reinsertion. The age group with highest risk of tube re-insertion was further determined. The rate of post-adenoidectomy bleeding was also explored.

Statistical Analysis

The tube insertion rate between children with adenoidectomy and tympanostomy tubes and those with tympanostomy tubes alone in all age groups was compared using the Fisher's exact test. The time between the first tympanostomy tube insertion and repeated procedures in the study period was compared by log-rank test for failure time. The adjusted hazard ratio of recurrence between children with and those without adenoidectomy and among age groups was obtained by Cox proportional hazard model. The statistical results were obtained via the software SAS 9.1 (SAS Institute, Cary, NC, USA). Statistical significance was set at $p<0.05$. All values were expressed as mean ± standard deviation (SD).

Results

According to the Taiwan National Statistics Report, there were 305,312 and 260,354 newborns in the year 2000 and 2001 respectively [40]. This study had a population-based birth cohort numbering 565,666 who were followed-up for 8 to 9 years. A total of 2221 children in the 2000 and 2001 birth cohorts had tympanostomy tube insertion before the age of 8 or 9 years. The cumulative incidence of tympanostomy tube insertion before 8 or 9 years of age was 0.393%. After excluding 437 children with cleft palate, and 29 children with adenotonsillectomy, 1755 were included in this study. Among them, 1627 cases had only one tube insertion before 8 or 9 years of age. There were 1065 males, or 60.7% of the total cases. Around 80% of children had their first tube surgery after 4 years of age. One hundred and eleven had two tubes insertions and 17 had more than two insertions. Additional adenoidectomy and age at tympanostomy tube insertions and adenoidectomy were shown in Table 1.

Of the 1755 cases included, 767 had adenoidectomy on their first tympanostomy tube insertion. The other 988 children had tube insertion alone, although 89 of them needed repeated tube insertions. There were 21 who had adenoidectomy on their second tubes insertion while 68 had tube insertion only. The age of children received adenoidectomy was 5.5±1.3 (mean±SD) years old. Children who received both adenoidectomy and tympanostomy tubes on their first tubes insertion had a lower recurrence rate than those who had tubes alone ($p = 0.002$). They also had a longer time to re-insertions ($p = 0.01$) (Fig. 2). However, the protective effect of adenoidectomy on the second tube insertion was not observed in terms of re-insertion rate and in time to re-insertions ($p = 0.29$ and $p = 0.22$, respectively) (Table 2).

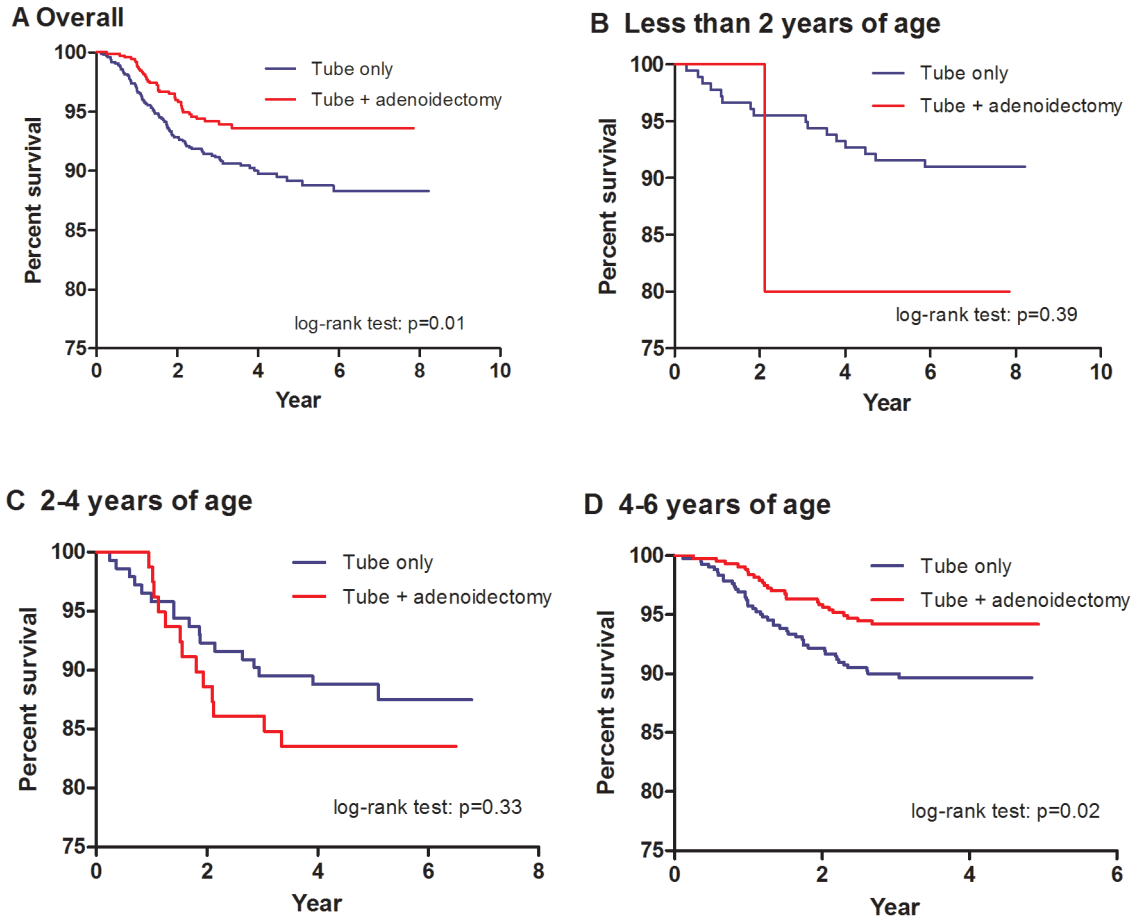

Figure 2. Survival curve of tube re-insertions. (A) Overall recurrence. (B) (C) and (D) Recurrence stratified by age.
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Stratifying the children into four age groups (0–2 years, 2–4 years, 4–6 years, and 6–9 years), those older than 4 years old who received both adenoidectomy and tympanostomy tubes had statistically significant lower tube re-insertion rate and longer time to tube re-insertions than those who had tympanostomy tubes alone (Table 2 & Figure 2). ($p = 0.02$, $p<0.001$ for age group 4–6 and 6–9 respectively) There was no difference in tube re-insertions regardless of adenoidectomy in the age group 0–2 and 2–4 years (Table 2).

After controlling for age, adenoidectomy reduced the rate of tube re-insertion by 40% compared to tympanostomy tubes alone (aHR: 0.60; 95% CI: 0.41–0.89). After controlling for the effect of adenoidectomy, children who had their first tube surgery at the age of 2–4 years were most prone to tube re-insertions, followed by the 4–6 years age group (Table 3). Among 767 patients who received adenoidectomy, only two had severe post-operative bleeding that required intra-operative monitoring.

Discussion

The 2000 and 2001 birth cohort in Taiwan had 565,666 children. Among them, 2221 had tympanostomy tube insertion before the age of 8 or 9 years for a cumulative incidence of 0.393%. Compared to other reports, one study showed the tympanostomy tube insertion rate in United states was 6.8% before the age of 3 and another study revealed middle ear surgical procedure was 9% in Norway [41,42]. The rate of tube re-insertion is about 20% to 50% [8–10,43]. The rate of tympanostomy tube insertion and tube re-sinsertion of children in Taiwan is low. This may be because Asian parents usually do not like their children to undergo surgery, leading to more conservative management or otolarygologists in Taiwan managed pediatric otitis media more conservatively under the suggestions of clinical practice guideline in comparison to surgeons in the United States [44–46].

This study demonstrates that adenoidectomy has a protective effect of preventing tube re-insertion in conjunction with the first tympanostomy tube insertion in children older than 4 years old compared to tube insertion alone. There were 849 cases in the 4–6 year old age group, which accounted for nearly half of the enrolled cases. Further stratifying this group into two groups of 4–5 years and 5–6 years for analysis, adenoidectomy had significant protective effects in the 4–5 year old age group but not in the 5–6 year old age group. The recurrence rate of children receiving adenoidectomy in the two age groups was 5.8% and 5.5%, respectively. The recurrence rates in tube only group was lower in the 5–6 year old age group (8.1%) than that in the 4–5 year old age group (12.1%). This may be due to the protective effect of age influencing the protective effect of adenoidectomy. We did not found the protective effect of adenoidectomy for children under 4 years old. Given small sample size for children under age of 4, post hoc power was calculated to examine whether the statistical power was large enough to detect differences in tube re-insertion rate between two surgical procedures. With an overall sample size of

Table 2. Tympanostomy tube re-insertions by previous surgical procedures and age groups.

	Recurrence of chronic OME			Test for failure time
Previous surgical procedures	**n**	**%**	**P Value***	**P Value†**
All age groups				
First re-insertion				
Tube only (n = 988)	89	9.0	0.002	0.01
Tube+ adenoidectomy (n = 767)	39	5.1		
Second re-insertion				
Tube only (n = 68)	12	17.6	0.29	0.22
Tube+ adenoidectomy (n = 21)	1	4.8		
Age stratification at first tube insertion				
0–2 years				
Tube only (n = 178)	16	9.0	0.39	0.39
Tube+ adenoidectomy (n = 5)	1	20.0		
2–4 years				
Tube only (n = 143)	17	11.9	0.41	0.33
Tube+ adenoidectomy (n = 79)	13	16.5		
4–6 years				
Tube only (n = 422)	43	10.2	0.02	0.02
Tube+ adenoidectomy (n = 434)	25	5.8		
6–9 years				
Tube only (n = 245)	13	5.3	<0.001	<0.001
Tube+ adenoidectomy (n = 249)	0	0.0		

*Fisher's exact test was performed.
†Time to OME recurrence was tested by log-rank test.
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183 0–2 years-old and 224 2–4 years-old children, the power achieves 37.1% and 33.6%, respectively, at a 0.05 significance level. This meant that there might be a protective effect which we could not detect due to small sample size for children under 4 years old.

After adjusting for the effect of age, adenoidectomy reduced the rate of tube re-insertion by 39%. These results are similar to those of most previous studies on this topic, most of them around 40% to 50% [10,15,17–19,35]. If a child requires tube insertion at the age of 2–4 years, he or she are more likely to have tube re-insertions. This may be due to children in this age group are more likely to have recurrent AOM episodes, attending day care services, or shorter tubes staying time. Clinicians should therefore pay more attention to this age group of patients with chronic OME because they are prone to have recurrence. On the other hand, adenoidectomy is not beneficial to patients in this age group. Education the parents to avoid exposure to risk factors [46], medical management of allergic rhinitis, and vaccination for

Table 3. Estimated hazard rations (HR) and 95% confidence intervals (95% CI) of tympanostomy tube re-insertions of 2000–2001 birth cohort of chronic OME who had undergone tympanostomy tubes before 9 years of age.

	Recurrence of chronic OME			
Variables	**HR†**	**95% CI**	**aHR†**	**95% CI**
Previous operation				
Tube only	1.00		1.00	
Tube+ adenoidectomy*	0.61	0.42–0.89*	0.60	0.41–0.89*
Age				
0–2 years	0.63	0.34–1.14	0.55	0.30–1.00*
2–4 years	1.00		1.00	
4–6 years	0.66	0.43–1.02	0.71	0.46–1.11
6–9 years	0.41	0.21–0.79*	0.44	0.23–0.86*

*$p<0.05$.
†HR = Hazard ratio; aHR = Adjusted hazard ratio; 95% CI = 95% confidence interval.
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pneumococcal conjugate vaccine [47–49] are efforts that can be done in order to prevent the need for repeated tubes.

This study is the first to explore the problem using a population-based birth cohort. Every case born in the 2000 and 2001 were demonstrated and followed-up in this study without sampling to show what really happened to all these children in Taiwan who needed tympanostomy tube insertion before the age of 8 or 9 years. With the advantage of a population-based administrative database and the uniqueness a birth-cohort design, the numbers of tube insertions after birth of every case can be clearly defined and the concurrent surgical procedure (adenoidectomy or adeno-tonsillectomy) can be identified accurately without ambiguity in history.

To improve the internal validity of this study, tympanostomy tube insertion is used instead of diagnosis codes in ICD-9 as a surrogate of chronic OME and recurrent AOM for the accuracy of defining the study population. If there was a code for certain surgical procedures for a patient in the claims data, that patient definitely had the disease and underwent the surgical procedure for it on the date of the surgery. In contrast, if diagnosis codes in ICD-9 were used as a surrogate for the disease, the probability of miscoding by the physician might be much higher. Physicians might use a certain diagnosis code by misdiagnosis. They also might do this for prescribing antibiotics or laboratory test in order to pass the review of the insurance payer or to improve reimbursement.

The major limitation of this study is the limitation of the administrative claims data. Medical records and the operative notes of every patient could not be obtained. In the NHIRD, there was no clinical data like patient history, physical examination findings, laboratory data results, hearing level or surgical findings. Medical records could not be checked to identify if the patient had adenoid hypertrophy, adenitis, obstructive sleep apnea, or persistent purulent nasal discharge. The appearance of ear drum and culture results were also not known, which might lead to selection bias because surgeons perform adenoidectomy for more severe cases. Disease severity in the adenoidectomy group might be higher than in the tube insertion alone group. In the real world, a population based randomized control trial for this problem is not feasible or ethical. This study does offer an alternative way to explore the protective effects of adenoidectomy on tympanostomy tube re-insertions without any ethical issue. Other unobserved confounders are very likely to be diluted in this population based birth cohort study design and may have little influence.

Although adenoidectomy has protective effects on preventing tube re-insertions for children who need tympanostomy tubes, especially those older than 4 years old, performing adenoidectomy for every kid who needs tubes is not being recommended. The complication rate may not be high but there are complications due to the general anesthesia or from the procedure itself, including post-operative bleeding and nasopharyngeal stenosis [32–34]. Surgeons should take consider both the benefits and harm for every individual patient and make the best decision accordingly.

Conclusions

Adenoidectomy has protective effect against the need for repeated tympanostomy tubes, especially for children older than 4 years. Children who need their first tube at the age of 2–4 years are most likely to have a tube re-insertion in the future. Surgeons should weigh the pros and cons for every individual patient before suggesting adenoidectomy to prevent recurrent chronic OME and AOM.

Author Contributions

Conceived and designed the experiments: MCW YPW CHC ASS PC. Performed the experiments: MCW YPW. Analyzed the data: MCW YPW. Contributed reagents/materials/analysis tools: MCW YPW TYT ASS. Contributed to the writing of the manuscript: MCW YPW CHC PC.

References

1. Tos M (1984) Epidemiology and natural history of secretory otitis. Am J Otol 5: 459–462.
2. Paradise JL, Rockette HE, Colborn DK, Bernard BS, Smith CG, et al (1997) Otitis media in 2253 Pittsburgh area infants: prevalence and risk factors during the first two years of life. Pediatrics 99: 318–333.
3. Stool SE, Berg AO, Berman S, Carney CJ, Cooley JR, et al. Otitis media with effusion in young children. Clinical Practice Guideline, Number 12. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services; AHCPR Publication No. 94-0622, 1994.
4. Williamson IG, Dunleavy J, Baine J, Robinson D. (1994) The natural history of otitis media with effusion: a three-year study of the incidence and prevalence of abnormal tympanograms in four South West Hampshire infant and first schools. J Laryngol Otol 108: 930–934.
5. Rosenfeld RM, Culpepper L, Doyle KJ, Grundfast KM, Hoberman A, et al (2004) Clinical practice guideline: otitis media with effusion. Otolaryngol Head Neck Surg 130: S95–S118.
6. Shiao AS, Guo YC (2005) A comparison assessment of video-telescopy for diagnosis of pediatric otitis media with effusion. Int J Pediatr Otorhinolaryngol 69: 1497–1502.
7. Rosenfeld RM, Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, et al (2013) Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg 149: S1–S35.
8. Mandel EM, Rockette HE, Bluestone CD, Paradise JL, Nozza RJ (1989) Myringotomy with or without tympanostomy tubes for chronic otitis media with effusion. Arch Otolaryngol Head Neck Surg 115: 1217–1224.
9. Mandel EM, Rockette HE, Bluestone CD, Paradise JL, Nozza RJ (1992) Efficiency of myringotomy with or without tympanostomy tubes for chronic otitis media with effusion. Pediat Infect Dis J 11: 270–277.
10. Boston M, McCook J, Burke B, Derkay C (2003) Incidence of and risk factors for additional tympanostomy tube insertion in children. Arch Otoloryngol Head Neck Surg 129: 293–296.
11. Gates GA, Avery CA, Prihoda TJ, Cooper JC Jr (1987) Effectiveness of adenoidectomy and tympanostomy tubes in the treatment of chronic otitis media with effusion. N Engl J Med 317: 1444–1451.
12. Maw AR (1983) Chronic otitis media with effusion (glue ear) and adenoid tonsillectomy: prospective randomized controlled study. Br Med J 287: 1586–1588.
13. Paradise JL, Bluestone CD, Rogers KD, Taylor FH, Colborn K, et al (1990) Efficacy of adenoidectomy for recurrent otitis media in children previously treated with tympanostomy-tube placement: Results of parallel randomized and non-randomized trials. J Am Med Assoc 263: 2066–2073.
14. Maw AR, Bawden R (1993) Spontaneous resolution of severe chronic glue ear in children and the effect of adenoidectomy, tonsillectomy and insertion of ventilation tube (grommets). Br Med J 306: 756–760.
15. Coyte PC, Croxford R, Mclsaac W, Feldman W, Friedberg J (2001) The role of adjuvant adenoidectomy and tonsillectomy in the outcome of insertion of tympanostomy tubes. N Engl J Med 344: 1188–1195.
16. MRC Multi-center Otitis Media Study Group (2012) Adjuvant adenoidectomy in persistent bilateral otitis media with effusion: hearing and revision surgery outcomes through 2 years in the TARGET randomized trial. Clin Otolaryngol 37: 107–116.
17. Black NA, Sanderson CFB, Freeland AP, Vessey MP (1990) A randomized controlled trial of surgery for glue ear. Br Med J 300: 1551–1556.
18. Kadhim AL, Spilsburry K, Semmens JB, Coates HL, Lannigan FJ (2007) Adenoidectomy for middle ear effusion: a study of 50,000 children over 24 years. Laryngoscope 117: 427–433.
19. Gleinser DM, Kriel HH, Mukerji S (2011) The relationship between repeat tympanostomy tube insertions and adenoidectomy. Int J Pediatr Otorhinolaryngol 75: 1247–1251.
20. Maw AR (1985) Factors affecting adenoidectomy for otitis media with effusion (glue ear). J R Soc Med 78: 1014–1018.
21. Hammaren-Malmi S, Saxen H, Tarkkanen J, Mattila PS (2005) Adenoidectomy does not significantly reduce the incidence of otitis media in conjunction with the insertion of tympanostomy tubes in children who are younger than 4 years: a randomized trial. Pediatrics 116: 185–189.
22. Kujala T, Alho OP, Luotonen J, Kristo A, Uhari M, et al (2012) Tympanostomy with and without adenoidectomy for the prevention of recurrence of acute otitis media: a randomized controlled trial. Pediatr Infect Dis J 31: 565–569.

23. Dempster JH, Browning GG, Gatehouse SG (1993) A randomized study of the surgical management of children with persistent otitis media with effusion associated with a hearing impairment. J Laryngol Otol 107: 284–289.
24. Casselbrant ML, Mandel EM, Rockette HE, Kurs-Lasky M, Fall PA, et al (2009) Adenoidectomy for otitis media with effusion in 2–3 year-old children. Int J Pediatr Otorhinolaryngol 73: 1717–1724.
25. Musher DM (2006) Pneumococcal vaccine-direct and indirect ("herd") effects. N Engl J Med 354: 1522–1524.
26. Wright ED, Alden JP, Manoukian JJ (1998) Laterally hypertrophic adenoids as a contributing factor in otitis media. Int J Pediatr Otorhinolaryngol 45: 207–214.
27. Nguyen LHP, Manoukian JJ, Yoskovitch A (2004) Adenoidectomy: selection criteria for surgical cases of otitis media. Larynogoscope 114: 863–866.
28. Yasan H, Dogru H, Tüz M, Candir O, Uygur K, et al (2003) Otitis media with effusion and histopathologic properties of adenoid tissue. Int J Pediatr Otorhinolaryngol 67: 1179–1183.
29. Cengel S, Akyol MU (2006) The role of topical nasal steroids in the treatment of children with otitis media with effusion and adenoid hypertrophy with otitis media with effusion and/or adenoid hypertrophy. Int J Pediatr Otorhinolaryngol 70: 639–645.
30. Abdullah B, Hassan S, Sidek D, Jaafar H (2006) Adenoid mast cell and their role in the pathogenesis of otitis media with effusion. J Laryngol Otol 120: 556–560.
31. Paradise JL, Bluestone CD, Colborn DK, Bernard BS, Smith CG, et al (1999) Adenoidectomy and adeno-tonsillectomy for recurrent acute otitis media: parallel randomized clinical trials in children not previously treated with tympanostomy tubes. J Am Med Assoc 282: 945–953.
32. van der Griend BF, Lister NA, McKenzie IM, Martin N, Ragg PG, et al (2011) Post-operative mortality in children after 101,885 anesthetics at a tertiary pediatric hospital. Anesth Anal 112: 1440–1447.
33. Randoll DA, Hoffer ME (1998) Complications of tonsillectomy and adenoidectomy. Otolaryngol Head Neck Surg 118: 61–68.
34. Thomas k, Boeger D, Buentzel J, Esser D, Hoffmann K, et al (2013) Pediatric adenoidectomy: A population-based regional study on epidemiology and outcome. Int J Pediatr Otorhinolaryngol 77: 1716–1720.
35. Mikals SJ, Brigger MT (2014) Adenoidectomy as an adjuvant to primary tympanostomy tube placement: a systematic review and meta-analysis. JAMA Otolaryngol Head Neck Surg 140: 95–101.
36. Sheahan P, Miller I, Sheahan JN, Earley MJ, Blayney AW (2003) Incidence and outcome of middle ear disease in cleft lip and/or cleft palate. Int J Pediatr Otorhinolaryngol 67: 785–793.
37. Kobayashi H, Sakuma T, Yamada N, Suzaki H (2012) Clinical outcomes of ventilation tube placement in children with cleft palate. Int J Pediatr Otorhinolaryngol 76: 718–721.
38. Marchica CL, Pitaro J, Daniel SJ (2013) Recurrent tube insertions for chronic otitis media with effusion in children over 6 years. Int J Pediatr Otorhinolaryngol 77: 252–255.
39. Kaufman FL (1991) Managing the cleft lip and palate patient. Pediatr Clin North Am 38: 1127–1147.
40. Taiwan National Statistics Report. Minister of the Interior. (Accessed December 31, 2013, at http://statis.moi.gov.tw/micst/stmain.jsp?sys = 100).
41. Kogan MD, Overpeck MD, Hoffman HJ, Casselbrant ML (2000) Factors associated with tympanostomy tube insertion among pre-school aged children in the United States. Am J Public Health 90: 245–250.
42. Kvaerner KJ, Nafstad P, Jaakkola JJK (2002) Otolaryngological surgery and upper respiratory tract infections in children: an epidemiological study. Ann Otol Rhinol Laryngol 111: 1034–39.
43. Spielmann PM, Adamson RM, Schenk D, Hussain SSM (2008) Follow up after middle ear ventilation tube insertion: what is needed and when. J Laryngol Otol 122: 580–583.
44. Wang MC, Huang CK, Wang YP, Chien CW (2012) Effects of increased payment for ventilation tube insertion on decision making for paediatric otitis media with effusion. J Eval Clin Pract 18: 919–922.
45. Keyhani S, Kleinman LC, Rothschild M, Bernstein JM, Anderson R, et al (2008) Clinical characteristics of New York City children who received tympanostomy tubes in 2002. Pediatrics 121: e24–33.
46. Keyhani S, Kleinman LC, Rothschild M, Bernestein JM, Anderson R, et al. (2008) Overuse of tympanostomy tubes in new York metropolitan area: evidence from five hospital cohort. Br Med J 337: a1067. doi:10.1136/bmj.a1607
47. Fireman B, Black SB, Shinefield HR, Lee J, Lewis E, et al (2003) Impact of the pneumococcal conjugate vaccine on otitis media. Pediatr Infect Dis J 22: 10–16.
48. Palmu AA, Verho J, Jokinen J, Karma P, Kilpi TM (2004) The seven-valent pneumococcal conjugate vaccine reduces tympanostomy tube placement in children. Pediatr Infect Dis J 23: 732–738.
49. Poehling KA, Szilagyi PG, Grijalva CG, Martin SW, LaFleur B, et al (2007) Reduction of frequent otitis media and pressure-equalizing tube insertions in children after introduction of pneumococcal conjugate vaccine. Pediatrics 19: 707–715.

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Pediatric malignant salivary gland tumors: 60 year follow up☆

Cara C. Cockerill, Brian C. Gross [1], Stephanie Contag, Sarah Rein, Eric J. Moore, Kerry D. Olsen, Laura J. Orvidas*

Mayo Clinic Department of Otorhinolaryngology, Head and Neck Surgery, 200 First St SW, Rochester, MN, 55905, USA

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ABSTRACT

Objective: To evaluate the presentation, treatments and outcomes in pediatric patients with salivary gland malignancies.
Study design: Retrospective chart review (1950–2012), Prospective phone interview.
Methods: Patients ≤18 years old with a salivary gland malignancy treated at our institution were identified. Patients were also contacted by phone for a follow up survey.
Results: Fifty-six patients were identified. Tumor origin was 88% parotid (n = 49), 5% (n = 3) submandibular and 7% (n = 4) minor salivary glands. Time from onset of symptoms to diagnosis was over one year (mean = 14.4 years). Fifteen out of 52 patients with major gland malignancy had a locoregional recurrence and local recurrences were almost all after initial enucleation. Two of these patients died of disease (overall disease specific survival = 96%). Three out of 4 patients with minor gland malignancy had a local recurrence and two patients with high grade pathology developed metastases and died of their disease (overall survival = 50%). On long term follow up survey in 13 patients (25%), 100% reported normal facial movement and 54% described symptoms of Frey's syndrome, which is higher than other reported series in children. Recurrence was noted up to 45 years after initial treatment.
Conclusions: The majority of malignant pediatric salivary gland tumors are low grade and have excellent survival, especially if found at an early stage. Minor salivary gland malignancies, particularly high grade, have a worse prognosis. Long term mild Frey's syndrome can be expected in approximately half of patients. We advocate a need for long term follow up and increased awareness among providers to diagnose these patients earlier.

1. Introduction

Salivary gland tumors are uncommon in children and adolescents and represent only 0.5% of pediatric malignancies [1]. In adults, approximately 15–25% of salivary gland tumors are malignant [2] compared to approximately 25–50% in the pediatric population [3–6]. As a whole, salivary gland malignancies are a heterogeneous group of cancers, with differing behaviors based on factors such as location, histologic type, grade and stage.

Due to the rarity of salivary gland malignancies in the pediatric population and lack of large single institution clinical studies, it is challenging to develop a consensus on treatment. The degree of surgery and the role of adjuvant treatment remain unclear. Optimizing a balance between good oncologic outcome and long term morbidity is paramount. Additionally, long term functional and cosmetic outcomes are somewhat unknown in this patient population as the majority of data in existence is via retrospective chart review which may not capture these complications.

The goal of this study is to examine a series of pediatric patients with salivary gland malignancies treated at a single tertiary care referral center and followed for up to 62 years to aid in answering the challenging question of treatment and long term functional outcomes for these children.

☆ This data was presented at the Combined Otolaryngology Sections Meeting in Boston, Massachusetts April 24–27, as part of the American Society of Pediatric Otolaryngology meeting.

* Corresponding author. Department of Otolaryngology, Head and Neck Surgery Mayo Clinic, 200 First St SW, Rochester, MN, 55905, USA.
E-mail addresses: Cockerill.Cara@mayo.edu (C.C. Cockerill), Briangross81@gmail.com (B.C. Gross), Wise.Stephanie@mayo.edu (S. Contag), reinx046@umn.edu (S. Rein), Moore.Eric@mayo.edu (E.J. Moore), Olsen.Kerry@mayo.edu (K.D. Olsen), Orvidas.Laura@mayo.edu (L.J. Orvidas).
[1] Present address: 1902 Braeburn Drive, Suite 130, Salem, Virginia 24153, USA.

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2. Materials and methods

After institutional review board approval, a retrospective chart review was performed (1950–2012) and all patients less than or equal to 18 years of age with a histologically confirmed salivary gland malignancy evaluated or treated at the Mayo Clinic in Rochester, Minnesota were identified. Patients' medical records were reviewed for demographic data, presentation, diagnostic testing, management strategy and clinical outcomes. Tumors were staged based upon the 2008 AJCC TNM staging classification system. Follow up length was calculated from the date of surgery until the last known contact with the patient.

Time from initial surgery to recurrence at the primary site or neck was the outcome. Subjects were censored at time of last follow-up or death. Kaplan-Meier estimates of the survival function were obtained using available case analysis and risk factors were compared using the log-rank test. A Bonferroni correction was used for multiple testing of definitive surgery types.

Patients and or the parents of underage patients were contacted for long term follow up conducted via standardized phone interview conducted by trained personnel of the Mayo Clinic Survey Research Center. The enrolled subjects provided written and oral consent.

3. Results

3.1. Demographics

Fifty six patients age less than or equal to eighteen years were identified. Twenty-four were male and 32 were female. The patients ranged in age from 3 to 18 years old, with a mean of 14.1 years.

3.2. Clinical presentation

All but one patient presented with a salivary gland mass. The majority of patients (91%) had painless masses. No patients presented with facial nerve weakness. Mean time between onset of symptoms and diagnosis was 14.4 months.

4. Major gland

4.1. Tumor characteristics

Of the 56 cases, 49 involved the parotid gland and 3 involved the submandibular gland. Information on histology, grade and stage can be found in Table 1. All patients were clinically N0 with no evidence of distant metastases. Tumor grade was available for 35 patients. All intermediate or high grade lesions were classified as mucoepidermoid carcinoma with the exception of one high grade synovial cell sarcoma. Five patients had adverse pathologic features; 4 tumors with extracapsular spread and 1 with vascular invasion.

4.2. Treatment

A large proportion of patients (55%) underwent some degree of operative management at another institution. Approximately half (14 of 29 cases) of these cases underwent an incomplete procedure and after obtaining final pathologic diagnosis were transferred to our tertiary center for definitive surgical management. The majority of these patients had either an enucleation or superficial parotidectomy and then underwent total parotidectomy after evaluation at our institution. Of the patients that had completion surgery at our institution, residual tumor was found in about half of the surgical specimens (47%). Definitive treatment for primary parotid malignancies was as follows: 22% enucleation of tumor, 10% superficial parotidectomy, 49% total parotidectomy with facial nerve preservation, 16% total parotidectomy with at least partial facial nerve resection and primary chemoradiation in 2% (Table 1). Approximately 40% of parotid tumors underwent a neck dissection. The majority of neck dissections (65%) were limited to area II; 15% included areas II and III. No cervical lymph nodes were involved, but 11% of patients had positive intraparotid lymph nodes. All submandibular gland malignancies were treated with resection of the gland as well as dissection of nodal area IB. No surrounding Ib lymph nodes were positive. One patient with rhabdomyosarcoma underwent primary chemotherapy and radiation due to the large and infiltrative nature of the tumor.

Three patients, all with primary parotid malignancies, received adjuvant radiation after surgery. These were as follows: T3 mucoepidermoid carcinoma with invasion into the masseter muscle, T3 high grade mucoepidermoid carcinoma with positive intraparotid lymph nodes and a T3 adenoid cystic carcinoma. Two patients received chemotherapy and radiation: one with rhabdomyosarcoma and one with T4b mucoepidermoid carcinoma. The average radiation dosage delivered to these patients was 5600 Gy. One patient with lymphoma of the parotid gland received chemotherapy alone after surgery (Table 1).

Table 1
Parotid and submandibular gland tumor characteristics and treatment outcomes.

	n	%
Histology		
Mucoepidermoid carcinoma	27	52
Acinic cell carcinoma	16	31
Adenoid cystic carcinoma	3	6
Rhabdomyosarcoma	2	4
Adenocarcinoma	1	2
Lymphoma	1	2
Polymorphous hemangioendothelioma	1	2
Synovial cell sarcoma	1	2
Tumor grade		
Low	23	66
Intermediate	9	26
High	3	8
T stage		
T1	22	49
T2	13	29
T3	9	20
T4	1	2
Stage		
Stage I	21	48
Stage II	14	32
Stage III	8	18
Stage IV	1	2
Definitive treatment (parotid tumors)		
Enucleation	11	22
Superficial parotidectomy	5	10
Total parotidectomy	32	65
Primary chemoradiation	1	2
Adjuvant radiation	3	6
Adjuvant chemoradiation	2	4
Recurrence		
Local	14	27
Regional (neck)	2	4
Distant metastasis	2	4
Outcomes		
Alive NED	48	85
Dead of disease	4	7
Dead of other cause	4	7

4.3. Outcomes

Fourteen out of 52 patients had a local recurrence, 2 had a cervical recurrence, 2 developed distant metastases and 2 died of their disease. A description of the clinical course for patients with a local recurrence can be found in Appendix 1. Local recurrences

were almost all after initial enucleation (10/14). Median time to recurrence in this group was 9.5 months (range 3–540 months). Two had a recurrence in the cervical lymph nodes that was treated with selective neck dissection. Neither of these patients had a neck dissection as part of their initial surgery. One patient with rhabdomyosarcoma developed lung metastases that were treated curatively with chemotherapy and radiation but ultimately died of treatment associated acute myeloid leukemia.

Mean length of follow up for patients with major salivary gland malignancies was 13.5 years (range: 0.2–62.3). Two patients died of major salivary malignancy making the overall disease specific survival 96%. Two patients died of acute myeloid leukemia thought to be secondary to chemoradiation treatment received for their salivary malignancy and two patients died of other causes.

4.4. Factors associated with recurrence

Information on factors associated with recurrence is presented in Table 2. There was evidence that adverse pathologic factors (extracapsular spread, vascular invasion and or perineural spread), enucleation or superficial versus total parotidectomy, and no neck dissection increased the risk of recurrence. However, statistical significance was only seen in patients who underwent enucleation versus total parotidectomy (p value = 0.005) (Fig. 1). There was insufficient evidence that low versus high grade pathologic types, T stage, and addition of adjuvant radiation was related to risk of recurrence.

4.5. Complications

Based on retrospective chart review, the most common complication involved the facial nerve with 4 patients having complete facial paralysis, and another 4 patients with limited branch facial paralysis. Gustatory sweating (Frey's syndrome) was recorded in 5 patients. Other complications related to surgery included hypertrophic scar and major depression associated with appearance from facial paralysis. Complications associated with radiation included facial lymphedema, xerostomia, paresthesias, external auditory canal stenosis and arrested mandibular growth requiring reconstructive surgery. Two patients developed treatment related acute myeloid leukemia.

4.6. Long term follow up survey data

An attempt was made to contact all 52 patients still alive at last follow up. Ultimately, 13 patients or parents of patients could be reached for a phone survey. Average follow up time for this cohort was 28.7 years (range 2.1–62.3 years). One hundred percent reported normal facial movement with no eye problems. One patient reported facial twitching or spasm despite not having any facial weakness after initial treatment. Over half (54%) described symptoms of Frey's syndrome. All of these patients reported that their gustatory sweating symptoms never resolved and stated that the effect on their quality of life was a “1” on a scale of 1–10.

Other reported long term side effects of treatment included facial numbness, change in ear position, speech impairment, difficulty eating, chronic facial pain, need for long term feeding tube, difficulty whistling/blowing, excessive scarring and drooling (n = 1 for all). Four patients that were treated with surgery alone reported excessively dry mouth. One patient reported a recurrence 45 years after being treated for mucoepidermoid carcinoma with surgery, radiation and chemotherapy.

5. Minor gland

There were 4 cases of minor salivary gland cancer (2 low grade mucoepidermoid, 1 high grade mucoepidermoid, 1 low grade adenocarcinoma). Three out of 4 patients suffered a local recurrence and one of these had a cervical lymph node recurrence 3.5 years later. Two patients (high grade mucoepidermoid and adenocarcinoma) developed metastases and both died of their disease, which made an overall disease specific survival of 50% for this group. Average length of follow up in this cohort was 6.9 years.

6. Discussion

We present our single institution experience treating pediatric salivary gland malignancies over a 62 year time period. Our series confirms that mucoepidermoid carcinoma is the most common histologic type in pediatric patients followed by acinic cell and adenoid cystic carcinoma [1,4,7]. An average age at presentation of 14–15 years also appears to be consistent across studies [1,7].

Table 2
Factors associated with locoregional recurrence of parotid and submandibular gland tumors.

	Locoregional recurrence n/total n (%)	p-value
Low grade pathology[a]	8/32 (25%)	
High grade pathology[b]	5/18 (28%)	
T1/T2	10/35 (29%)	
T3/T4	3/10 (30%)	
Adverse pathologic factors	2/5 (40%)	0.6
No adverse pathologic factors	13/46 (28%)	
Positive intraparotid LN	0/4 (0%)	
No positive intraparotid LN	14/45 (31%)	
Enucleation	7/11 (64%)	
Superficial parotidectomy (SP)	2/5 (40%)	
Total parotidectomy (TP)	5/32 (16%)	
Definitive surgery		
Enucleation vs. TP		0.005
Enucleation vs. SP		0.15
SP vs. TP		0.10
Neck dissection	3/22 (14%)	0.09
No neck dissection	12/30 (40%)	
Adjuvant radiation	1/6 (17%)	0.57
No adjuvant radiation	14/46 (30%)	

LN: lymph nodes.
[a] Low grade mucoepidermoid, acinic cell, lymphoma.
[b] Intermediate and high grade mucoepidermoid, adenoid cystic, rhabdomyosarcoma, high grade synovial cell sarcoma.

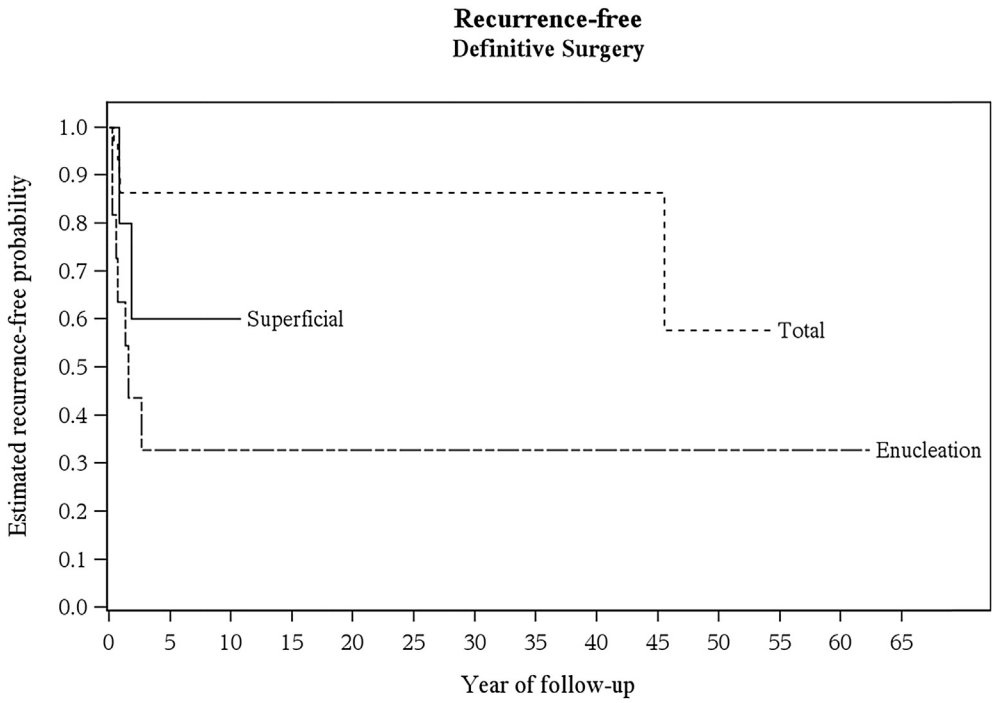

Fig. 1. Kaplan-Meier curve for recurrence free survival (Major gland). Total parotidectomy vs superficial parotidectomy vs. enucleation of tumor.

6.1. Major gland

Major salivary gland tumors appear to behave substantially different than minor salivary gland tumors and therefore these findings are reported separately. For major gland malignancies, we found that the majority of these tumors are low grade (66%) and present at an early stage (80%). This may explain why the patients in our series had an excellent prognosis with an overall disease specific survival of 96%. Comparatively, the adult literature reports a 47–65% ten year overall survival [1,8,9]. Sultan et al. reviewed the SEER database from 1974 to 2006 and likewise demonstrated that pediatric salivary gland malignancies are generally less advanced and have a better outcome than their adult counterparts [1]. Due to the good overall survival in our series we were unable to identify statistically significant factors associated with poor prognosis. However, Kupferman et al. found that age greater than 14 years, non-Caucasian ethnicity, high-grade histopathology and perineural invasion predicted for adverse survival [7].

Based on the outcomes in our series, we believe that the majority of these patients can be managed with surgery alone. In fact, only 11% of patients received adjuvant radiation. Complications from radiation in our series included facial lymphedema, xerostomia, paresthesias, external auditory canal stenosis and arrested mandibular growth requiring reconstructive surgery. Additionally, two patients developed and died from acute myeloid leukemia thought to be secondary to chemoradiation treatment received for their salivary malignancy. Risk versus benefit of radiation should be carefully weighed in this population given the potential for morbidity. We believe radiation therapy should be considered in patients with positive margins, high grade tumors, advanced stage, adverse pathologic factors (perineural spread, extracapsular extension, vascular invasion) and bone or soft tissue invasion.

Over half (65%) of the patients with parotid tumors in our series underwent total parotidectomy (TP). The most common indications for TP in our series were deep lobe tumors or intermediate grade mucoepidermoid carcinoma. Patients who underwent TP were much less likely to recur than those who underwent enucleation or superficial parotidectomy (Table 2; 16% vs 64% and 40% respectively). Based on our experience we recommend TP for deep lobe tumors, high grade, positive intraparotid lymph nodes or positive cervical lymph nodes. Enucleation of parotid tumors is strongly discouraged. Patients that present to our institution who have undergone enucleation alone at an outside facility are recommended to undergo completion superficial parotidectomy at a minimum. We recommend resection of the facial nerve only if it is grossly involved by tumor.

Locoregional recurrence in our series was 28%, similar to other published series reporting 25–31% [10,11]. Recurrence was more likely in patients with adverse pathologic features (vascular/perineural invasion or extracapsular spread), who underwent enucleation or superficial parotidectomy as opposed to total parotidectomy and patients with no neck dissection (Table 2). However, given the limited sample size, the only factor that reached statistical significance was enucleation versus total parotidectomy. Recurrence occurred at a median time of 9.5 months and at a maximum time of 45 years. Therefore, we recommend at least yearly surveillance for a prolonged period in this patient population.

Nodal metastasis is rare in pediatric salivary malignancies. The majority of patients who underwent neck dissection in our series had intermediate grade mucoepidermoid carcinoma and no patients were found to have positive lymph nodes. In the series by Kupferman et al., only 17% of neck dissections specimens were found to harbor positive nodes [7]. The two patients in our series who developed cervical recurrences did not originally undergo neck dissection. Therefore, despite the low occurrence of cervical metastasis, we recommend neck dissection for patients with positive intraparotid lymph nodes, high grade histology, clinical or radiographically suspicious lymph nodes, submandibular gland pathology and T3/T4 tumors. Neck dissection should include levels II and III for parotid tumors and level Ib for submandibular tumors unless there is clinical or radiologic evidence of suspicious lymphadenopathy outside of those regions.

There is scarce literature regarding long term outcomes of patients with pediatric parotid malignancies. In order to determine

this, we conducted a standardized phone survey and approximately a quarter of the patients in our series participated. This allowed for an average follow up time of 28.7 years in this group, which is longer than any published study. Our data suggest that, overall; children treated for parotid malignancies have minimal long term sequelae. None of the surveyed patients reported current facial weakness or eye problems. There was a high rate of persistent Frey's syndrome in our series at 54%. This compares to other series which report an incidence of 2–47% in pediatric patients [3,7], however, Frey's syndrome may be under-represented in these retrospective studies due to reporting bias. A quality of life survey study by Feng et al. found that 9% of patients with pediatric parotid tumors reported Frey's syndrome at an average follow up time of 8.5 years. However all their patients underwent superficial parotidectomy and only 12% had malignant tumors [12]. Our results concur with this series in that patients reported that their Frey's syndrome had a minimal impact on their quality of life.

6.2. Minor gland

Lastly, patients with minor salivary gland malignancies in our series fared much worse than those with major gland tumors. Recurrence in this group was 75% and rate of distant metastases and death was 50%. Due to the small number of patients in our series with minor gland tumors (n = 4), conclusions are difficult to make. A larger series of 35 children by Galer et al. revealed a more favorable prognosis with a recurrence rate of 11% and overall disease-specific survival of 88.4% at 5 years [13]. More studies should be conducted on this topic; however, we would favor a more aggressive management strategy in these patients.

A potential limitation is the retrospective nature of our study which could cause information on outcomes and complications for those who did not participate in the survey to be limited by loss of follow up or interview/reporting bias. A strength of this study is the comparably large number of patients as malignant salivary tumors are uncommon in children and each institution has limited case numbers. Our series has the longest reported follow up of its kind (mean = 14 years) with the addition of 23% of patients responding to a formalized long term outcome and quality of life survey.

7. Conclusion

We report a single institution's experience with pediatric salivary malignancies over a 62 year time period with the longest post treatment follow up in the currently published literature. We found that the majority of these tumors are low grade and have excellent survival if found at an early stage. In our series, minor salivary gland malignancies, particularly high grade, tended to do worse. Primary treatment should be surgery with every attempt to spare the facial nerve unless grossly involved by tumor. Radiation therapy should be administered sparingly and only when strongly indicated, as there is a high potential for long term morbidity. Recurrence in our series was more likely with the presence of adverse pathologic features and enucleation versus total parotidectomy. On long term follow up, our patients had good facial movement and were without eye complications. Future studies should attempt to pool patients from multiple institutions in order to further investigate ideal treatment algorithms.

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Conflicts of interest

None to report.

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Appendix 1. Description of patients with a local recurrence – major gland

Pt#	T stage, pathology	Initial treatment	Time to recurrence (months)	Recurrence treatment	Outcome	Length of follow up (years)
1	T3, high grade MEC with ECS	1. Enucleation (OSH) 2. TP with FN rsxn and ND	9.5	RP and placement of radon beads	Alive NED	6
2	T2, MEC	TP with FN rsxn	8.8	RP	Alive NED	11
3	T1 low grade MEC	SP with ND	22.4	1. RP and ND 2. Recurred again 9 months later, treated with RP and radon beads	Alive NED	11
4	T1 low grade acinic cell	Enucleation	31.9	TP	Alive NED	20
5	Tx low grade acinic cell	Enucleation (OSH)	15.9	TP and ND	Alive NED	20
6	T1 low grade MEC	SP (OSH)	9.8	1.TP 2. Recurred again 4 years later. Treated with RP.	Alive NED	18
7	T1 low grade MEC	Enucleation (OSH)	2.9	SP (OSH)	Alive NED	1
8	T1 intermediate grade MEC	Enucleation (OSH)	Unknown	TP and ND	Alive NED	2
9	T3 intermediate grade MEC with ECS		9.2	Partial temporal bone resection	Alive NED	2

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Pt#	T stage, pathology	Initial treatment	Time to recurrence (months)	Recurrence treatment	Outcome	Length of follow up (years)
		1. Enucleation (OSH) 2. TP				
10	Tx low grade MEC	Enucleation (OSH)	3	TP	Alive NED	17.7
11	T2 intermediate grade MEC	Enucleation (OSH)	8	1. TP with FN sacrifice (OSH). 2. Multiply recurrent. Treated with RP, Radical ND, radiation and chemotherapy	DOD	3.1
12	T1 low grade acinic cell	Enucleation (OSH)	18.7	1. Enucleation (OSH). 2. Recurred again and treated with TP	Alive NED	45.8
13	T4 high grade synovial cell sarcoma	SMG excision	7.2	Revision SMG excision	Alive NED	4.7
14	T1 low grade MEC	1. Enucleation 2. TP	540	RP, chemotherapy, radiation	Alive NED	51.5

MEC: Mucoepidermoid carcinoma, ECS: extracapsular spread, OSH: outside hospital, FN rsxn: facial nerve resection, SP: superficial parotidectomy, TP: total parotidectomy; RP: revision parotidectomy, SMG: submandibular gland, NED: no evidence of disease, DOD: dead of disease.

References

[1] I. Sultan, C. Rodriguez-Galindo, S. Al-Sharabati, M. Guzzo, M. Casanova, A. Ferrari, Salivary gland carcinomas in children and adolescents: a population-based study, with comparison to adult cases, Head Neck 33 (2011) 1476–1481.

[2] C.M. Eneroth, Incidence and prognosis of salivary-gland tumours at different sites. A study of parotid, submandibular and palatal tumours in 2632 patients, Acta Otolaryngol. Suppl. 263 (1969) 174–178.

[3] L.J. Orvidas, J.L. Kasperbauer, J.E. Lewis, K.D. Olsen, T.G. Lesnick, Pediatric parotid masses, Arch. Otolaryngol. Head. Neck Surg. 126 (2000) 177–184.

[4] M. Ellies, R. Laskawi, Diseases of the salivary glands in infants and adolescents, Head Face Med. 6 (2010) 1.

[5] D.E. Schuller, B.F. McCabe, Salivary gland neoplasms in children, Otolaryngol. Clin. North Am. 10 (1977) 399–412.

[6] E.B. Castro, A.G. Huvos, E.W. Strong, F.W. Foote Jr., Tumors of the major salivary glands in children, Cancer 29 (1972) 312–317.

[7] M.E. Kupferman, G.O. de la Garza, A.A. Santillan, et al., Outcomes of pediatric patients with malignancies of the major salivary glands, Ann. Surg. Oncol. 17 (2010) 3301–3307.

[8] C.H. Terhaard, H. Lubsen, I. Van der Tweel, et al., Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group, Head Neck 26 (2004) 681–692 discussion 692–683.

[9] R.H. Spiro, J. Armstrong, L. Harrison, N.L. Geller, S.Y. Lin, E.W. Strong, Carcinoma of major salivary glands. Recent trends, Arch. Otolaryngol. Head Neck Surg. 115 (1989) 316–321.

[10] M. Guzzo, A. Ferrari, I. Marcon, et al., Salivary gland neoplasms in children: the experience of the Istituto Nazionale Tumori of Milan, Pediatr. Blood Cancer 47 (2006) 806–810.

[11] A.H. Shikhani, M.E. Johns, Tumors of the major salivary glands in children, Head Neck Surg. 10 (1988) 257–263.

[12] Q.G. Fang, S. Shi, X. Zhang, M. Li, F.Y. Liu, C.F. Sun, Long term quality of life in pediatric patients surviving parotid tumors, Int. J. Pediatr. Otorhinolaryngol. 78 (2014) 235–237.

[13] C. Galer, A.A. Santillan, D. Chelius, et al., Minor salivary gland malignancies in the pediatric population, Head Neck 34 (2012) 1648–1651.

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Pediatric thyroid cancer: An update from the SEER database 2007–2012☆

Sarah Dermody [a, *], Andrew Walls [c], Earl H. Harley Jr. [a, b]

[a] Georgetown University School of Medicine, Washington, DC, 20007, USA
[b] Department of Otolaryngology – Head & Neck Surgery, Georgetown University Hospital, Washington, DC, 20007, USA
[c] Department of Surgery Division of Otolaryngology, Yale New Haven Hospital, New Haven, CT, 06510, USA

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ABSTRACT

Objective: To update the medical literature regarding the incidence, disease specific survival, and treatment modalities utilized in pediatric patients diagnosed with thyroid carcinomas.
Study design: Cross Sectional Analysis of a National Database.
Study setting: SEER Database.
Methods: The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Database was queried for all cases of pediatric thyroid cancer between the years 2007 and 2012. Patients ages 0–19 were grouped by histological subtypes and demographic data, overall incidence rate, and disease specific survival after surgery and surgery with radiation therapy. Fifteen-Year Disease Specific Survival Curves were generated and treatment modalities were compared to assess for statistical differences at each yearly interval.
Results: A total of 1723 pediatric patients were identified and the average age-adjusted rate of malignancy was determined to be 0.59 per 100,000 patients. The incidence of pediatric thyroid cancer was approximately 4.4:1 when comparing females to males, respectively. Papillary subtype was the most common (n = 1014, 58.8%), followed by follicular variant subtype (n = 397, 23%), follicular subtype (n = 173, 10.1%) and medullary subtype (n = 139, 8.1%). As pediatric patients reached fifteen to nineteen years of age, the incidence of papillary and follicular variant subtypes increased. Analysis of medullary thyroid cancer data revealed that incidence was highest in the zero to four age group and declined at later years. Pediatric patients presenting with metastatic medullary thyroid carcinoma maintained significantly poorer fifteen-year disease specific survival when compared to other histologic subtypes ($p < 0.05$). Intervention with surgery and radiation therapy provided significant benefit across all histologic subtypes when evaluating disease specific survival at fifteen-years past the initial diagnoses ($p < 0.05$).
Conclusions: Pediatric thyroid carcinoma remains an uncommon diagnosis despite an annual increase in incidence of approximately one percent since the development of the SEER database. Overall, pediatric thyroid carcinomas demonstrate an excellent prognosis if identified early and appropriate management is available. Caucasian female patients have higher incidence of carcinoma diagnoses when compared to males. Medullary histologic subtype, especially when metastatic at initial diagnoses, demonstrates statistically poorer outcomes when compared to other subtypes.

1. Introduction

Thyroid cancer is a relatively uncommon pediatric diagnosis, yet previous analyses have revealed that the incidence rate is increasing at a rate of approximately one percent annually [1,2]. Recent studies have characterized thyroid malignancies as the third

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* Corresponding author. Georgetown University School of Medicine, 3900 Reservoir Road, NW, Washington, DC, 20007, USA.
E-mail address: Smd95@georgetown.edu (S. Dermody).

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most common head and neck malignancy in the pediatric population, accounting for 21% of all head and neck cancer in pediatric patients [3]. Differentiated thyroid carcinomas in children include papillary, follicular, and variant subtypes. Specifically, the papillary subtype accounts for approximately 90% of pediatric thyroid carcinomas and maintains an excellent prognosis, which parallels findings in the adult literature [3]. The overall prognosis of pediatric thyroid cancer may be skewed due to the large number of papillary thyroid cancer diagnoses, which inherently yield excellent outcomes [4]. Very few studies have stratified each variant subtype by disease specific survival to determine if this statistical finding is, in fact, true [6].

Of the differentiated thyroid carcinomas, follicular subtype is less common in children, but is considered more aggressive and maintains a poorer prognosis if vascular invasion is present [3]. Also of note, medullary thyroid carcinoma in pediatric patients is associated with markedly shorter mean survival even if individual risk factors such as metastatic spread or lymphovascular invasion are absent [6]. Among those diagnosed with thyroid carcinomas, pediatric patients present with more advanced manifestation of disease than adult patients, yet mortality is comparatively infrequent [4,6]. In the pediatric population, thyroid carcinomas typically present in teenage years, especially in Caucasian females, with a mean age of diagnosis of 16 years [6]. Previous studies have characterized the female predominance of pediatric thyroid carcinomas and have identified papillary carcinoma as the most common histological subtype within this population [3,6].

Currently, the American Thyroid Association Guidelines dictate that there is no indicated disease screening for thyroid cancer in the pediatric population aside from genetic testing and periodic ultrasound evaluation for patients with mutated genes such as BRAF, RET oncogene mutations (MEN2A/2B), Cowden Syndrome, Werner Syndrome and PTEN Related Syndromes. Further considerations include patients who received radiation for Hodgkin Lymphoma, Leukemias and CNS Tumors especially with radiation doses between 20 and 29 Gy [7–9,11]. The American Thyroid Association Task Force on Pediatric Thyroid Cancer reports insufficient evidence for utilizing ultrasound to screen for non-palpable thyroid nodules in patient populations not already described due to the likelihood of false positives associated with an enlarged thymus or simple cysts [9,11]. As such, pediatricians and otolaryngologists are forced to rely on early identification of neck masses by physical examination in order to yield the excellent prognosis for pediatric patients currently described in the literature [9]. While mortality is rare, past studies have identified factors associated with poorer prognosis of well-differentiated pediatric thyroid carcinomas, such as presence of distant metastases, large primary tumor size, lymphovascular invasion, and male sex [5,6]. Interestingly, one recent study has demonstrated that the V600 BRAF mutation implicated in adult papillary thyroid carcinoma does not significantly contribute to the development of pediatric thyroid cancer at the same rate as currently described in older cohorts [10]. The findings of this study are significant because they provide primary care providers with a more refined risk factor approach when evaluating patients [8].

This population-based analysis is imperative since children maintain a greater chance of recurrence of differentiated thyroid cancer compared to the adult population [9]. Thus, our group analyzed the new SEER Database updates provided up until the year 2012 and compared them to the current literature to determine if there have been any significant changes in incidence and disease specific survival based on the various risk factors reported in previous studies [10]. This study provides the most recent analysis of the SEER database with respect to pediatric thyroid carcinoma.

2. Materials and methods

2.1. Description of source database

This manuscript was deemed exempt from Georgetown University IRB review due to the use of de-identified data and was approved for data collection. The Surveillance, Epidemiology and End Results (SEER) Database was queried to identify pediatric patients with pathologically confirmed “thyroid carcinoma” between 0 and 19 years of age from the years 2007–2012. The SEER Database, available at: “seer.cancer.gov”, provides the public with population-based data regarding cancer incidence, frequency, and disease specific survival data from 1973 to 2012. At this time, the SEER database includes approximately 10% of the United States cancer population and is updated annually by the National Cancer Institute coding technicians. The SEER registry includes patient information from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco, Louisiana, Seattle, Utah, Los Angeles, Alaska, and San Jose in order to provide its users with a normalized distribution of patient cohorts in terms of geographic location and age groups.

2.2. Patient cohort selection

The SEERstat analysis program was downloaded from “seer.cancer.gov” as previously described. Our study group utilized the “Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases 1973–2012” database and performed a multivariable frequency analysis to determine the total number of patients with the below described pediatric thyroid subtypes. Each specific thyroid cancer subtype was queried using the following criteria: “malignant behavior”, “known age”, “cases in research database” for the initial query. Additional clinicopathologic factors including age, sex, ethnicity, extent of disease, and lymphovascular invasion were also included within the aforementioned multivariable outcomes query.

Within the Case Selection Statement, the following search limitations were applied to obtain frequency data regarding our patient cohorts: Pediatric Thyroid Subtypes, “Papillary”, “Follicular”, “Medullary”, and “Papillary Follicular Variant.” Coding for each of the described thyroid carcinoma subtypes were collected from the SEER Database Manual and inputted into the Case Selection Command Feature [9]. Tumor recurrence events were not available in the SEER database at the time the query was performed and consequently were not included. Patients that expired within the first four months after surgery were excluded since these individuals were likely unable to complete a full course of radioactive iodine uptake or external beam therapy. Patients with uncoded primary tumor subsite were excluded from this study as well as those with anaplastic thyroid carcinomas and non-epithelial cancers, such as lymphomas, due to paucity of data. The cohort was then further subdivided according to treatment modality into a “surgery alone” group and “surgery with adjuvant radiation” group, which included individuals who received radioactive iodine uptake as well as those who received external beam therapy.

2.3. Statistical analysis

2.3.1. Fifteen-year disease specific survival curves

Fifteen-year disease specific curves were generated for the surgery group and surgery with adjuvant radiation group utilizing the SEERstat, “Survival Session” search query. Within the survival session, the Observed Survival “Method” was employed to include fifteen years with intervals of twelve months. Exclusion criteria included: “Alive with No Survival Time” and “All Death Certificate

Only and Autopsy Only" in order to prevent the inclusion of patients who would skew the disease specific survival calculations. Data was then combined for each of the pediatric thyroid subtypes and standard error of the mean and 95% confidence intervals were calculated. Disease specific survival data points at each study interval were compared using T-Test analysis to determine significant difference between the treatment groups.

2.3.2. Statistical analysis calculations

Statistical analysis was performed utilizing the Minitab Inc. software (State College, PA) to determine statistical differences between treatment groups. Fifteen-Year Disease Specific Survival data was compared utilizing the Student's T test to determine benefit of each treatment modality. The log rank test was not utilized for statistical comparison because the disease specific survival curves do not reflect a patient's full life span from the point of diagnosis, but rather illustrate survivorship at fifteen years from the time of initial diagnosis. The disease specific survival calculations were weighted similarly to prevent bias of survivorship within the earlier or later time periods. Calculations were considered statistically significant if P-values were less than 0.05 and 95% confidence intervals did not overlap between the two groups of interest.

3. Results

3.1. Patient cohort demographics

A total of 1723 pediatric patients were located in the SEER Database and further stratified based on age, sex, and ethnicity. According to our analysis, teenage Caucasian females maintained the highest frequency of obtaining a diagnosis of thyroid carcinoma when evaluating rates per 100,000 patients. Furthermore, females maintained an age-adjusted rate of diagnosis compared to males of approximately 4.4:1 per 100,000 patients. Lastly, African Americans and the unspecified cohorts demonstrated less frequent diagnoses across each age group when compared to the Caucasian cohort (Table 1).

3.2. Average age adjusted incidence rate of pediatric thyroid cancer subtypes

The overall age adjusted average rate of pediatric thyroid cancer from 2007 to 2012 was determined to be 0.59 new diagnoses per 100,000 individuals (see Table 2). When evaluating papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and papillary follicular carcinoma thyroid subtypes, the average rates of incidence were determined to be: 0.30 (47.6%), 0.14 (23.8%), 0.05 (6.7%), and 0.13 (21.9%) per 100,000 reported patients, regardless of age, respectively. Furthermore, papillary, follicular, and papillary follicular variant became more prominent in terms of frequency of diagnosis as pediatric patients reached the fifteen to nineteen age groups (Fig. 1). Medullary thyroid cancer was the most frequent in terms of incidence in the zero to four years of age group, but subsequently declined once the five to nineteen years of age group demographics were analyzed (Fig. 1).

Table 1
Demographics of pediatric patients diagnosed with papillary thyroid cancer as rate per 100,000 patients from 2007 to 2012.

Age group		1–4	5–9	10–14	15–19
Sex	Male	0.001	0.04	0.11	0.31
	Female	0.01	0.05	0.36	1.48
Ethnicity	Caucasian	0.01	0.08	0.38	0.27
	African American	0.00	0.007	0.03	0.08
	Unspecified	0.001	0.003	0.05	0.19

Table 2
Demographics of pediatric patients diagnosed with thyroid cancer.

Carcinoma subtype	Diagnosis count	Frequency of total
Papillary	1014	58.8
Papillary follicular variant	397	23.0
Follicular	173	10.1
Medullary	139	8.1

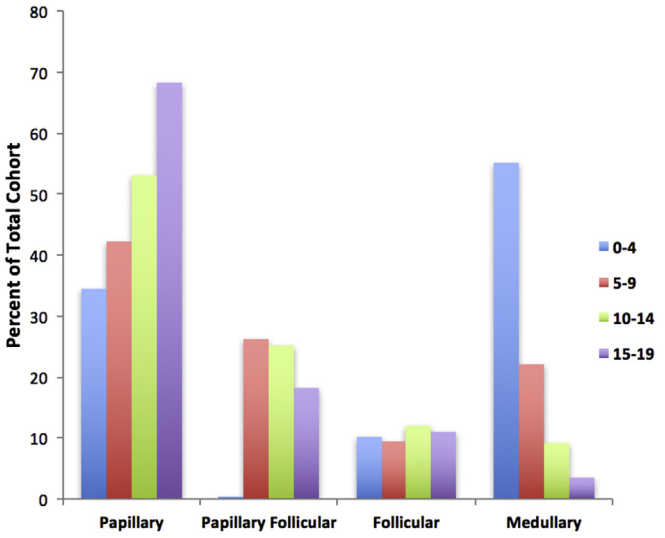

Fig. 1. Incidence of pediatric thyroid carcinoma based on most frequent subtype per 100,000 as a percent of total cohort. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Overall fifteen year disease specific survival of individuals diagnosed with pediatric thyroid cancer

At fifteen years post diagnosis, the disease specific survival for each age group, regardless of tumor subtype, demonstrated greater than ninety percent survival. Specifically, the younger demographics, including the zero to four and five to nine years of age groups, maintained a fifteen-year disease specific survival of approximately ninety-nine percent when surgery and radiation therapy, radioactive iodine uptake or external beam therapy, were utilized. Interestingly, patients who were diagnosed in the ten to fourteen and fifteen to nineteen age groups maintained excellent survival outcomes, yet fifteen-year disease specific survival were significantly lower compared to the two younger age groups ($p < 0.05$). Despite this statistically significant difference, the two older cohorts still demonstrated a disease specific survival greater than 95% (Fig. 2).

3.4. Fifteen year disease specific survival based on cancer subtype and therapeutic intervention

Pediatric patients, regardless of age group, demonstrated excellent fifteen-year disease specific survival after intervention with surgery or surgery with adjuvant radiation, radioactive iodine uptake or external beam therapy. Individuals demonstrated significantly improved survival outcomes if they underwent radiation therapy in conjunction with their primary surgery management regardless of tumor subtype ($p < 0.001$). The fifteen-year disease

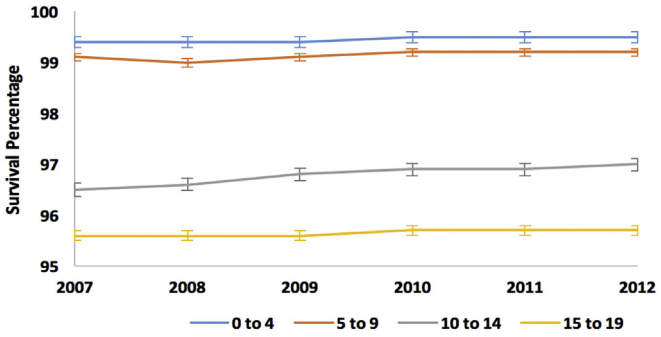

Fig. 2. Fifteen-year disease specific survival based on age group between 2007 and 2012. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

specific survival of pediatric patients who were diagnosed with medullary thyroid cancer was significantly worse, but appeared to benefit from combined surgery and external beam therapy (Fig. 3). Furthermore, patients with the papillary follicular variant at fifteen years did not appear to derive benefit from surgery with adjuvant radiation therapy compared to surgery alone when evaluated at yearly intervals ($P = 0.763, 0.689, 0.829, 0.629, 0.728$).

3.5. Fifteen year disease specific survival based on extent of disease at initial diagnosis and therapeutic intervention

When evaluating fifteen-year disease specific survival for each tumor subtype based upon clinical staging of localized or distant disease, our group identified that patients diagnosed with localized papillary, follicular, and papillary follicular thyroid carcinoma demonstrated excellent outcomes after combined surgery with radiation. Regardless of subtype, patients demonstrated statistically worse outcomes at fifteen years if the initial diagnosis included distant metastases to bone, lung and brain, especially in the medullary thyroid cohort, despite surgery and adjuvant radiation therapy ($p < 0.05$) (Fig. 4).

4. Discussion

Previous literature reporting pediatric thyroid carcinoma outcomes have demonstrated the importance of early diagnosis and prompt initiation of therapy in order to yield favorable survival outcomes [1–7]. After assessing the current literature, our group wished to update the medical community with recent data from the SEER Database, analyzing pediatric thyroid carcinomas from 2007 to 2012. Furthermore, we wished to determine if there is any significant difference in the incidence and disease specific survival outcomes based on individual cancer subtypes between the years of 2007 and 2012. To the best of our knowledge, this study provides the medical community with the most recent analysis of the SEER Database with regard to pediatric thyroid cancer.

After evaluating the SEER Database for the most common thyroid cancer subtypes in the pediatric population, our study elucidated findings that were in accordance with several former publications in the medical literature regarding the incidence of the various carcinoma subtypes [2–6]. Overall, the incidence of pediatric thyroid cancer appears to be increasing at an average age-adjusted rate of approximately one percent when the four most common malignancies were taken into account (Fig. 1). Additionally, after evaluating the pattern of cancer predominance based upon age cohort, it is apparent that medullary and papillary thyroid carcinoma incidence are the most frequent before ten years of age and the incidence of papillary carcinoma increases as one enters the teenage years. Interestingly, our group determined that between the years 2007 and 2012, patients at fifteen-year disease specific survival demonstrated significantly improved outcomes if the age at diagnosis was before nine years of age compared to individuals first diagnosed at ten or older. Our findings parallel those reported in previous medical literature and remain stable since last SEER dataset was published [3,6].

In order to further expand on disease specific survival, our group analyzed the four most common pediatric thyroid cancer subtypes and determined if surgery alone or in combination with adjuvant radiation therapy provided additional benefit. For both papillary and follicular thyroid carcinomas, a patient's fifteen-year

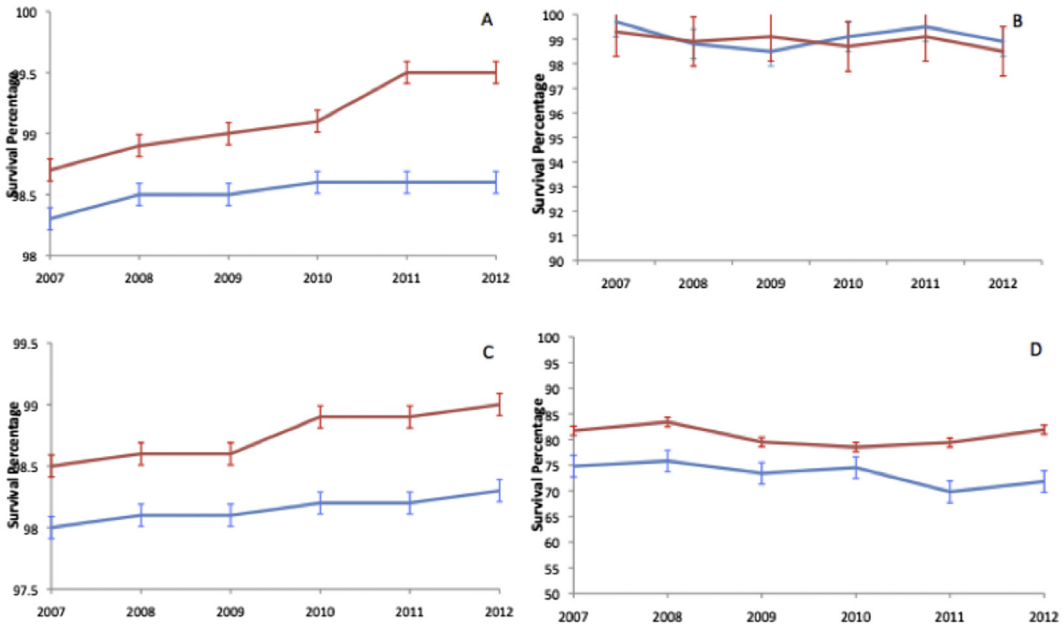

Fig. 3. Fifteen-year disease specific survival for each thyroid carcinoma subtype between 2007 and 2012 (A: Papillary, B: Papillary follicular Variant, C: Follicular, D: Medullary; blue: Surgery, red: Surgery and adjuvant radiation). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

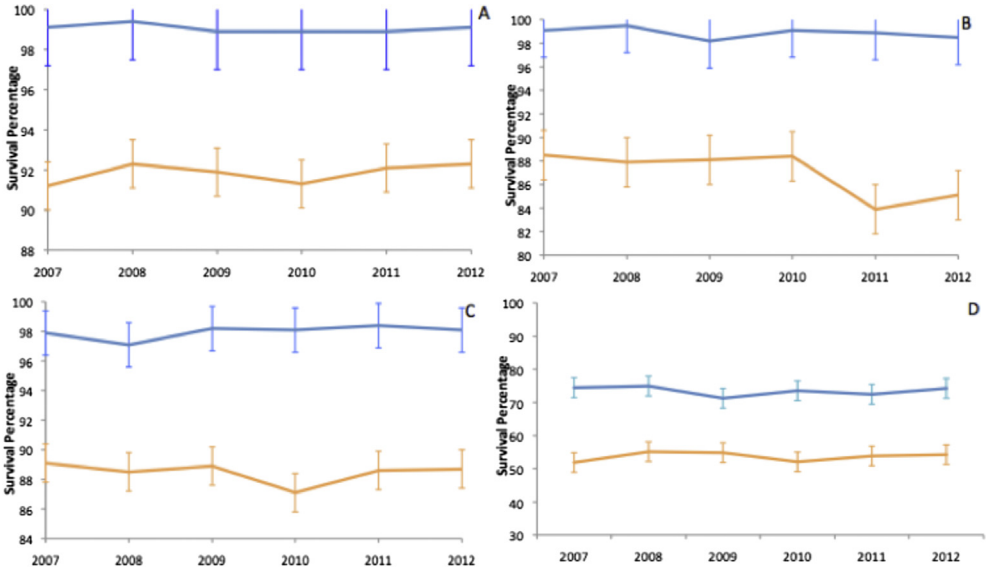

Fig. 4. Fifteen year disease specific survival after surgery and radiation therapy for each subtype based on extent of disease between 2007 and 2012 (A: Papillary, B: Follicular, C: Medullary, D: Papillary follicular; blue: Localized at initial diagnosis, orange: Distant metastases at initial diagnosis). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

disease specific survival demonstrated significant benefit when adjuvant radioactive iodine uptake was instituted in the course of treatment. Interestingly, the medullary thyroid subtype demonstrated some benefit with external beam radiation therapy, but since the cells that constitute the medullary thyroid carcinoma do not uptake iodine, there does not appear to be the same improvement in disease specific survival when compared to the papillary or follicular subtypes when utilizing I^{131} isotopes. For pediatric patients diagnosed with papillary follicular variant thyroid carcinoma, there was no statistically significant difference in survival between those who underwent surgery or surgery with adjuvant radioactive iodine uptake therapy at fifteen years post-diagnosis. It is possible that true differences are difficult to discriminate because survival of both groups is excellent, or perhaps survival outcomes must be analyzed at a later time point, beyond fifteen-years, to identify a statistically significant benefit in terms of disease specific survival.

Lastly, our group evaluated the differences in fifteen-year disease specific survival in pediatric patients diagnosed with localized or distant metastatic disease at initial evaluation and were subsequently treated with surgery with adjuvant radiation. Overall, patients who demonstrated localized involvement at initial diagnoses maintained statistically better fifteen-year disease specific survival at each year, while patients who presented with distant metastases at initial diagnosis demonstrated poorer outcomes regardless of each subtype. The juxtaposition between survival outcomes in pediatric patients with localized involvement compared to those with distant metastases at initial diagnosis is most apparent for medullary thyroid carcinoma, where approximately only fifty percent of the original patient cohort with distant metastases survived fifteen years post-diagnosis (Fig. 4). Fortunately, a diagnosis of localized or distant metastatic disease in the papillary, follicular, and papillary follicular variant subtypes maintained excellent outcomes after surgery and adjuvant radioactive iodine uptake therapy.

Based on our group's analysis of the most recently available data from the SEER database, the survival outcomes amongst patients with papillary, follicular and papillary follicular variants reach upwards of 95% at fifteen years post-diagnosis, illustrating that the current treatment regimes afford the pediatric population with excellent survival outcomes. However, medullary thyroid carcinoma continues to demonstrate less desirable outcomes, especially if one presents with metastatic disease at initial diagnosis.

The SEER database has several limitations that must be addressed when evaluating this manuscript. Overall, the database retrospectively reviews patient incidence and disease specific survival when it is uploaded to the National Cancer Institute's database and thus, this study maintains all of the typical biases associated with a retrospective analysis and possible coding errors. Furthermore, the database does not present perineural invasion or recurrence data, which could affect the survival outcomes of the patients that it reports, especially since recurrence is common in the pediatric population. It is also important to note that the database does not specify which patients underwent prophylactic total thyroidectomy for the medullary carcinoma subtype and thus may have skewed the disease specific survival to more improved disease specific survival as reported within this study. Based on the current literature, it is undetermined if neck dissection provides benefit to pediatric patients; however, based on the search query, the SEER database limits users to total thyroidectomy without knowledge if a neck dissection was performed. Even with these limitations, the SEER database is the gold standard in obtaining surveillance data for the multitude of cancer diagnoses in both the pediatric and adult populations.

5. Conclusion

While thyroid cancer is a difficult diagnosis to provide to both pediatric patients and families, survival outcomes are excellent if identified before the teenage years. According to our analysis of the most recent data available through the SEER database, the current treatment modalities utilized provide pediatric patients with greater than 95% survival for the most common thyroid carcinoma subtypes, excluding medullary thyroid carcinoma. This study demonstrates that the incidence of pediatric thyroid cancer has continued to increase by approximately one percent yearly between 2007 and 2012, but the overall outcomes remain very favorable.

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References

[1] L. Davies, H. Welch, Increasing incidence of thyroid Cancer in the United States, 1973–2002, JAMA 295 (18) (2006) 2164–2167.
[2] M. Qaisi, I. Eid, Pediatric head and neck malignancies, Oral Maxillofac. Surg. Clin. North Am. 28 (1) (2016 Feb) 11–19.
[3] N.L. Shapiro, N. Bhattacharyya, Population-based outcomes for pediatric thyroid carcinoma, Laryngoscope 115 (2) (2005 Feb) 337–340.
[4] C.A. Dinauer, C. Breuer, S.A. Rivkees, Differentiated thyroid cancer in children: diagnosis and management, Curr. Opin. Oncol. 20 (1) (2008 Jan) 59–65.
[5] B.J. Shayota, S.C. Pawar, R.S. Chamberlain, MeSS: a novel prognostic scale specific for pediatric well-differentiated thyroid cancer: a population-based, SEER outcomes study, Surgery 154 (3) (2013 Sep) 429–435.
[6] A.R. Hogan, Y. Zhuge, E.A. Perez, L.G. Koniaris, J.I. Lew, J.E. Sola, Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients, J. Surg. Res. 156 (1) (2009 Sep) 167–172.
[7] C. Sklar, J. Whitton, A. Mertens, M. Stovall, D. Green, N. Marina, B. Greffe, S. Wolden, L. Robison, Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the childhood cancer survivor study, J. Clin. Endocrinol. Metab. 85 (2000) 3227–3232.
[8] A.T. Meadows, D.L. Friedman, J.P. Neglia, A.C. Mertens, S.S. Donaldson, M. Stovall, S. Hammond, Y. Yasui, P.D. Inskip, Second neoplasms in survivors of childhood cancer: findings from the childhood cancer survivor study cohort, J. Clin. Oncol. 27 (2009) 2356–2362.
[9] G. Francis, Management Guidelines for children with thyroid nodules and differentiated thyroid cancer, Thyroid. 25 (7) (2015 July) 716–759.
[10] R.J. Gertz, Mutation in BRAF and other members of the MAPK pathway in papillary thyroid carcinoma in the pediatric population, Arch. Pathol. Lab. Med. 140 (2) (2016 Feb) 134–139.
[11] M.T. Parisi, Management of differentiated thyroid Cancer in children: focus on the American Thyroid Association Pediatric Guidelines, Semin. Nucl. Med. 46 (2) (2016 Mar) 147–164.

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Lumps and Bumps of the Neck in Children—Neuroimaging of Congenital and Acquired Lesions

Marjolein H.G. Dremmen, Aylin Tekes, Samantha Mueller, Donna Seyfert, David E. Tunkel, Thierry A.G.M. Huisman

From the Division of Pediatric Radiology and Pediatric Neuroradiology, Department of Radiology and Radiological Science, Johns Hopkins Hospital, Baltimore, MD (MHGD, AT, SM, DS, TAGMH); Division of Pediatric Radiology, Department of Radiology, Erasmus MC – University Medical Center Rotterdam, Rotterdam, The Netherlands (MHGD); and Division of Pediatric Otolaryngology, Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins Hospital, Baltimore, MD (DET).

ABSTRACT

Neck masses present as palpable lumps and bumps in children with acquired lesions more common than congenital ones. Assessment of the anatomical site of origin, signal, and contrast enhancement characteristics may help define the etiology of the lesions, eg, developmental, inflammatory, vascular, or neoplastic. The age of the patient along with detailed clinical history and physical exam findings are important element to narrow down the differential diagnosis. The correct final diagnosis is essential to guide treatment as well as the urgency of intervention.

The objective of this review is to define the characteristic location, classic and differentiating imaging features of the most frequent congenital and acquired cervical lumps and bumps in the pediatric population.

Keywords: Congenital, acquired, neck lesions, children, imaging.

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Correspondence: Address correspondence to Marjolein H.G. Dremmen, Department of Radiology, Erasmus MC – University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: m.dremmen@erasmusmc.nl

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Introduction

Congenital masses (lumps and bumps) of the neck are by definition present at birth. Despite the congenital origin of this type of lesions, some of these may not be clinically present until later in life. The etiology of congenital neck masses varies from developmental anomalies to vascular, inflammatory, and tumoral lesions.[1]

Many of the neck masses seen in children are acquired lesions. These acquired lumps are most often benign, however, rarely can be malignant in children. The etiology is inflammatory, vascular, neoplastic, or of traumatic origin.[1]

Mass lesions of the neck are often identified as bumps on physical examination. Imaging plays an essential role in the characterization and final diagnosis of the various entities. A systematic imaging approach to masses of the neck helps to narrow down the differential diagnosis. This approach includes determining the primary site of origin, involvement of, and extension across the various anatomic spaces of the neck, to evaluate the normal contents of the involved anatomic space and to assess the characteristic imaging features of the lesion. The age of the patient and the clinical presentation are also important factors and often characteristic for the type of lesion, and should consequently be taken into account during the interpretation of the imaging studies. The correct final diagnosis is essential to determine the proper treatment strategy.

Ultrasonography (US) and magnetic resonance (MR) imaging are the primary imaging modalities of choice for many congenital neck lesions in the pediatric population.

US offers a high-resolution image quality, is noninvasive, is readily available, and does not require sedation. Furthermore, the real-time character of US examinations allows for the evaluation of mobility and compressibility of the mass or changes in the internal structure of the lesion during, eg, respiration and swallowing. The additional use of Doppler US contributes in the assessment of the degree of vascularity/perfusion of the lesion and analysis of the spectral blood flow waveforms is valuable in differentiating several types of vascular anomalies.

Anatomical MR imaging renders excellent soft-tissue contrast, optimal visualization and delineation of involved or displaced anatomic spaces, vascular anatomy and neural elements, and more detailed internal tissue characteristics of the lesion. Advanced MR imaging techniques, like diffusion-weighted imaging (DWI) or susceptibility-weighted imaging (SWI), may provide additional valuable information on intralesional features, thus facilitating more specific diagnoses.[1–6] Multiphasic dynamic contrast–enhanced MR angiography (cMRA) is a noninvasive MRI technique used to determine the hemodynamics of the lesion, thereby providing valuable clues for the diagnoses. For vascular anomalies in particular, the time-resolved dynamic cMRA technique using a blood-pool contrast agent (eg, gadofosveset trisodium) provides rapid acquisition combined with detailed temporal information of lesion hemodynamics and flow characteristics.[7,8] MRI has, however, the disadvantage of longer data acquisition times, and may require sedation for use in children. However, currently available fast sequence MR imaging techniques provide satisfactory assessment of the abnormality in a significant number of cases, thereby eliminating the need for sedation.

The use of CT should be limited in children because of the potential long-term risks of ionizing radiation in this vulnerable

patient group. However, CT occasionally is contributive as a fast and readily available imaging technique in the emergency setting, and is helpful for lesions that involve bony structures and for the acute diagnostic work-up of infections/abscesses in the neck according to the American College of Radiology (ACR) Appropriateness Criteria.[9]

Basic knowledge of the normal contents of each anatomical space is essential in evaluating the various pathologies and masses that can arise within each space.

The goal of this review is to identify the characteristic location and imaging features, differential diagnosis, and differentiating features of the most frequent congenital and acquired cervical mass lesions (lumps and bumps) in the pediatric population.

Congenital Cystic Masses

Thyroglossal Duct Anomalies

Thyroglossal duct remnants are reported in 7% of the population.[10] These anomalies are the most common congenital anomalies of the neck, representing 70% of the congenital neck masses (second most common neck mass after cervical adenopathy in the pediatric age group).[6] The formation of the thyroid gland begins with an endodermal thickening in the floor of the primitive pharynx-tuberculum impar in the third embryonic week. From this site, the thyroid diverticulum develops and its opening forms the foramen cecum. Due to progressive growth/elongation of the embryo, the diverticulum descends caudally into the neck and forms the thyroglossal duct. This duct is a temporary structure coursing from the foramen cecum at the tongue base, descending in the anterior midline, looping posterior to the hyoid bone, and continuing its descent anterior to the thyrohyoid cartilage and trachea to the level of the thyroid. The descent of the thyroglossal duct occurs before formation of the hyoid bone, and therefore remnants of the duct can become trapped within the hyoid bone.[6,11] The duct generally involutes around gestational week 8–10.

Thyroglossal duct cysts are diagnosed in 40% of surgically removed neck masses in the pediatric population.[6] The lesion manifests from infancy until young adulthood. Thyroglossal duct cysts are often asymptomatic until enlargement or inflammation occurs associated with infection or trauma. The cyst arises from a remnant of the thyroglossal duct. Any portion of the duct, from the foramen caecum to the pyramidal lobe of the thyroid gland, may persist and cause cyst formation due to secretions from the epithelial lining of the duct.[1,12] In pathologic specimens of excised thyroglossal duct cysts, thyroid tissue is reported in up to 62% of cases.[13] As a result of the course of the duct, thyroglossal duct cysts are primarily located in the midline (75%) or just off-midline (25%). Paramedian location occurs more often on the left. The vast majority of the cysts are located at or about the level of the hyoid bone, and a minority has an infrahyoid position or is located in the suprahyoid neck.[1,3] The thyroglossal duct cysts located at the level of the tongue base can be difficult to differentiate from vallecular cyst occurring at the exact same location based on imaging appearance alone. The imaging features of thyroglossal duct cysts comprise a well-defined, thin-walled cystic structure in the typical midline or paramidline location. Heterogeneous cyst content may reflect proteinaceous material/hemorrhage or infection as evidenced by debris and fluid levels both on US and MR imaging. In particular, T1 hyperintensity may indicate prior hemorrhage, and this can be further verified with SWI. Noncomplicated cysts do not demonstrate wall thickening or postcontrast enhancement (Fig 1). The cyst wall thickness and degree of contrast enhancement of the cyst wall may vary with inflammation/infection. US enables dynamic evaluation, a characteristic imaging upward movement of the cyst with tongue protrusion or swallowing due to the origin of the duct at the foramen cecum is typically observed.[12] The majority of the cysts show a close relation to the hyoid bone. At the level of the hyoid bone, the cyst may demonstrate a tail "diving" into the hyoid bone, reflecting entrapment of duct remnants in the hyoid bone. To minimize the risk of recurrence after resection, removal of the central portion of the hyoid bone is typically included in the *curative* excision of the cyst and/or sinus tract (eg, Sistrunk procedure, modified Sistrunk procedures).[14] Factors influencing the recurrence rate after the Sistrunk procedure (2.6%) are, eg, postoperative infection, the presence of multiple tracts and distorted anatomy due to preoperative infection.[15,16]

Infrahyoid cysts favor an off-midline position, deep to or embedded within the strap muscles (Fig 2) with a tail toward the midline (Fig 2).[3] Evaluation of the presence of a normal thyroid gland in the normal location is important in the preoperative

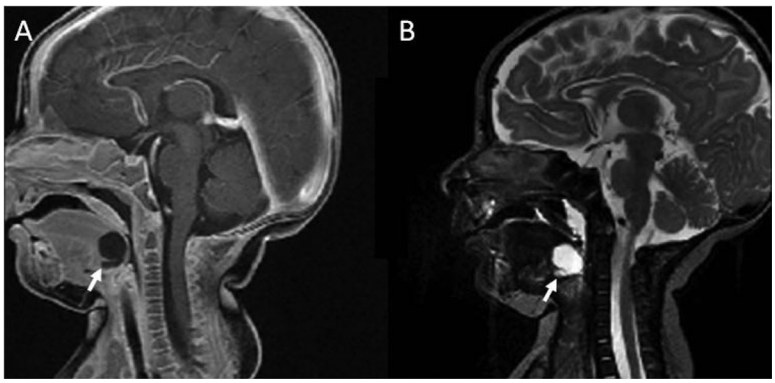

Fig 1. Sagittal contrast-enhanced T1-weighted (A) and sagittal fat-suppressed T2-weighted (B) MR images of a child with a suprahyoid thyroglossal duct cyst. The images reveal a well-defined, thin-walled cystic structure in the typical midline location at the level of the foramen cecum at the tongue base. No cyst wall enhancement is encountered on postcontrast imaging. Differentiation between a thyroglossal duct cyst located at the tongue base and a vallecular cyst is not possible based on imaging appearance alone.

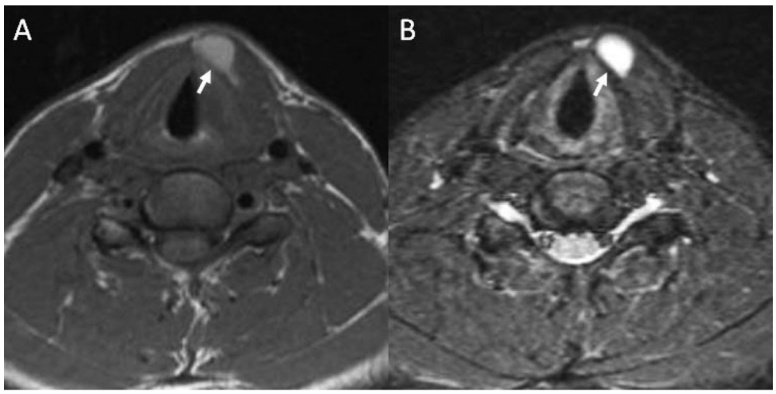

Fig 2. Axial T1-weighted (A) and fat-suppressed T2-weighted (B) MR images of a child with an infrahyoid thyroglossal duct cyst. The images demonstrate a thin-walled cystic structure embedded within the left strap muscles (pathognomonic feature) in an off-midline position. The axial T1-weighted image (A) shows hyperintense signal intensity of the cyst content reflecting intralesional proteinaceous material.

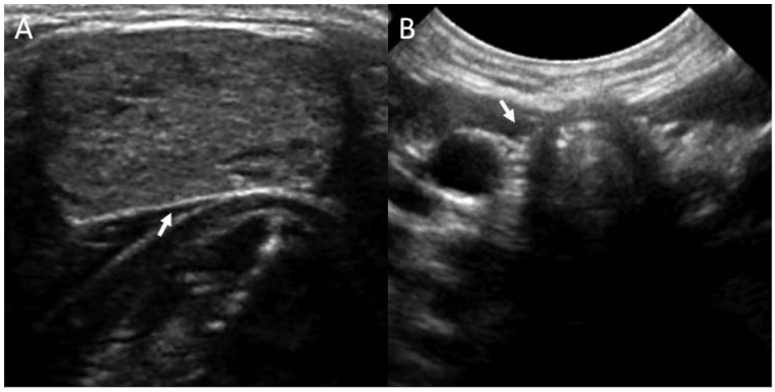

Fig 3. US images at the level of the tongue base (A) and at the level of the thyroid (B) of a child with an ectopic thyroid gland. Image A demonstrates the appearance of thyroid tissue in an ectopic location. Image B reveals the absence of thyroid tissue in the normal orthotropic position.

evaluation. US is the imaging modality of choice to demonstrate the normal positioned thyroid gland.[17]

Ectopic thyroid tissue is another potential consequence of persistence of a portion of the thyroglossal duct. Ectopic thyroid tissue is often accompanied by additional cyst formation derived from the thyroglossal duct.[13] To differentiate between a thyroglossal duct cyst or ectopic thyroid tissue mimicking a thyroglossal duct cyst, preoperative verification of the presence of a normally located thyroid gland by US is essential. On imaging, ectopic thyroid tissue has identical imaging features as normal positioned thyroid tissue and may be identified anywhere along the course of the thyroglossal duct is, however, most commonly seen in a lingual location (Fig 3). In incidental cases, ectopic thyroid tissue is reported lateral to the typical midline or off-midline location. The origin of lateral ectopic thyroid tissue remains unclear.[18] Rarely, thyroid carcinoma can arise from ectopic rests of thyroid tissue in the persistent thyroglossal duct.[12]

Branchial Apparatus Anomalies

Anomalies of the branchial apparatus are the second most common congenital neck lesions in children representing 20% of the surgically removed pediatric cervical masses.[19,20] Branchial cleft anomalies are postulated to arise from an incomplete obliteration of portions of the branchial apparatus. The apparatus consists of five pairs of ectoderm-lined branchial clefts (external) and six mesodermal branchial arches in the lateral wall of the foregut separated by five endodermal-lined pharyngeal pouches (internal). The fifth arch is considered a rudimentary appendage of the fourth pouch and no structures are derived from this arch in mammals.[12,21] The arches give rise to specific osseous, cartilaginous, muscular, and neurovascular structures in the head and neck (Table 1). The first branchial cleft is the only branchial cleft giving rise to a normal anatomic structure. Branchial apparatus anomalies present as cysts (75%), fistulae, and/or sinuses.[6,11,22] Cysts manifest in older children and young adults. Fistulas are typically diagnosed as focal skin pits in infants and younger children. They form a canal and open externally on the neck surface and internally in the pharyngeal mucosa. Blind ending sinuses open externally to the surface of the neck.[12] The general imaging features of branchial cleft cysts comprise of a well-defined, thin-walled anechoic cystic structure on US corresponding with a T1 hypointense and T2 hyperintense cyst without wall enhancement on MR imaging. The contents of the cyst (fluid or proteinaceous/mucoid), cyst wall thickness, definability of the margins, and degree of enhancement of the cyst wall and adjacent structure may be affected by infection/inflammation and trauma to the lesion.

First branchial cleft anomalies (5-8% of branchial apparatus anomalies) arise along the embryonic tract of the first branchial cleft. The first branchial cleft tract courses from the external auditory canal, via the parotid gland, to the submandibular

Table 1. Table of Embryologic Origin of Head and Neck Structures Derived from the Branchial Apparatus (Simplified)

	Cleft	Arch	Pouch
1st	External auditory canal	Mandible, incus, malleus, muscles of mastication	Eustachian tube, tympanic cavity, mastoid
2nd	Cervical sinus of His	Part of hyoid bone, styloid process, stapes, muscles of facial expression, stapedius muscle, posterior belly of digastric muscle, cranial nerve VII and VIII	Palatine tonsil
3rd	Cervical sinus of His	Part of hyoid bone, superior constrictor muscle, stylopharyngeus muscle, cranial nerve IX, internal carotid artery	Inferior parathyroid gland, thymus, pyriform fossa
4th	Cervical sinus of His	Cuneiform cartilage, superior laryngeal nerve, aortic arch and right subclavian artery, thyroid gland	Superior parathyroid gland
5th	Rudimentary	Laryngeal cartilage, laryngeal	Thyroid cells
6th		muscles, inferior pharyngeal constrictors, cranial nerve XI, recurrent laryngeal nerve	

triangle.[12,21] The lesions often present as a mass or swelling in the periauricular or mandibular region, with a history of recurrent infection/inflammation likely due to the presence of a sinus tract. The Work classification of first branchial cleft cysts describes two subtypes. The Work type I cyst (periauricular cyst) is located close to the external auditory canal. On imaging, a cystic structure around the pinna anterior, inferior, or posterior to the external auditory canal is identified. The structure may beak toward the bony-cartilaginous junction of the external auditory canal.[3] The sinus tract often runs parallel to the external auditory canal (Fig 4). The imaging appearance of a Work type II cyst (periparotid cyst) is that of a cystic structure superficial to, in, or deep to the parotid gland (Fig 5). In case of involvement of the deep lobe of the parotid gland, extension into the parapharyngeal space or even the posterior submandibular space may occur. There are no reliable imaging features to differentiate Work type II branchial cleft cysts from other cystic parotid lesion.[3,12] Surgical removal of first branchial cleft anomalies requires familiarity with the complex and intimate relationship of these lesions with the facial nerve.[23]

Second branchial cleft anomalies (75-95% of branchial apparatus anomalies) occur along the second branchial cleft tract extending from the oropharyngeal mucosa in the tonsillar fossa, coursing lateral in between the glossopharyngeal and hypoglossal nerve through the carotid bifurcation region and descending lateral to the common carotid artery to the supraclavicular region.[12,24] The lesion often manifests as an asymptomatic slowly enlarging mass in childhood or early adulthood and may be painful if secondarily infected. The Bailey classification distinguishes four subtypes of second branchial cleft cysts. Only the Baily type III cyst is of clinical relevance (Fig 6), because the cyst may show the pathognomonic imaging finding of a small extension of the cyst between the proximal internal/external carotid artery close to the common carotid artery bifurcation (beak sign).[3]

Third branchial cleft cysts are rare anomalies, but remain the second most common congenital lesion of the posterior cervical space after lymphatic malformations.[12,25] They arise in the third branchial cleft tract coursing from the piriform sinus, through the thyrohyoid membrane and subsequently posterior to the common or internal carotid artery between the glossopharyngeal and hypoglossal nerve. The tract of the third branchial cyst is located above the course of the laryngeal nerve, a discriminative feature for differentiating these cysts from fourth branchial cleft anomalies.[12] On imaging, the anomaly is identified as a thin-walled unilocular cystic structure located anterior or deep to the sternocleidomastoid (SCM) muscle.[3,26]

Fourth branchial apparatus anomalies are extremely rare and arise in the fourth branchial cleft tract coursing from the piriform sinus, through the thyrohyoid membrane and descending into the mediastinum along the tracheoesophageal groove. On imaging, lesions involving the fourth branchial cleft tract are

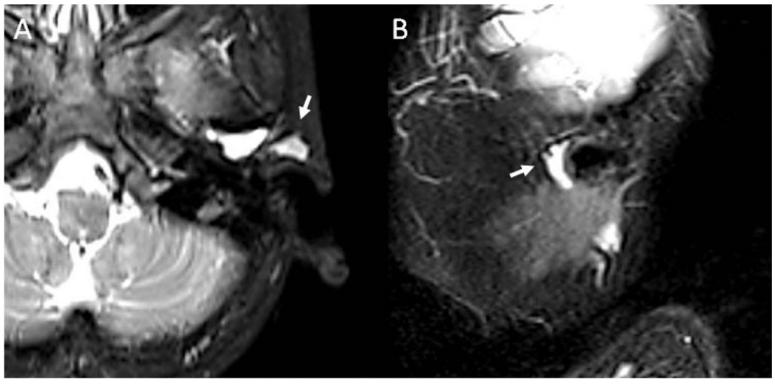

Fig 4. Axial (A) and sagittal (B) fat-suppressed T2-weighted MR images of a child with a Work type I first branchial cleft anomaly. The images demonstrate a cystic structure in the left pinna region anterior to the external auditory canal. The sinus tract runs parallel to the external auditory canal.

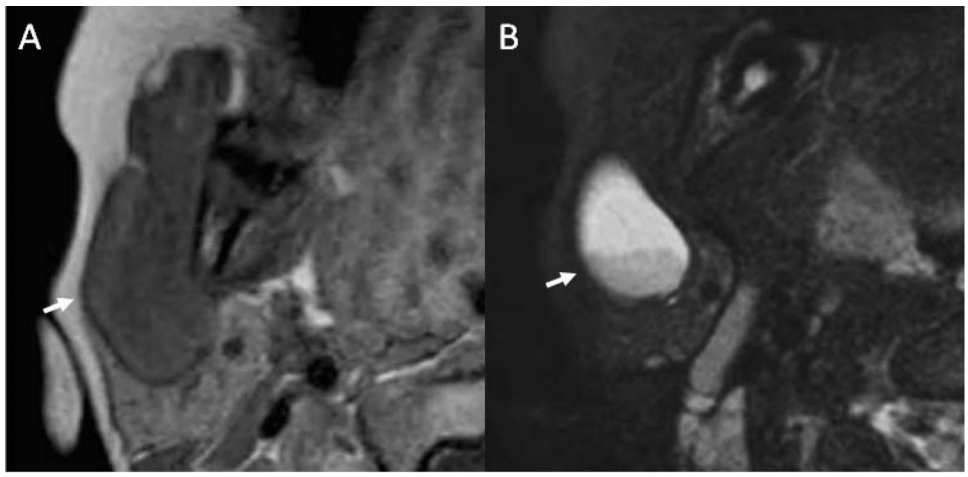

Fig 5. Axial T1-weighted (A) and axial fat-suppressed T2-weighted (B) MR images of a child with a Work type II first branchial cleft anomaly. The images demonstrate a well-defined, thin-walled cystic structure in the right parotid gland. On the axial T2-weighted image (B), the cyst content reveals debris in the dependent portion of the lesion, possibly due to prior infection, inflammation, or trauma.

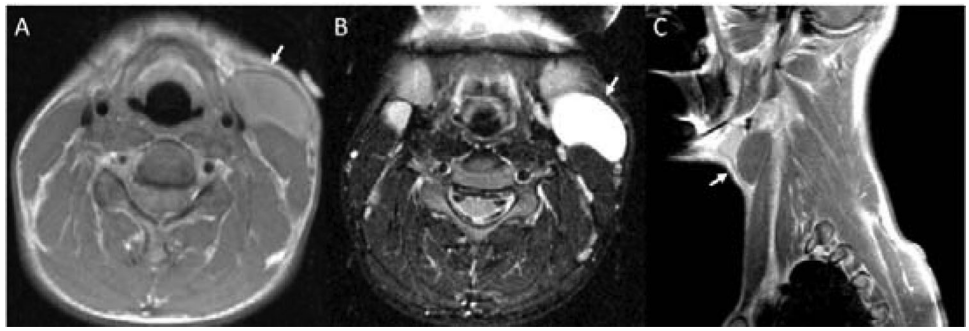

Fig 6. Axial T1-weighted (A), axial fat-suppressed T2-weighted (B), and sagittal T1-weighted (C) MR images of a child with a Bailey type II second branchial cleft anomaly. The images demonstrate a well-defined, thin-walled cystic structure situated in the lateral neck. The axial images (A, B) demonstrate the classic location of the cyst lateral to the carotid space. The sagittal image (C) shows the other classical location landmarks of the cyst, positioned along the anterior surface of the sternocleidomastoid muscle and posterior to the submandibular space.

identified as sinus tracts or sinus tract complications (eg, abscess) and are in general left-sided lesions. The left thyroid lobe is a preferred location. In this specific location, a fourth branchial cleft cyst can be confused with thyroglossal duct cysts or thyroid cysts. Furthermore, the imaging features of a fourth branchial cleft cyst can appear similar to an external or mixed laryngocele. The position of the branchial cleft anomaly in reference to the laryngeal nerve differentiates fourth from third branchial cleft anomalies. Anomalies derived from the fourth branchial cleft are typically located below the laryngeal nerve.[12,24,26]

Thymopharyngeal Duct Anomalies

Thymopharyngeal duct anomalies are very rare congenital anomalies. These lesions show a slight male predominance and frequently present in the first decade of life as this is the age of maximal thymic activity and size. A common presentation is that of a slow growing asymptomatic neck lesion with symptoms of mass effect and compression (eg, dysphagia, dyspnea, pain, and hoarseness) of adjacent structures in 10% of cases. During embryonic development, the thymus derives from the third branchial pouch. Subsequent descending migration of the thymus into the mediastinum is facilitated through the thymopharyngeal duct. The course of the duct extends from the level of the mandibular angle, lateral to the thyroid gland, into the anterior superior mediastinum.[12,27] Thymopharyngeal duct anomalies have a high preference for the left side of the neck; however, midline and right-sided anomalies are seen.[21]

Cervical thymic cysts arise along the tract of the thymopharyngeal duct. The etiology of these cysts is controversial. One of the prevailing theories for the pathogenesis is the congenital persistence of thymopharyngeal duct remnants as origin of the lesions. A less favored hypothesis is that the cysts result from acquired progressive cystic degeneration of thymic elements (corpuscles, epithelium reticulum).[3] US imaging may show a large unilocular or multilocular cystic structure anterior or deep to the SCM muscle with downward extension parallel to the SCM muscle. A characteristic imaging finding during US examination is rapid enlargement of the lesion during Valsalva maneuver. The typical location of the cyst adjacent to the carotid space and the degree of extension into the superior mediastinum are better appreciated on MR imaging (Fig 7). The T1 signal of the cyst varies from hypointense to hyperintense, depending on the protein content of the cyst material or prior intracystic hemorrhage.[3,12]

Ectopic or residual thymic tissue can occur as solitary thymopharyngeal duct anomaly or in association with cervical thymic cyst formation. On imaging, ectopic thymic tissue has imaging features identical to normal positioned thymic tissue

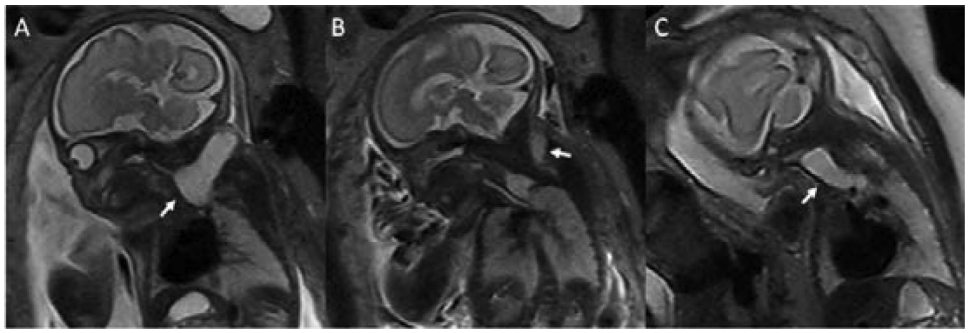

Fig 7. Sagittal T2-weighted fetal MR images of a fetus with a cervical thymic cyst (A-C). The images show a well-defined, thin-walled, unilocular cystic structure in the left lateral neck. The images demonstrate the typical location of the cyst (A) adjacent to the carotid space (B) and the continuity with the mediastinal thymus (C).

and may be identified anywhere along the course of the thymopharyngeal duct. US may reveal the typical "starry sky" appearance of thymic tissue in an aberrant location. If solid components are identified in cervical thymic cysts, this will probably represent additional ectopic thymic tissue. These focal elements of ectopic thymic tissue demonstrate mild enhancement on postcontrast MR imaging sequences.[3,21]

In 50% of cases of thymopharyngeal duct anomalies, either cervical thymic cysts or ectopic thymic tissue, a connection can be identified between the anomaly and the mediastinal thymic tissue by direct extension, also referred to as cervical extension of the thymus, or through a fibrous cord (representing a remnant of the thymopharyngeal duct).[12]

Laryngeal Anomalies

Laryngeal anomalies are uncommon congenital or acquired malformations that rarely present during childhood and are more commonly seen in adults. Laryngoceles and saccular cysts arise from the saccule, or appendix, of the laryngeal ventricle. The orifice of the laryngeal ventricle (of Morgagni) is located between the false and true vocal cords. The laryngeal saccule originates from the roof of the laryngeal ventricle and extends superiorly bounded by the false vocal cord and aryepiglottic fold medially and by the thyroid cartilage laterally. Because of the numerous amount of mucous glands in the saccule, it has been hypothesized that it provides lubrication of the vocal cords.[12] From birth to the sixth year of life, the saccule is relatively large and starts to involute by the end of the sixth year. Congenital laryngeal anomalies typically manifest with respiratory difficulties or dysphagia during the neonatal time period.[6,12]

Laryngoceles are air-filled dilated laryngeal saccules communicating with the cavity of the larynx. They may arise from congenital anomalous large saccules with a potential subsequent narrow ventricular orifice and demonstrate progressive expansion with increased *intraluminal* laryngeal pressure (eg, crying). Acquired laryngoceles are often associated with laryngeal carcinoma causing (partial) occlusion of the ventricular orifice.[12,28,29]

Saccular cysts are saccular dilatations filled with mucus and develop secondary to atresia of the orifice of the ventricle (congenital) or obstruction of the ventricular orifice due to mucus retention (acquired).[6,28]

Both laryngoceles as well as saccular cysts demonstrate similar modes of potential distension and expansion through structurally weak areas of the larynx. They may extend beyond the superior border of the thyroid cartilage but remain confined to the larynx (internal type). In contrast, the dilated laryngeal saccules can penetrate the thyrohyoid membrane and extend into the supraglottic subcutaneous tissues of the neck (external type). The component superficial to the thyrohyoid membrane is typically dilated, while the saccular portion inside the membrane is normal in size. The combined type shows abnormal dilatation of the saccule on both sides of the thyrohyoid membrane.[12,28,42] The external type as well as the combined type will result in a neck mass. On imaging, a well-defined mass in the lateral

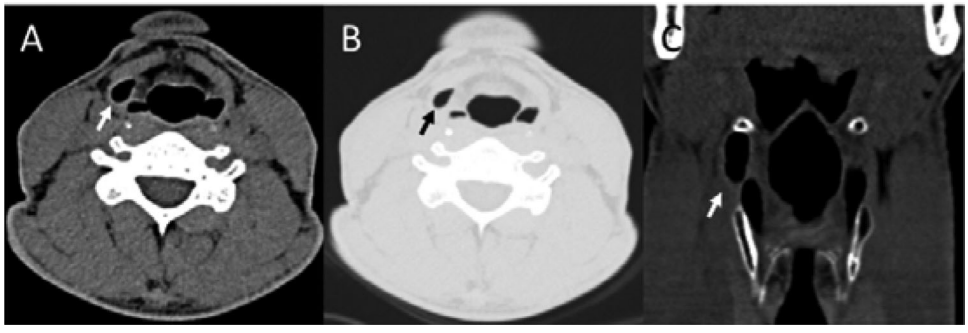

Fig 8. Axial CT image in soft tissue window (A) and lung window (B) and coronal CT image in soft tissue window (C) of a child with a laryngocele. The images show an air-filled well-defined mass in the lateral aspect of the superior paralaryngeal space (A, B) in keeping with a dilated laryngeal saccule. Note that the mass extends beyond the superior border of the thyroid cartilage (C) but remains confined to the larynx and therefore represents an internal type laryngocele.

aspect of the superior paralaryngeal space is identified. Lesions of the internal type are limited by the thyrohyoid membrane (Fig 8). External and combined types are located superficial to thyrohyoid membrane at the point of insertion of the neurovascular bundle (superior laryngeal nerve, vessels). Laryngoceles will typically demonstrate a connection to the laryngeal cavity. The echogenicity and MR signal intensity of the lesions depend on the amount of air or mucus secretions.[12]

Congenital Inclusion Cysts

Dermoid and epidermoid cysts are congenital inclusion cysts and originate from entrapped epithelial elements along embryonic lines of fusion during development. These cysts are lined by squamous epithelium. Dermoid cysts are more commonly encountered than epidermoid cysts in this region. Seven percent of all dermoids and epidermoids occur in the head and neck region.[6] The clinical distinction between dermoid and epidermoid cysts is hard to make and in the majority of cases insignificant.

Dermoid cysts are commonly located in the midline of the neck, the floor of the mouth, and the submandibular or the sublingual spaces (Fig 9). The lesion manifests as a slow-growing asymptomatic mass during childhood or young adulthood. Rapid enlargement of the lesion may occur in association with a sinus tract and is possibly due to an increase in desquamation.[3,12] Dermoid cysts contain variable amounts of dermal *derivatives* such as fluid, lipid material, cholesterol, keratinaceous debris, calcification, and hair. Depending on the content of the cyst, the imaging features may vary. Typical imaging findings include a moderately thin-walled unilocular mass with fat and/or calcifications and no contrast enhancement on MR imaging. US typically demonstrates a pseudosolid mass due to mixed internal echoes of proteinaceous material, fat, and calcifications. The presence of posterior acoustic enhancement on ultrasound reveals the cystic nature of the mass. On fat-saturated MR sequences, the fatty elements show signal dropout. The "sack-of-marbles" appearance, due to coalescence of fat into small nodules, is pathognomonic for a dermoid cyst. In some cases, fluid/fluid or fluid/debris levels are demonstrated. Local mass effect with displacement of the adjacent structures may occur. Commonly, a sinus tract toward the skin surface is identified. The lesion typically shows no movement related to tongue protrusion or swallowing on US. In rare instances, dermoids may have fibrous attachments to the hyoid and may consequently move with protrusion of the tongue (similar to thyroglossal duct cyst). The topographic relationship of the dermoid cyst inferior or superior to the mylohyoid muscle can be determined in the coronal plane and is an important preoperative information to help choose between an external or intraoral approach.[3,6] Lack of enhancement differentiates these lesions from teratomas with solid components.

Epidermoid cysts are typically located off-midline or asymmetric to one side of the midline at the base of the tongue or in the anterior cervical triangle. They often become evident during infancy. The degree of proteinaceous fluid in the epidermoid cyst varies. On imaging, the cystic structure is relatively well circumscribed. A predominantly fluid filled structure is seen on US. MR imaging shows either subtle T1 hypointensity or T1 hyperintensity depending on the protein content.[18] Although presence of restricted diffusion has been initially associated with epidermoids, restricted diffusion is not pathognomonic of epidermoid cysts and can also be seen with dermoid cysts.[3,30]

Both lesions may demonstrate significant overlap in imaging features and to a lesser degree in location. Identification of these cysts as inclusion cysts and confirming the presence or absence of a track is most useful for management of these cases.[31]

Bronchogenic Cyst

Cervical bronchogenic cysts are extremely rare congenital foregut anomalies. The etiology for the aberrant position of the lesion in the neck is unclear. The lesion manifests in infancy as an asymptomatic neck mass or as a draining sinus. There is a male predilection. Imaging features comprise a well-defined cystic structure in the sternal notch region anterior to the trachea (Fig 10). The cyst or sinus tract can become infected and evolve into a neck abscess.[3,12]

Congenital Solid Masses

Teratoma

Teratomas in the cervical region account for 2–5% of all germ cell tumors and 10% of all teratomas. The lesions are often identified on prenatal imaging (Fig 11). In the postnatal period, they generally present before the age of 3 years as a large firm mass in the neck region and depending on the location with complicating airway obstruction/compression. There is a slight female predominance. Teratomas are composed of all

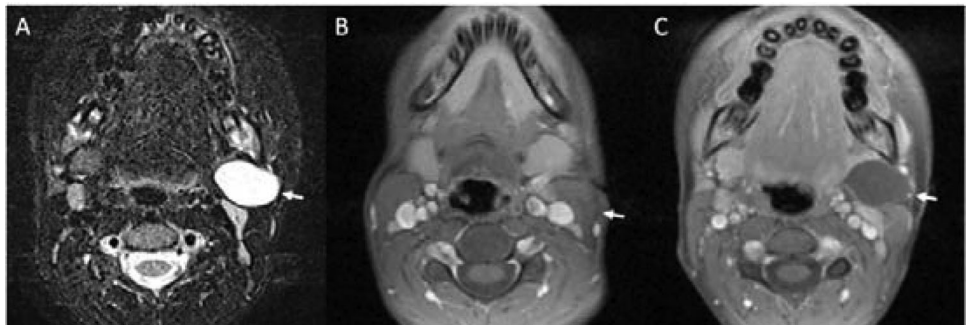

Fig 9. Axial fat-suppressed T2-weighted (A) and contrast enhanced fat-suppressed T1-weighted (B, C) MR images of a child with a dermoid cyst. The images demonstrate a well-defined, thin-walled cystic structure in the left lateral neck. On the contrast-enhanced T1-weighted (B, C) images, the anterolateral location of the cyst in relation to the carotid space is well demonstrated. Note that this precise location differentiates this lesion from a second branchial cleft anomaly (typical lateral to carotid space).

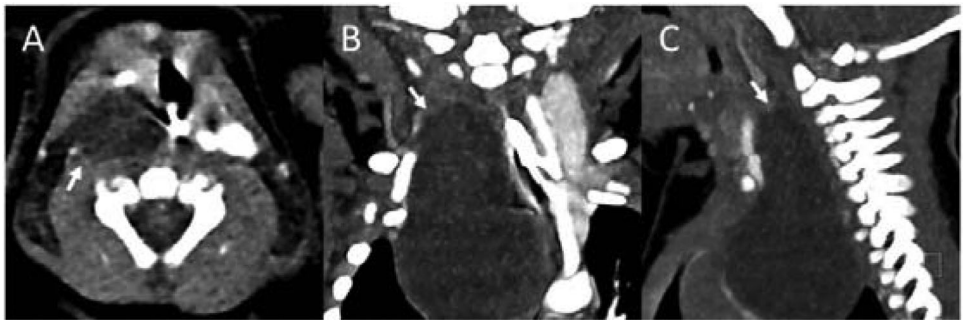

Fig 10. Axial (A), coronal (B), and sagittal (C) CT images in soft tissue window of a child with cervical extension of a bronchogenic cyst. The images show a well-defined cystic structure (A-C) in the sternal notch region (C). The predominant volume of the cystic structure is found in the upper thoracic region (B, C) and therefore the cervical part of the lesion presumably represents cervical extension of a thoracic bronchogenic cyst.

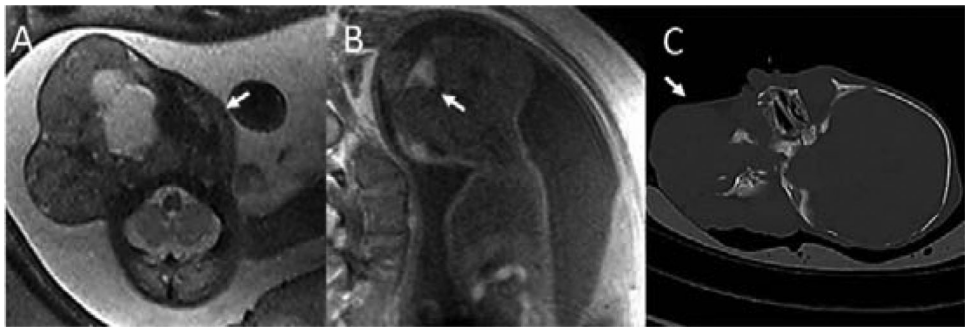

Fig 11. Axial T2-weighted (A) and sagittal T1-weighted (B) fetal MR images of a fetus with a large cervical teratoma. The axial image (A) shows a large right-sided neck lesion with widespread infiltrative extension. The cystic components are T2 hyperintense. The sagittal image (B) demonstrates the typical area of fat as T1 hyperintense signal intensity (arrow). Polyhydramnios is noted and is due to impaired fetal swallowing. The postnatal CT image (C) of the child shows the calcification / ossification in the lesion.

three embryonic cell layers involving endodermal, mesodermal, and/or ectodermal elements. They are hypothesized to arise either from pluripotent stem cells sequestered during embryogenesis or from embryonic tissue that escaped the regional influences of the primary organizer.[6] Teratomas are classified as mature or immature lesions.[18,32] The risk of malignant congenital cervical teratomas increases with advanced age at diagnosis. Alpha-fetoprotein (AFP) is an indicator for teratoma in infants and children; however, in neonates, AFP has high normal baseline values. Cervical teratomas typically are located in the midline in the suprahyoid region.[1,32] They may extend into the mediastinum or compress the trachea. If tracheal compression occurs during embryonic development, this may result in pulmonary hypoplasia. In prenatally identified lesions, polyhydramnios may be seen secondary to impaired fetal swallowing.[32] On US, the lesion shows heterogeneous echogenicity with solid and cystic components. MR imaging demonstrates the typical areas of fat as T1 hyperintense signal intensity. The cystic components are T2 hyperintense. Intralesional calcifications can be identified on susceptibility-weighted MR imaging sequences or on selective CT examinations. At time of diagnosis, cervical teratomas are often large lesions with widespread infiltrative extension.[1,5] There are no reliable imaging features to differentiate mature from immature teratomas. On histology, these lesions tend to be generally benign mature tumors.[33] Immature cervical teratoma or malignant transformation is rare.

Congenital and Acquired Vascular Masses

Vascular Malformations

Vascular malformations include several types of anomalies and are identified in the head and neck region in 1–4% of the pediatric population. They demonstrate normal endothelial cell turnover and are classified as nonneoplastic lesions according to the International Society for the Study of Vascular Anomalies (ISSVA) classification system recently updated in 2014 (Table 2), which stems from the early work of Mulliken and Glowacki.[34] Vascular malformations may remain stable, grow commensurate to the child, or demonstrate enlargement after infection, trauma, or endocrine changes (eg, puberty, pregnancy). Vascular malformations are grouped based on the predominant anomalous tissue or vessel type into lymphatic malformations, venous malformations, arteriovenous malformations (AVMs), capillary malformations, and mixed-type lesions.[35,36] The capillary malformations (previously named as port wine stain) are rather cutaneous lesions than a neck mass, therefore are beyond the scope of this review.

Lymphatic malformations are the most common congenital anomalies in the posterior cervical triangle accounting for 75–80% of the cystic lesions in this region, but they can occur in any of the different neck regions. The majority of these lesions are present at birth or appear before the age of 2 years as a soft mass of variable size.[3] Lymphatic malformations can be

Table 2. International Society for the Study of Vascular Anomalies Classification of Vascular Anomalies (Simplified and Adapted from www.issva.org)

VASCULAR ANOMALIES				
Vascular tumors				
Benign vascular tumors	**Locally aggressive or borderline vascular tumors**	**Malignant vascular tumors**		
Infantile hemangiomas Congenital hemangiomas -Rapidly involuting -Noninvoluting -Partially involuting Tufted angioma Epithelioid hemangioma Others	Kaposiform hemangioendothelioma Retiform hemangioendothelioma Kaposi sarcoma Others	Angiosarcoma Epithelioid hemangioendothelioma Others		
Vascular Malformations				
Simple vascular malformations				
Capillary malformations	**Lymphatic malformations**	**Venous malformations**	**Arteriovenous malformations**	**Arteriovenous fistula**
-Cutaneous and/or mucosal -Telangiectasia -Cutis marmorata telangiectatica congenital -Nevus simplex -Others	-Common -Generalized lymphatic anomaly -Gorham-Stout disease -Channel type -Primary lymphedema -Others	-Common -Familial cutaneo-mucosal -Blue rubber bleb nevus syndrome -Glomuvenous -Cerebral cavernous malformation -Others	-Sporadic -In hereditary hemorrhagic telangiectasia -In capillary malformation – arterio-venous malformation syndrome	-Sporadic -In hereditary hemorrhagic telangiectasia -In capillary malformation – arterio-venous malformation syndrome
Combined vascular malformations				
Anomalies of major named vessels				
Vascular malformations associated with other anomalies				

macrocystic, microcystic, or mixed. The typical location is posterior to the SCM muscle. However, microcystic lesions tend to occur above the mylohyoid level in the oral and perioral structures and submandibular spaces and may involve the parotid gland. Lymphatic malformations have a tendency to infiltrate across various cervical spaces or extend into the mediastinum and adjacent anatomic structures are encircled/wrapped rather than displaced. Typical imaging characteristics include the trans-spatial extension including engulfment and encasement of neurovascular structures as well as fluid-fluid levels in a multilocular cystic structure with macrocystic and/or microcystic elements. On US, echogenic appearance of parts of the lesion is due to clusters of small abnormal lymphatic channels. The content of the cystic elements varies from homogenous to heterogeneous due to prior hemorrhage or infection.[1,3,35] The hemorrhagic component or debris from previous infection layering in the dependent portion of the cystic elements causes the fluid-fluid levels. Postcontrast MR imaging sequences and multiphasic time-resolved dynamic cMRA typically show no contrast enhancement but may demonstrate enhancement of the walls and septa of the cystic elements, particularly in case of concomitant (prior) infection (Fig 12).[7] The presence of a lymphatic malformation in the posterior cervical triangle may be associated with Turner syndrome and trisomy 21, 18, and 13.[3,12]

Venous Malformation

Venous malformations are the most common low-flow vascular malformations and the second most common vascular lesions of the head and neck region (after hemangiomas). In the neck region, the lesions manifest at birth or in early infancy (although they may stay dormant till adulthood) as a painless soft blue or purplish mass or may be symptomatic depending on potential accompanying local inflammatory changes. Local pain, bleeding, and cosmetic concerns are the leading symptoms at the time of presentation. Venous malformations are developmental anomalies composed of dysmorphic venous channels lined by flattened endothelium. They are characteristically located in the skeletal muscles of the neck, including the masseter, pterygoid, trapezius, and SCM muscles, or may involve the mandibular region. The presence of phleboliths is a key imaging feature of venous malformations. US demonstrates a compressible, hypoechoic heterogeneous lesion with detectible flow on Doppler in about 40% of the cases.[35] The phleboliths appear as hyperechoic foci and show posterior acoustic shadowing. On MR imaging studies, trans-spatial extension of the venous malformation may be identified. The lesion is typically T1- isointense and T2-hyperintense to normal muscle, with heterogeneous contrast enhancement. Distinct areas of T2 hyperintense signal may represent venous lakes. Fluid-fluid levels

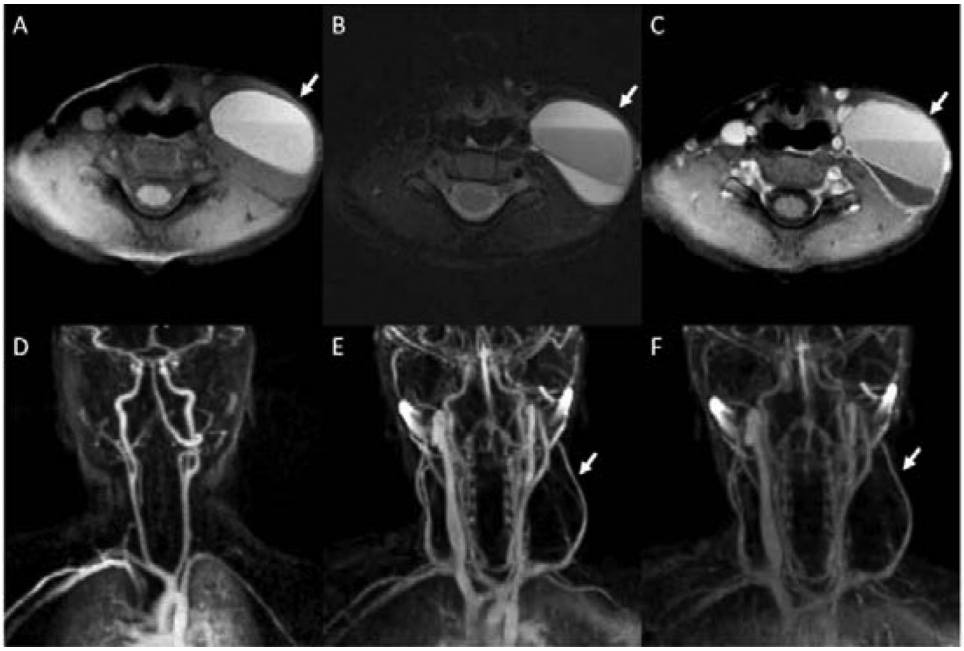

Fig 12. Axial fat-suppressed T1-weighted (A), fat-suppressed T2-weighted (B), and contrast enhanced fat-suppressed T1-weighted (C) MR images of a child with a lymphatic malformation. The axial images show a large, well-defined macrocystic cystic structure in the left posterior cervical triangle. The cyst demonstrates fluid-fluid levels and enhancement of the peripheral cyst wall and septa (C). Multiphasic dynamic contrast–enhanced MRA images (D-F) reveal no arterial or venous enhancement of the lesion. Note the displacement of the external jugular vein due to mass effect (E, F).

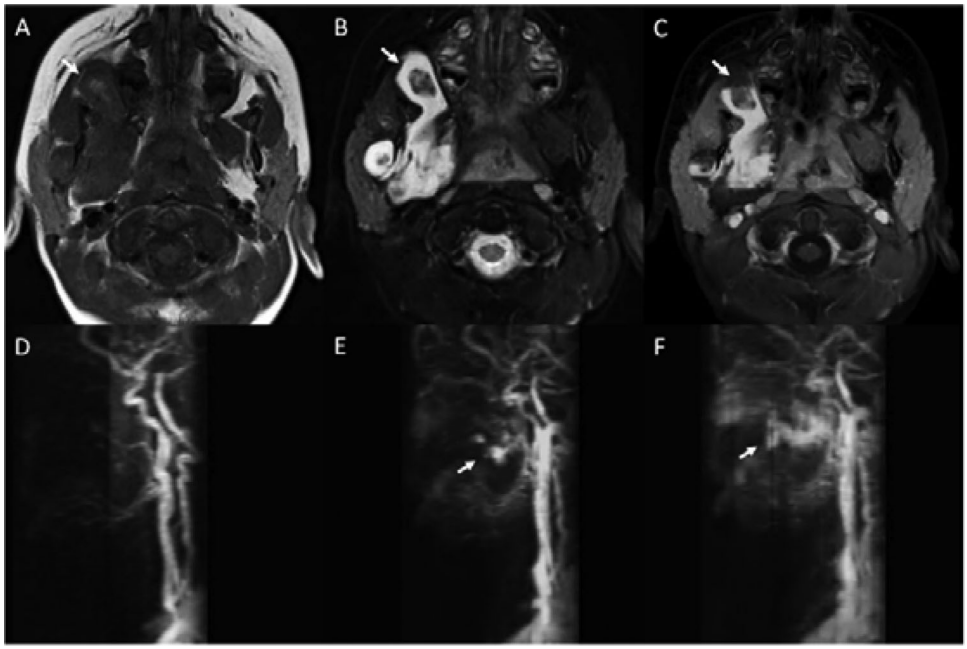

Fig 13. Axial T1-weighted (A), fat-suppressed T2-weighted (B), and contrast enhanced fat-suppressed T1-weighted (C) MR images of a child with a venous malformation. The T2-weighted images (B) show a hyperintense mass in the right masticator space with trans-spatial infiltrative extension. Hypointense phleboliths are present in the mass. Multiphasic dynamic contrast enhanced MRA images (D-F) demonstrate progressive enhancement during the early (E) and late (F) venous phase (arrows).

can appear in the lesion, and although this finding is more typical for lymphatic malformations, all slow-flow vascular malformations have the potential to show fluid-fluid levels. *Phleboliths* are best depicted on susceptibility weighted sequences. Intralesional fluid-fluid levels are rarely present and this may be used as a differentiating feature to distinguish venous malformations from lymphatic malformations. Involvement of the adjacent osseous structures includes osteal defects, demineralization, hypoplasia, and cortical thickening. Multiphasic time-resolved dynamic cMRA imaging demonstrates a slow flow pattern revealing typical slow gradual venous enhancement with variable degree of contrast enhancement on delayed images (Fig 13).[7,8,35,36] Venous malformations are occasionally seen in blue rubber bleb nevus, Proteus and Maffucci syndromes.[37]

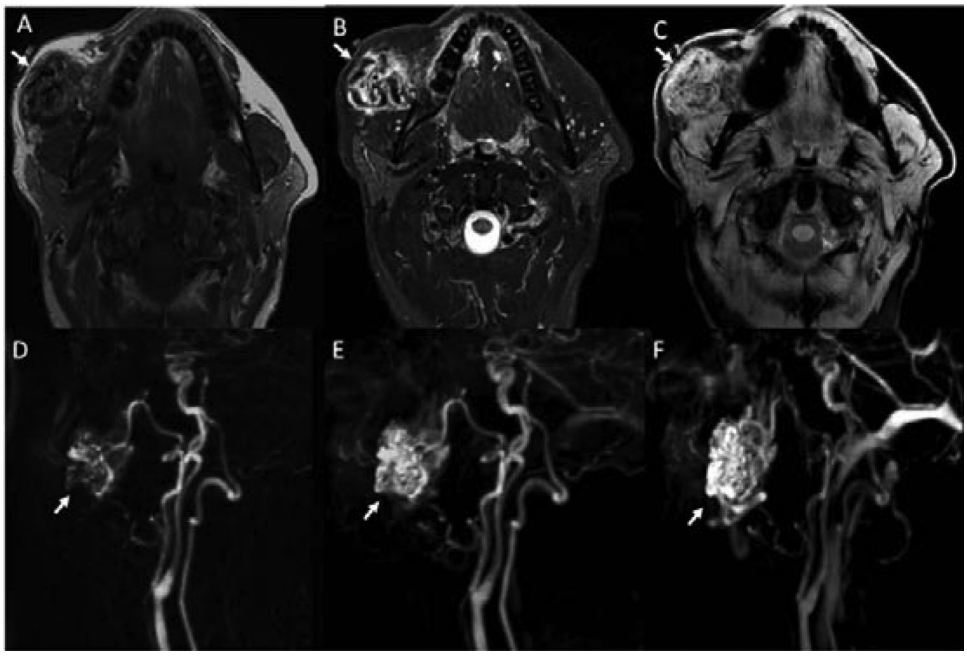

Fig 14. Axial T1-weighted (A), fat-suppressed T2-weighted (B), and contrast enhanced fat-suppressed T1-weighted (C) MR images of a child with an arteriovenous malformation. The T2-weighted images (B) show dark, serpiginous flow voids infiltrating the subcutaneous fat of the right cheek. The contrast-enhanced image (C) reveals an additional soft tissue infiltrating component of the lesion. Multiphasic dynamic contrast–enhanced MRA images (D-F) reveal early arterial enhancement of the lesion with feeders identified from the external carotid artery. Note the intralesional nidus formed by the tangle of vessels (E, F).

Arteriovenous Malformation

AVM of the neck presents later in childhood or in the adolescent age group as skin discoloration with or without underlying compressible (pulsatile) mass. The lesion consists of enlarged feeding arteries draining into veins without an intervening capillary network. On Doppler US and multiphasic dynamic cMRA imaging studies, the lesions show a high-flow pattern as important differentiating feature from other vascular malformations. Furthermore, multiphasic time-resolved dynamic cMRA imaging studies may identify dilated feeding arteries and draining veins, early enhancement of the feeding arteries, and an intralesional nidus with shunting to draining veins and therefore early venous drainage.[7,8,37] Anatomic MR imaging sequences demonstrate no well-defined mass, but rather enlarged serpiginous flow voids with an additional soft tissue infiltrating component (Fig 14). Evaluation of extension of the lesion and potential adjacent soft tissue and osseous involvement is important to determine.[35,36]

Mixed-type Vascular Malformation

Mixed-type vascular malformations are less common than solid-type lesion and mainly comprise mixed veno-lymphatic malformations; however, other mixed-type lesions may be identified. These lesions demonstrate clinical features and imaging characteristics of the involved vascular malformations.

Vascular Tumors

Vascular tumors, particularly infantile hemangiomas, are common in the pediatric population. These are neoplastic lesions manifesting with a high endothelial cell turnover. The growth of these lesions is independent of body size. Various vascular tumors are encountered in the head and neck region, including infantile hemangioma, carotid body tumors, glomus jugulare tumors, and juvenile nasopharyngeal angiofibromas (Table 2).[35] As only hemangiomas potentially present as a neck mass in the pediatric age group, this entity is discussed in greater detail in this review.

Infantile hemangiomas represent one of the most common tumors of infancy with most lesions occurring in the head and neck (60%). The lesion initially presents as a red superficial skin lesion in the first couple weeks of life that was not visible at the time of birth. There is a female predilection with a female to male ratio of 3:1.[35] Infantile hemangiomas are benign vascular neoplasms. Several specific stages have been identified in the natural course of this entity. In the postnatal time period, the lesion starts to proliferate and enlarge rapidly and consists of hyperplastic proliferating endothelial cells (proliferative phase). At approximately 10 months of age, the hemangioma typically will gradually start to involute and shows progressive perivascular deposition of fibrofatty tissue (involution phase). About 50% of the lesions are completely resolved by the age of 5 years (involuted phase).[36,37] Favorable locations in the cervical region include subcutaneous lesions, subglottic lesions, and less common deep-seated lesions and lesions extending over multiple tissue planes. Additional infantile hemangiomas may be identified in approximately 20% of the affected children.[35,36] Imaging reveals the exact anatomic location of the lesion, the extent of the lesion, and the relation to adjacent structures (Fig 15). On US, the hemangioma manifests as a well-defined lobulated heterogeneous lesion with high vascular flow on Doppler interrogation in the proliferative phase and fibrofatty features in the involuting phase. The most characteristic MR imaging feature of a proliferating infantile hemangioma is a well-defined solid mass that shows avid enhancement in the arterial phase. Additional multiphasic dynamic time-resolved

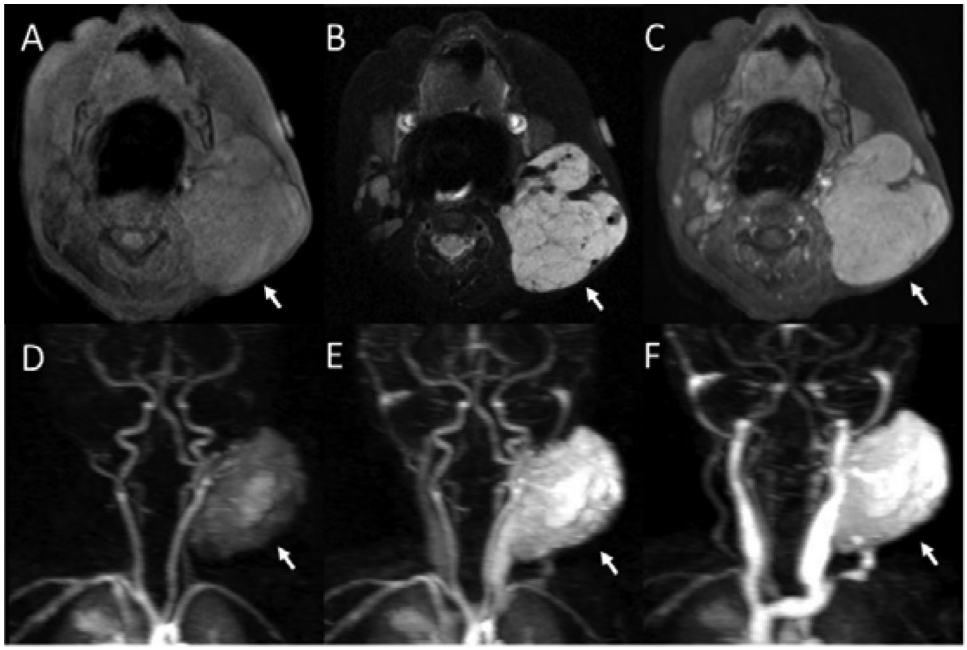

Fig 15. Axial T1-weighted (A), fat-suppressed T2-weighted (B), and contrast-enhanced fat-suppressed T1-weighted (C) MR images of a child with an infantile hemangioma. The T2-weighted image (B) shows a well-defined hyperintense mass in the left carotid space with transspatial infiltrative extension. Flow voids are present in the mass. Multiphasic dynamic contrast–enhanced MRA images (D-F) demonstrate avid enhancement in the arterial phase (D). The arterial feeders and venous drainage of the mass lesion can easily be identified (D, F).

cMRA imaging studies may show prominent arterial feeders and draining veins of these solid tumors. The lesion shows an isointense to slight hyperintense T1 signal and hyperintense T2 signal. In the involuting, phase elements of the lesion may be replaced by fatty tissue.[7,8,35]

Acquired Cystic Masses

Ranula

Ranulas are not common in the pediatric age group. The peak frequency is in the second decade. Incidentally, congenital mucoceles and ranulas have been reported.[38] There is a slight female predilection for oral ranulas and a predilection for males for cervical ranulas.[39] A ranula is a mucous retention cyst (mucocele) or pseudocyst arising from salivary extravasation from a sublingual gland or minor salivary gland into the surrounding soft tissues of the oral cavity or neck. The extravasation is in the vast majority the consequence of infection, inflammation, or trauma to the involved gland causing an occluded gland duct. Ranulas are categorized into simple (oral) ranulas with a peripheral epithelial layer or plunging/diving (cervical) ranulas.[40,41] A plunging ranula is the consequence of a ruptured simple ranula and therefore lacks an epithelial lining (pseudocyst). The lesion manifests as a swelling in, respectively, the floor of the mouth or the submandibular space. The location of both simple and plunging ranulas is typically off midline. Simple ranulas appear in the sublingual space in or superficial to the mylohyoid sling. US demonstrates a thin-walled ovoid or lobulated cyst with or without debris deep to the mylohyoid muscle. MR imaging features consist of a T2 hyperintense cystic lesion in the sublingual space with variable T1 intensity depending on the amount of protein in the cyst (Fig 16). Plunging (ruptured) ranulas tend to extend posteriorly from the sublingual space into the submandibular space. Less commonly, the lesion

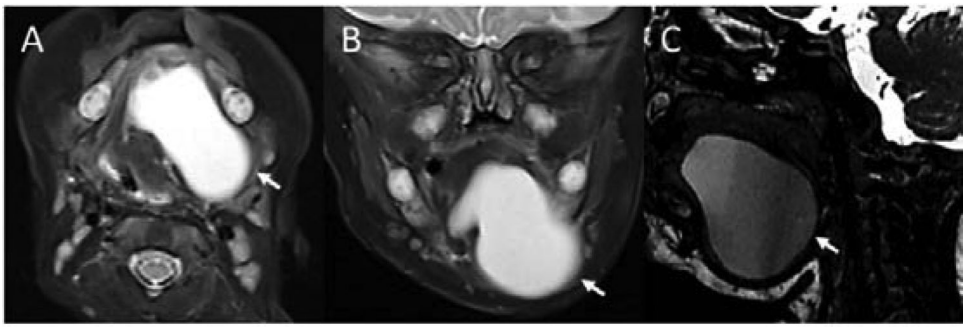

Fig 16. Axial T2-weighted (A), coronal T2-weighted (B), and sagittal fat-suppressed T2-weighted (B) MR images of a child with a large plunging ranula. The axial image (A) demonstrates a large thin-walled cystic structure in the floor of the mouth. The coronal image (B) shows posterior extension of the cystic structure from the sublingual space into the left submandibular space. The maximal volume of the plunging ranula is localized in the submandibular space. Note the layering debris due to protein-rich material in the cyst on the sagittal image (C).

extends into the anterior submandibular space through a defect in the mylohyoid musculature.[41] On MR imaging, the maximal volume of the cystic lesion is localized in the submandibular space (Fig 16). A narrow T2 hyperintense tail originating from the floor of the mouth can typically be identified, but is not necessary to suggest the diagnosis. The cystic component of a plunging ranula shows a more irregular shape than simple ranulas. In incidental cases, a giant ranula may extend posterosuperiorly into the parapharyngeal space. Identification of the narrow tail connecting to the sublingual space on MR imaging may be an important diagnostic clue.[40,41] Plunging ranulas have to potential to demonstrate trans-spatial extension, similar to vascular malformations.

Laryngeal Anomalies

Laryngeal anomalies are uncommonly congenital, rarely present during childhood, and are more commonly acquired of the adult age. Laryngeal anomalies are described in detail in the paragraph on congenital cystic lesions.

Acquired Solid Masses

Fibromatosis colli

Fibromatosis colli, also called sternomastoid tumor of infancy or congenital torticollis, has a reported prevalence of 0.4% of live births.[43] In the majority of affected infants, there is a history of birth trauma, difficult delivery, or breech delivery. The etiology is not clearly understood and in general terms, it is caused by a reaction to trauma at or around birth. In addition, a genetic component is suspected due to positive family history in affected infants.[1,43] *Fibromatosis colli* is almost exclusively encountered in the SCM muscle, although some cases of involvement of the trapezius muscle have been reported. In the 2002 WHO classification of soft-tissue tumors, the lesion is categorized as a benign fibroblastic proliferation.[43] The lesion manifests as an enlarging unilateral neck mass or swelling 10–14 days after birth and may result in torticollis with rotation of the head toward the side of the lesion. There is a predilection for the right side. Because of the characteristic history and distinct features in physical exam of these lesions, imaging is not always required. US may be useful to confirm the diagnosis, demonstrating fusiform thickening in the caudal two-third part of the SCM muscle with homogeneous or heterogeneous echogenicity of the affected muscle. A rim of normal peripheral muscle can be encountered. On US, synchronously movement of the mass and the SCM muscle is a characteristic imaging feature.[1,43,44] No further imaging is usually necessary. If MR imaging is obtained, it may show mild increased T2 signal and contrast enhancement as well as mass effect on adjacent structures (Fig 17). Features suggestive of more aggressive lesions (eg, soft-tissue sarcomas), for instance, involvement of surrounding structures, vascular encasement, bone involvement, or lymphadenopathy, can be excluded on MR imaging studies. *Fibromatosis colli* typically regress spontaneously over a period of 4–8 months.[4,43,44]

Thyroid Mass

Thyroid masses are uncommon in the young age group, although older teens and genetically predisposed children can develop thyroid cancer. Diffuse enlargement is demonstrated in association with thyrotoxicosis or Hashimoto thyroiditis. On US, an abnormal echogenicity of the thyroid gland differentiates Hashimoto thyroiditis from the preserved thyroid gland echogenicity in thyrotoxicosis. In the pediatric population, focal solid thyroid masses are rare and include adenomas, carcinomas, and lymphomas. Thyroid nodules in children are mainly benign. There are no distinctive US, CT, or MR imaging features to further characterize these solid lesion. On US, a well-delineated diffuse anechoic or slight hypoechoic nodule with or without a vascular rim favors a benign lesion.[45] An isotope thyroid scan can identify "cold" nodules as an indication for fine needle aspiration or biopsy.[1]

Adenomas are the most common thyroid nodules in the pediatric population. US demonstrates a hypoechoic mass relative to the normal thyroid gland tissue, although cases of hyperechoic and isoechoic adenomas are reported.[46] A hypoechoic rim is hypothesized to represent pericapsular inflammatory infiltrate, compressed thyroid parenchyma or fibrous capsule. Calcifications, cysts, and heterogeneous areas are due to hemorrhage or necrosis.[45]

Multinodular goiter is rare in the pediatric age group. The condition can result from congenital defects of thyroid hormone synthesis, dietary iodine insufficiencies, or thyrotropic medications. Imaging demonstrates an enlarged thyroid gland with heterogeneous echogenicity and multiple scattered hyperechoic areas on US.[45,46]

Thyroid carcinoma is very rare in children and comprises 1–1.5% of all pediatric malignancies.[47] There is predilection for females in the age group from 7 to 12 years. Papillary thyroid carcinoma is the most common subtype in the pediatric age group

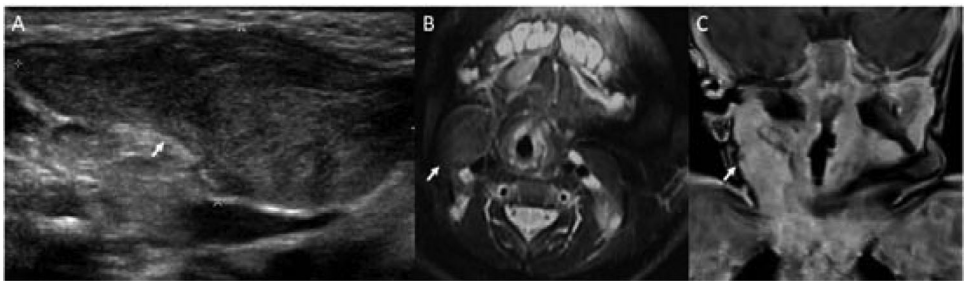

Fig 17. Sagittal US image (A), axial fat-suppressed T2-weighted (B), and coronal contrast-enhanced fat-suppressed T1-weighted (C) MR images of a child with *Fibromatosis colli*. The ultrasound image (A) demonstrates heterogeneous hyperechoic fusiform enlargement of the caudal part of the sternocleidomastoid muscle. A rim of normal peripheral muscle is shown. The axial MR image (B) reveals mild increased T2 signal intensity of the sternocleidomastoid muscle as well as mass effect on adjacent structures. The sagittal MR image (C) demonstrates contrast enhancement of the sternocleidomastoid muscle.

(70–90%), followed by follicular thyroid carcinoma (10–20%) and medullary thyroid carcinoma (1–10%). The medullary carcinoma subtype is associated with multiple endocrine neoplasia syndromes types 2a and 2b.[45] Thyroid carcinoma in children tends to present at more advanced disease stages compared to adults, with lymphatic, pulmonary, and/or osseous metastasis. However, the prognosis is more favorable.[47] Suspicious imaging finding on US include a pronounced hypoechoic thyroid mass, a predominantly solid nature, disrupted eggshell calcifications, an irregular border, and "taller than wide" in shape.[48] Intralesional punctate echogenic foci of calcification and intranodular vascularity may be detected.[45,47] In case of a suspicious thyroid nodule, ultrasound-guided biopsy is an important diagnostic tool.[45–49]

Sialadenitis

Sialadenitis or inflammation of the salivary gland is a potential consequence of either viral or bacterial infections or results from inflammatory etiology. US is the first-line imaging modality of choice in the evaluation of sialadenitis in the pediatric population. MRI is hardly ever indicated and only used as problem-solving tool.

Acute parotitis is in the majority of cases caused by a viral infection (eg, mumps virus, paromyxovirus). Acute viral parotitis may be bilateral. The imaging characteristics are nondistinctive with diffuse enlargement of the involved gland. On US, the enlarged gland has a heterogeneous texture and is relatively hypoechoic. There is no ductal dilation. Bacterial infection leading to acute parotitis is more common in children younger than 1 year of age (eg, infections of the oral cavity or dental sepsis due to *Staphylococcus aureus*). US imaging demonstrates unilateral involvement of the parotid gland with anechoic or hypoechoic foci due to suppuration. Enlarged intraparotid lymph nodes may be encountered.[1,50]

Chronic recurrent parotitis of childhood or juvenile recurrent parotitis is a noninflammatory process of the parotid gland of unknown etiology associated with nonobstructive sialectasis. It is the second most common cause of pediatric salivary gland swelling after mumps. This entity results in recurrent episodes of painful unilateral or bilateral swelling of the parotid gland potentially with subsequent fever and general malaise. There is a variable symptom-free interval between the episodes. The peak age of onset of the first episode is reported to be 3–6 years (ranging from infant to puberty). Chronic recurrent *parotitis* of childhood is a self-limiting disease over a time period of 5–10 years and in the majority of cases, there is resolution of symptoms after puberty. US imaging is used to differentiate recurrent parotitis of childhood from other causes of parotid swelling (eg, sialolithiasis).[51,52] US imaging demonstrates diffuse heterogeneous enlargement of the parotid gland with multiple hypoechogenic foci representing sialectasis or lymphocytic infiltration. The texture of the involved gland remains abnormal during the symptom-free periods. The potential value of MRI may be to identify acute versus chronic inflammation patterns. In case of acute inflammation, the gland appears T2 hyperintense and T1 hypointense with concomitant contrast enhancement, whereas chronic inflammation shows a T2 and T1 hypointense parotid gland without contrast enhancement.[53] The radiological differential diagnosis includes benign *lymphoepithelial* cyst, juvenile *Sjögren* syndrome, systemic lupus erythematosus, and acute paramyxovirus parotitis. These conditions can be identified by detection of antibodies or based on serology.[51]

Human Immunodeficiency virus (HIV) can cause diffuse swelling of the parotid gland in the pediatric population. The parotid enlargement is typically bilateral and not painful. On US, different imaging patterns are identified. Demonstration of multiple scattered hypoechogenic foci in the gland parenchyma is related to lymphoid infiltration of the gland. On the other hand, large cystic lesions replacing the gland parenchyma can be identified on US, representing benign *lymphoepithelial* cysts.[50] Disease involvement of the lungs is often seen in the setting of this entity.

Salivary Gland Mass

Sialolithiasis is a frequent cause of salivary gland masses in the adolescent population. The mass is caused by ductal obstruction due to calculi. The calculi can be identified on US as well as glandular sialectasis and swelling of the salivary gland.

Salivary gland neoplasms are rare in the pediatric age group and comprise 1% of all pediatric neoplasms.[54] The majority of solid salivary gland tumors in the pediatric age group are benign lesions. The only benign lesion of salivary gland tissue origin is the pleomorphic adenoma, comprising 11.6% of all solid tumors. Imaging features include a well-defined solitary mass with a capsule. On US, the echogenicity is variable. On CT and MR imaging, the degree of enhancement is not a consistent feature. Large pleomorphic adenomas may show cystic changes, necrosis, and hemorrhage.[54] Reparative granulomas are the second most common solid tumors of the salivary gland (9.3%) followed by reactive lymph nodes and granular cell tumors (both 7%).[55] Furthermore, nontuberculous mycobacterial adenitis can involve the intraparotid lymph nodes and the lymph nodes adjacent to the submandibular gland.

Malignant tumors of the salivary gland are extremely rare in children. The most frequent malignant lesions are low-grade mucoepidermoid carcinomas. Imaging features of malignancy are ill-defined borders and focal areas of necrosis. On MR imaging, malignant salivary gland tumors typically show iso- to hyperintense T2 signal and restricted diffusion.[56] Rhabdomyosarcomas, liposarcomas, and aggressive fibromatosis are also reported in the salivary gland.[55]

An important note is that many presumed salivary gland masses in the pediatric age group are, in fact, branchial cyst anomalies or vascular (lymphatic) malformations. The majority of vascular lesions in the salivary gland are hemangiomas followed by lymphangiomas.[55]

Lipoma

Lipomas are rare in the pediatric age group. In the neck, the posterior cervical triangle is the most frequent location. These benign tumors of fat have characteristic imaging features of a homogenous mass with signal intensity similar to subcutaneous fat on all MR imaging sequences and do not show enhancement. Fat-suppressed MR sequences confirm diagnosis (Fig 18). Lipomas displace or compress adjacent anatomical structures rather than demonstrating infiltrative extension.[1,57]

Neuroblastic Tumors

Neuroblastic tumors are frequently encountered in the adrenal region; however, 1–5% of primary neuroblastic tumors will occur in the cervical region. Metastatic neuroblastoma lesions

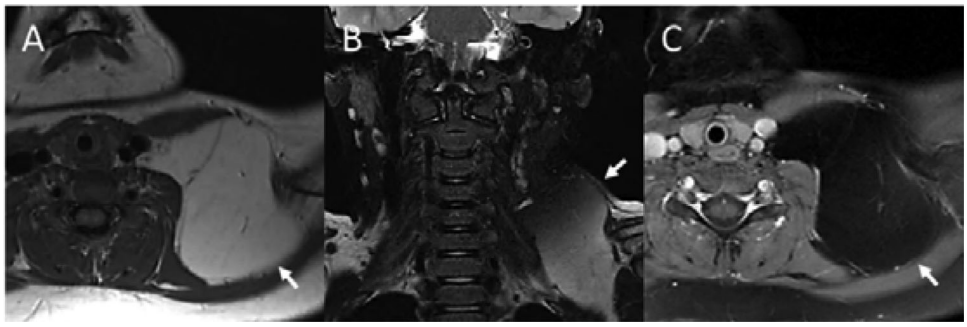

Fig 18. Axial T1-weighted (A), coronal fat-suppressed T2-weighted (B), and axial fat-suppressed postcontrast T1-weighted (B) MR images of a child with a large lipoma. The axial image (A) shows a homogenous mass in the left periclavicular region with signal intensity similar to subcutaneous fat. The postcontrast image (C) demonstrates no enhancement after contrast administration. The fat suppressed images (B, C) confirm the diagnosis of lipoma by homogenous suppression of the lesion in comparison with the conventional T1-weighted image (A).

of the cervical region are more common.[5] The lesion often presents in young childhood, before the age of 5 years, as an asymptomatic mass or with symptoms due to compression of adjacent structures (eg, dysphagia, airway obstruction, Horner's syndrome). Primary cervical neuroblastic tumors have a more favorable outcome compared to lesions of adrenal origin.[1,5] Neuroblastomas, ganglioneuroblastomas, and ganglioneuromas are tumors of varying maturity derived from primordial neural crest cells destined for sympathetic differentiation and may arise anywhere along the sympathetic ganglia. Neuroblastomas are primarily composed of undifferentiated neuroblasts, ganglioneuromas consist of mature ganglion cells and other mature tissue, and ganglioneuroblastomas have both immature and mature cell types. As a consequence, neuroblastomas and ganglioneuroblastomas are potential malignant lesions and ganglioneuromas are considered benign.[58] Imaging features consist of an echogenic posterior cervical mass on US and a T2 hyperintense mass with contrast enhancement on MR imaging. The overall aspect of the mass may vary from homogeneous to heterogeneous with necrosis and hemorrhage based on the degree of maturation and aggressiveness of the lesion. Meta-iodobenzylguanidine (mIBG) scintigraphy shows vigorous radiotracer uptake in neuroblastic tumors and aids in differentiating these tumors from other posterior cervical mass lesions.[59] Furthermore, catecholamines in the urine are in most cases elevated.

Lymphadenitis

Enlarged cervical lymph nodes are the most common palpable neck masses in the pediatric population as 80–90% of the children between 4 and 8 years have palpable cervical lymph nodes.[60]

The most frequent etiology in cervical lymphadenitis is a viral infection of the upper respiratory tract. The bilateral submandibular and upper internal jugular lymph nodes are typically involved. In case of bacterial infection, unilateral lymph node involvement is frequently noted.[6,60] US is the imaging method of choice to identify reactive lymphadenopathy and possible complications including suppurative inflammation or abscess formation. Reactive lymph nodes are enlarged (>1 cm short axis), ovoid, and rounded in shape and may be hypervascular on Doppler US. The vascular hilum is preserved and the vessels fan out from the hilum. Inflammatory lymph nodes are enlarged and may appear as confluent lesions. Liquefaction and suppuration causes the central part of the lymph node to become hypoechoic on US or hypodens on CT (Fig 19). Necrotic lesions may have areas of decreased vascularity.[6,61] Infected cystic anomalies of the head and neck region (eg, thyroglossal duct cysts, branchial cleft cysts, and thymopharyngeal duct cysts) can mimic suppurative lymphadenitis on US and CT.

Nontuberculous mycobacteria (NTM) is an increasing recognized cause of infection in the pediatric population. The most common causative organisms are *Mycobacterium avium* or *Mycobacterium intracellulare*. Typically, this entity manifests as persistent, and sometimes gradually enlarging, unilateral cervical lymphadenitis in immunocompetent children. There is a preference for submandibular, parotid, or preauricular lymph nodes. Signs of acute inflammation, tenderness, fever, or other systemic signs of infection are frequently lacking. The peak age of incidence is between 2 and 4 years.[62,63] Because nontuberculous mycobacterial lymphadenitis is unresponsive to conventional antibiotics, as opposed to suppurative bacterial lymphadenitis, early recognition of this specific type of adenitis leads to appropriate therapy (surgical excision) early in the course of the disease. The CT or MR imaging findings include asymmetric enlarged cervical lymph nodes and extranodal extension as contiguous necrotic ring-enhancing mass lesions involving the subcutaneous fat and skin. Inflammatory stranding of the subcutaneous fat is typically minimal or absent (unlike bacterial abscesses).[62] Bacterial lymphadenitis and cat-scratch disease in general cause painful enlarging lymph nodes. Tuberculosis demonstrates bilateral lymphadenitis in the posterior cervical triangle and is usually painless.

Abscesses are hypoechoic or anechoic lesions on US imaging with a variable thick rim of solid tissue and they may show septations. Gentle pressure applied with the US probe typically causes swirling of the contents of the abscess.[61] CT as well as MRI are useful in the evaluation in children suspected of having a deep neck abscess (Fig 19). The ACR Appropriateness Criteria prefer CT over MRI because of the short examination time and lack of need for anesthesia. The use of intravenous contrast administration is essential for detecting neck abscesses, in particular intramuscular abscesses and retropharyngeal abscesses.[9] The use of diffusion-weighted MRI sequences in the evaluation of a suspected neck abscess is of great value because of the characteristic demonstration of restricted diffusion of the content of

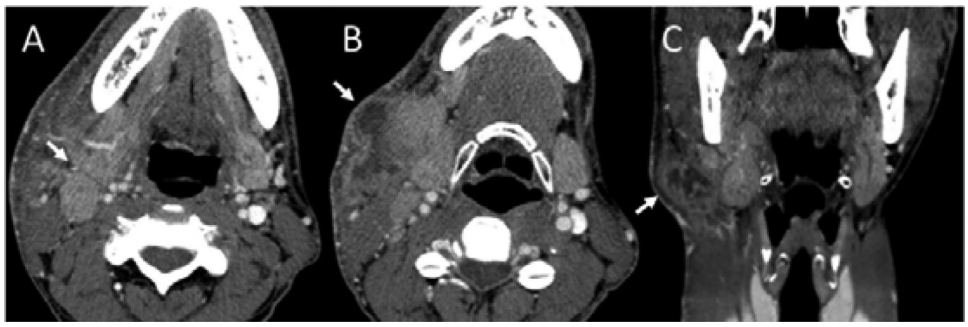

Fig 19. Axial (A, B) and coronal (C) contrast-enhanced CT images in soft tissue window of a child with cervical lymphadenitis as a consequence of a bacterial infection of the upper respiratory tract. Multiple enlarged reactive lymph nodes are demonstrated in the right upper cervical region (A). Some of the involved lymph nodes appear as confluent lesions (A). Liquefaction and suppuration causes the central part of the lymph node to become hypodens (B, C). Subsequent abscess formation is shown by extranodal extension (B, C). Note the unilateral lymph node involvement as frequently occurs in case of bacterial infection.

the abscess due to reduced water mobility within the pus.[2] Additional MRA and MRV imaging sequences may be of great value to exclude associated vascular complications, eg, venous thrombosis or development of Lemierre's syndrome.

Lymphoma

Lymphoma is the most common malignancy arising from the head and neck region in the pediatric population (55% of head and neck tumors in children). In general, lymphomas account for 10–15% of all childhood malignancies.[1,5] The lesion typically presents as a painless posterior neck mass or supraclavicular mass, often in association with lymph node enlargement in other cervical regions. The vast majority of cervical lymph node enlargement in children is the result of viral or bacterial upper respiratory tract infection. Persistent nodal enlargement (for more than 6 weeks) requires further evaluation.[5] On US (including color Doppler), features differentiating nodal malignancies from benign reactive lymph nodes include increased size (>3 cm in longest diameter), round shape, decrease in internal echogenicity, loss of normal echogenic hilum, detection of peripheral subcapsular vessels, and focal areas of absent perfusion.[1,5] Currently, disease staging of lymphoma is preferably performed with CT of the neck, chest, abdomen, and pelvis. Lymph nodes demonstrating a short axis >2 cm are considered to be involved in the disease process. For intermediate-sized lymph nodes (10-20 mm), radiotracer uptake on positron emission tomography (PET) indicates involvement.[5] MR imaging is typically used for evaluation of central nervous system involvement. However, diffusion-weighted MR imaging sequences may also play a role in differentiating involved from noninvolved lymph nodes by calculating the mean apparent diffusion coefficient (ADC) value. The ADC value of involved lymph nodes is significantly lower compared to noninvolved lymph nodes due to the high cellularity in lymphoma.[2] The future role for PET MR imaging in the staging of this disease is promising.

Hodgkin lymphoma is more common in adolescents. The classical appearance of Hodgkin lymphoma is involvement of contiguous lymph node groups. Coexistent mediastinal lymph node involvement is common. The disease is often confined to the neck and chest region (Fig 20). Staging of disease is performed according to the Cotswold modification of the Ann Arbor staging system.[5,64] The staging system differentiates single from multiple lymph node group involvement and takes into account if the lymph node groups are located on the same side or on both sides of the diaphragm, bulk size, extranodal sites of disease, and presence of clinical symptoms (B-symptoms including night sweating, weight loss, and malaise).

Non-Hodgkin lymphoma is more common than Hodgkin lymphoma in children younger than 10 years of age. Four subtypes are differentiated in the World Health Organization (WHO) classification: Burkitt lymphoma, diffuse large B-cell lymphoma, anaplastic large cell lymphoma, and lymphoblastic lymphoma. Cervical non-Hodgkin lymphoma is often accompanied by disseminated disease. Furthermore, non-Hodgkin lymphoma may involve extranodal lymphatic sites (eg, Waldeyer ring) or other extranodal sites (eg, jaw) in the cervical region. In the pediatric age group, cervical extranodal disease in non-Hodgkin lymphoma is less common than in other body parts.[5] In 2015, a new staging system for the pediatric age group has been introduced based on identification of new pathologic entities, improvements in cytogenetic, molecular, and immunophenotypic characterizations of disease and major advances in imaging applicable to childhood and adolescent non-Hodgkin lymphoma. The revised International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS) maintains the general structure of the St. Jude staging system and introduces some modifications and more explicit indications on peculiar sites of disease.[65] The staging system basically assesses tumor load and differentiates limited disease form extensive disease.

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue sarcoma in children younger than 5 years of age. Forty percent of the rhabdomyosarcomas are located in the head and neck region.[1,5,66] The lesion generally manifests in the first decade of life and demonstrates a slight male predominance. There are three principal histologic subtypes acknowledged, the embryonal, alveolar, and pleomorphic type. The embryonal subtype has in general a better prognosis, whereas alveolar rhabdomyosarcomas belong to the most aggressive types. Tumors of the embryonal subtype account for 60% of the rhabdomyosarcomas, and therefore site of origin of the tumor in the head and neck region is associated with favorable outcome. Head and neck rhabdomyosarcomas are categorized into orbital, parameningeal

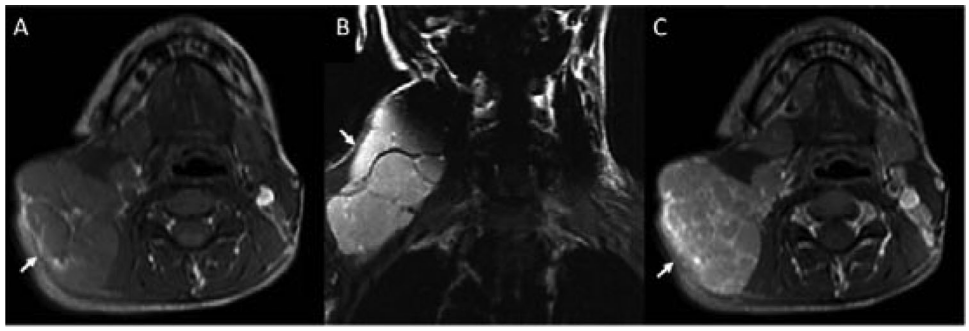

Fig 20. Axial T1-weighted (A), coronal fat-suppressed T2-weighted (B), and axial contrast-enhanced fat-suppressed T1-weighted (C) MR images of a child with a lymphoma. The images show a large mass in the right posterior cervical triangle. Multiple contiguous enlarged lymph nodes are demonstrated and show trans-spatial extension (A, C) and caudal extension of involved lymph nodes in continuum (B). The postcontrast images (C) reveal peripheral enhancement of the enlarged lymph nodes with central focal areas of absent enhancement (necrosis).

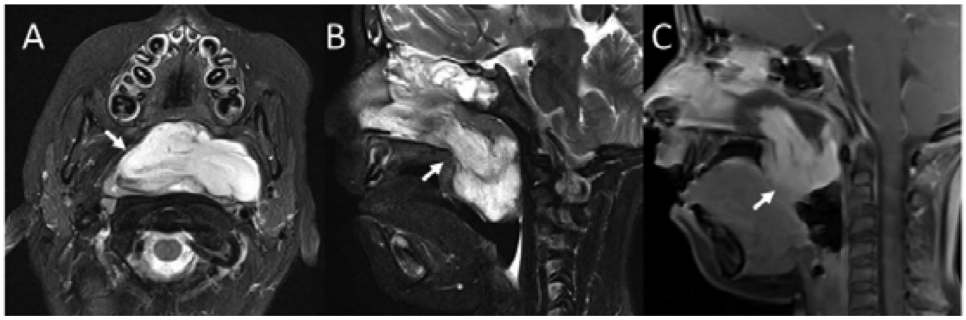

Fig 21. Axial fat-suppressed T2-weighted (A), sagittal fat-suppressed T2-weighted (B), and sagittal contrast-enhanced fat-suppressed T1-weighted (C) MR images of a child with a rhabdomyosarcoma. The axial image (A) shows a large T2 hyperintense mass primary arising from the oropharynx. The surrounding cervical spaces are predominantly displaced by the mass. The sagittal T2-weighted image (B) demonstrates the extension into the nasopharynx and ethmoid sinus. Bony involvement is seen. On the contrast-enhanced image (C), relative homogenous enhancement of the lesion with some areas of focal necrosis is seen.

(nasal cavity, paranasal sinuses, nasopharynx, pterygoid fossa, middle ear), and nonparameningeal tumor site.[4,5,67] The extension of disease is evaluated preoperatively as well as postoperatively and the staging system includes tumor size, nodal status, site of primary tumor, and extent of residual disease. MR imaging is the preferred imaging modality to assess the volume of the lesion, the site of origin, and the relationship of the mass to adjacent anatomical structures as well as potential intracranial extension. The lesion demonstrates T2 hyperintense and T1 isointense to slight hyperintense signal intensity compared to skeletal muscle. Heterogeneity of the lesion can be due to focal necrosis. There is moderate to intense enhancement on postcontrast imaging sequences (Fig 21). On diffusion-weighted MR imaging sequences, low intralesional ADC values correlate with the malignant nature of the lesion. CT may be helpful to evaluate bone involvement or destruction. The imaging staging requires chest CT, abdominal US, and bone scintigraphy to search for distant metastatic disease.[1,5,67]

Conclusion

Congenital and acquired neck masses in the pediatric population comprise a variety of diverse conditions. By definition, congenital anomalies are present at birth. Lymphadenitis accounts for the majority of acquired cervical masses in the pediatric age group, and therefore the bulk of acquired neck masses are benign lesions. Imaging plays a key role in establishing diagnosis and is essential for precise localization and characterization of the lesions. US allows an efficient assessment of neck masses in young children and is the initial imaging technique of choice. MRI provides better detailed information of the anatomic relationship and extension of these masses and can better depict the nature of solid lesions. CT scans should be used conservatively for selected, specific indications, in order to minimize ionizing radiation exposures. By taking the patient's age and clinical history into consideration, as well as the involved anatomical cervical region, the extent of the lesion, and the characteristic imaging features, accurate definite diagnosis of neck masses can be provided.

References

1. Turkington JR, Paterson A, Sweeney LE, et al. Neck masses in children. Br J Radiol 2005;78:75-85.
2. Abdel Razek AA, Gaballa G, Elhawarey G, et al. Characterization of pediatric head and neck masses with diffusion-weighted MR imaging. Eur Radiol 2009;19:201-8.
3. Gaddikeri S, Vattoth S, Gaddikeri RS, et al. Congenital cystic neck masses: embryology and imaging appearances, with clinicopathological correlation. Curr Probl Diagn Radiol 2014;43:55-67.
4. Imhof H, Czerny C, Hormann M, et al. Tumors and tumor-like lesions of the neck: from childhood to adult. Eur Radiol 2004;14(Suppl 4):L155-65.
5. Lloyd C, McHugh K. The role of radiology in head and neck tumours in children. Cancer Imaging 2010;10:49-61.
6. Rosa PA, Hirsch DL, Dierks EJ. Congenital neck masses. Oral Maxillofac Surg Clin North Am 2008;20:339-52.

7. Higgins LJ, Koshy J, Mitchell SE, et al. Time-resolved contrast-enhanced MRA (TWIST) with gadofosveset trisodium in the classification of soft-tissue vascular anomalies in the head and neck in children following updated 2014 ISSVA classification: first report on systematic evaluation of MRI and TWIST in a cohort of 47 children. Clin Radiol 2016;71:32-9.
8. Tekes A, Koshy J, Kalayci TO, et al. S.E. Mitchell Vascular Anomalies Flow Chart (SEMVAFC): a visual pathway combining clinical and imaging findings for classification of soft-tissue vascular anomalies. Clin Radiol 2014;69:443-57.
9. National Guideline C. ACR Appropriateness Criteria; neck mass/adenopathy. Date of origin 2009, Last review date 2012. Avaliable at: https://acsearch.acr.org/docs/69504/Narrative. Accessed May 15, 2016.
10. Ellis PDM, Van Nostrand AWP. The applied anatomy of thyroglossal tract remnants. Laryngoscope 1977;87:765-70.
11. Koch BL. Cystic malformations of the neck in children. Pediatr Radiol 2005;35:463-77.
12. Koeller KK, Alamo L, Adair CF, et al. Congenital cystic masses of the neck: radiologic-pathologic correlation. Radiographics 1999;19:121-46.
13. Som PM, Sacher M, Lanzieri CF, et al. Parenchymal cysts of the lower neck. Radiology 1985;157:399-406.
14. Ibrahim FF, Alnoury MK, Varma N, et al. Surgical management outcomes of recurrent thyroglossal duct cyst in children–a systematic review. Int J Pediatr Otorhinolaryngol 2015;79:863-7.
15. Deane SA, Telander RL. Surgery for thyroglossal duct and branchial cleft anomalies. Am J Surg 1978;136:348-53.
16. Rohof D, Honings J, Theunisse HJ, et al. Recurrences after thyroglossal duct cyst surgery: results in 207 consecutive cases and review of the literature. Head Neck 2015;37:1699-704.
17. Tunkel DE, Domenech EE. Radioisotope scanning of the thyroid gland prior to thyroglossal duct cyst excision. Arch Otolaryngol Head Neck Surg 1998;124:597-9; discussion 600-1.
18. Zander DA, Smoker WR. Imaging of ectopic thyroid tissue and thyroglossal duct cysts. Radiographics 2014;34:37-50.
19. Bajaj Y, Ifeacho S, Tweedie D, et al. Branchial anomalies in children. Int J Pediatr Otorhinolaryngol 2011;75:1020-3.
20. Doshi J, Anari S. Branchial cyst side predilection: fact or fiction? Ann Otol Rhinol Laryngol 2007;116:112-4.
21. Prosser JD, Myer CM, 3rd. Branchial cleft anomalies and thymic cysts. Otolaryngol Clin North Am 2015;48:1-14.
22. Fordham LA, Chung CJ, Donnelly LF. Imaging of congenital vascular and lymphatic anomalies of the head and neck. Neuroimaging Clin N Am 2000;10:117-36.
23. Solares CA, Chan J, Koltai PJ. Anatomical variations of the facial nerve in first branchial cleft anomalies. Arch Otolaryngol Head Neck Surg 2003;129:351-5.
24. Spinelli C, Rossi L, Strambi S, et al. Branchial cleft and pouch anomalies in childhood: a report of 50 surgical cases. J Endocrinol Invest 2016;39:529-35.
25. Joshi MJ, Provenzano MJ, Smith RJ, et al. The rare third branchial cleft cyst. AJNR Am J Neuroradiol 2009;30:1804-6.
26. Thomas B, Shroff M, Forte V, et al. Revisiting imaging features and the embryologic basis of third and fourth branchial anomalies. AJNR Am J Neuroradiol 2010;31:755-60.
27. Kuperan AB, Quraishi HA, Shah AJ, et al. Thymopharyngeal duct cyst: a case presentation and literature review. Laryngoscope 2010;120(Suppl 4):S226.
28. Rutter MJ. Congenital laryngeal anomalies. Braz J Otorhinolaryngol 2014;80:533-9.
29. Werner RL, Schroeder JW, Castle JT. Bilateral laryngoceles. Head Neck Pathol 2014;8:110-3.
30. Matthys MK, Long SS, Huisman TA, et al. Posterior fossa dermoid cyst with a sinus tract and restricted diffusion on MR imaging: value of structural imaging findings and signal characteristics. J Neuroradiol 2012;39:134-5.
31. Gordon PE, Faquin WC, Lahey E, et al. Floor-of-mouth dermoid cysts: report of 3 variants and a suggested change in terminology. J Oral Maxillofac Surg 2013;71:1034-41.
32. Paradis J, Koltai PJ. Pediatric teratoma and dermoid cysts. Otolaryngol Clin North Am 2015;48:121-36.
33. Alexander VR, Manjaly JG, Pepper CM, et al. Head and neck teratomas in children–a series of 23 cases at Great Ormond Street Hospital. Int J Pediatr Otorhinolaryngol 2015;79:2008-14.
34. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982;69:412-22.
35. Griauzde J, Srinivasan A. Imaging of vascular lesions of the head and neck. Radiol Clin North Am 2015;53:197-213.
36. Bhat V, Salins PC, Bhat V. Imaging spectrum of hemangioma and vascular malformations of the head and neck in children and adolescents. J Clin Imaging Sci 2014;4:31.
37. Flors L, Leiva-Salinas C, Maged IM, et al. MR imaging of soft-tissue vascular malformations: diagnosis, classification, and therapy follow-up. Radiographics 2011;31:1321-40.
38. Morton RP, Ahmad Z, Jain P. Plunging ranula: congenital or acquired? Otolaryngol Head Neck Surg 2010;142:104-7.
39. Zhao YF, Jia Y, Chen XM, et al. Clinical review of 580 ranulas. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;98:281-7.
40. Edwards RM, Chapman T, Horn DL, et al. Imaging of pediatric floor of mouth lesions. Pediatr Radiol 2013;43:523-35.
41. La'porte SJ, Juttla JK, Lingam RK. Imaging the floor of the mouth and the sublingual space. Radiographics 2011;31:1215-30.
42. Verret DJ, DeFatta RJ, Sinard R. Combined laryngocele. Ann Otol Rhinol Laryngol 2004;113:594-6.
43. Murphey MD, Ruble CM, Tyszko SM, et al. From the archives of the AFIP: musculoskeletal fibromatoses: radiologic-pathologic correlation. Radiographics 2009;29:2143-73.
44. Skelton E, Howlett D. Fibromatosis colli: the sternocleidomastoid pseudotumour of infancy. J Paediatr Child Health 2014;50:833-5.
45. Rosenberg HK. Sonography of pediatric neck masses. Ultrasound Q 2009;25:111-27.
46. Wienke JR, Chong WK, Fielding JR, et al. Sonographic features of benign thyroid nodules: interobserver reliability and overlap with malignancy. J Ultrasound Med 2003;22:1027-31.
47. Chaukar DA, Rangarajan V, Nair N, et al. Pediatric thyroid cancer. J Surg Oncol 2005;92:130-3.
48. Xie C, Cox P, Taylor N, et al. Ultrasonography of thyroid nodules: a pictorial review. Insights Imaging 2016;7:77-86.
49. Nobrega LH, Paiva FJ, Nobrega ML, et al. Predicting malignant involvement in a thyroid nodule: role of ultrasonography. Endocr Pract 2007;13:219-24.
50. Sodhi KS, Bartlett M, Prabhu NK. Role of high resolution ultrasound in parotid lesions in children. Int J Pediatr Otorhinolaryngol 2011;75:1353-8.
51. Gadodia A, Seith A, Sharma R, et al. MRI and MR sialography of juvenile recurrent parotitis. Pediatr Radiol 2010;40:1405-10.
52. Roby BB, Mattingly J, Jensen EL, et al. Treatment of juvenile recurrent parotitis of childhood: an analysis of effectiveness. JAMA Otolaryngol Head Neck Surg 2015;141:126-9.
53. Huisman TA, Holzmann D, Nadal D. MRI of chronic recurrent parotitis in childhood. J Comput Assist Tomogr 2001;25:269-73.
54. Boyd ZT, Goud AR, Lowe LH, et al. Pediatric salivary gland imaging. Pediatr Radiol 2009;39:710-22.
55. Bentz BG, Hughes CA, Ludemann JP, et al. Masses of the salivary gland region in children. Arch Otolaryngol Head Neck Surg 2000;126:1435-9.
56. Mamlouk MD, Rosbe KW, Glastonbury CM. Paediatric parotid neoplasms: a 10 year retrospective imaging and pathology review of these rare tumours. Clin Radiol 2015;70:270-7.
57. Lerosey Y, Choussy O, Gruyer X, et al. Infiltrating lipoma of the head and neck: a report of one pediatric case. Int J Pediatr Otorhinolaryngol 1999;47:91-5.
58. Lonergan GJ, Schwab CM, Suarez ES, et al. Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma: radiologic-pathologic correlation. Radiographics 2002;22:911-34.
59. Fendler WP, Melzer HI, Walz C, et al. High (1)(2)(3)I-MIBG uptake in neuroblastic tumours indicates unfavourable histopathology. Eur J Nucl Med Mol Imaging 2013;40:1701-10.

60. Rosenberg TL, Nolder AR. Pediatric cervical lymphadenopathy. Otolaryngol Clin North Am 2014;47:721-31.
61. Williams H. Paediatric neck lumps i - inflammatory and neoplastic lesions including salivary gland abnormalities. Ultrasound 2007;15:124-35.
62. Robson CD, Hazra R, Barnes PD, et al. Nontuberculous mycobacterial infection of the head and neck in immunocompetent children: CT and MR findings. AJNR Am J Neuroradiol 1999;20: 1829-35.
63. Tebruegge M, Pantazidou A, MacGregor D, et al. Nontuberculous mycobacterial disease in children - epidemiology, diagnosis & management at a tertiary center. PLoS One 2016;11:e0147513.
64. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7: 1630-6.
65. Rosolen A, Perkins SL, Pinkerton CR, et al. Revised international pediatric non-Hodgkin lymphoma staging system. J Clin Oncol 2015;33:2112-8.
66. Wang C. Childhood rhabdomyosarcoma: recent advances and prospective views. J Dent Res 2012;91:341-50.
67. Reilly BK, Kim A, Pena MT, et al. Rhabdomyosarcoma of the head and neck in children: review and update. Int J Pediatr Otorhinolaryngol 2015;79:1477-83.

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Utility of Fine-Needle Aspiration Biopsy in the Evaluation of Pediatric Head and Neck Masses

Phillip Huyett, MD[1], Sara E. Monaco, MD[2], Sukgi S. Choi, MD[3], and Jeffrey P. Simons, MD[3]

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Abstract

Objectives. Fine-needle aspiration biopsy (FNAB) has a well-established role in the evaluation of an adult head and neck mass (HNM) but remains underused in children. The objectives of this study were to assess the diagnostic accuracy, safety profile, use of anesthesia, and influence on surgical decision making of FNAB of HNM in the pediatric population.

Study Design. Case series with chart review.

Setting. Tertiary care children's hospital.

Subjects and Methods. In total, 257 consecutive patients with HNM who underwent 338 FNABs from July 2007 to July 2014 were reviewed. Patients ranged in age from 0 to 21 years (mean, 9.3 years); lesions ranged in size from 0.3 to 12.5 cm (mean, 2.4cm). Fine-needle aspiration biopsies were performed in the interventional radiology suite, operating room, clinic, or ward.

Results. The most common patient final diagnoses included reactive lymphadenopathy (n = 99, 38.5%), benign thyroid colloid nodule (n = 31, 12.1%), malignancies (n = 21, 8.2%), and atypical mycobacterial infection (n = 15, 5.8%). On surgical histopathologic and clinical follow-up, overall sensitivity of FNAB was 94.6% and specificity was 97.7%. The complication rate was 2.1%, and general anesthesia or sedation was used for 73% of FNAB. Surgery occurred only 9 times following the 191 patients with negative FNAB results, indicating that 95.3% of unnecessary surgeries were avoided with the assistance of the FNAB result.

Conclusions. Fine-needle aspiration biopsy is an accurate and safe diagnostic tool for guiding management of persistent lymphadenopathy, thyroid nodules, and other HNM in pediatric patients. Negative FNABs can often obviate the need for surgical intervention.

Keywords

fine-needle aspiration biopsy, head and neck mass, thyroid nodule, pediatrics, sensitivity and specificity

Fine-needle aspiration biopsy (FNAB) dates back as far as 1857 and has been established in the diagnosis of head and neck masses (HNMs) since the late 1920s.[1] In the adult population, FNAB is widely used and accurate for diagnosis of both benign and malignant lesions throughout the head and neck region.[2,3] For example, FNAB has been used with great success as the primary screening test for thyroid nodules in adults,[4] but such a structured approach has lagged in the evaluation of pediatric thyroid nodules.[5,6]

This diagnostic modality has gradually become more accepted in the pediatric population but remains underused. The first studies examining pediatric FNAB were published in the 1980s,[7-9] and the first report dedicated to pediatric HNM FNAB was published in 1991 by Mobley et al.[10] Since that time, several publications have related the safety, accuracy, and feasibility of FNAB in pediatric HNM[11-16] but have been limited by case numbers or restricted anatomic subsites.

The potential avoidance of surgery with associated scarring, complications, general anesthetic risk, recovery time, and expense have all been heralded as benefits of FNAB, especially given the high prevalence of nonneoplastic pediatric HNM. The objectives of this study were to assess the diagnostic accuracy and safety profile of FNAB in a large number of thyroid and nonthyroid pediatric HNMs. In addition, we examined the clinical application of FNAB, including the use of

[1]Department of Otolaryngology–Head and Neck Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
[2]Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
[3]Department of Otolaryngology, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Corresponding Author:
Phillip Huyett, MD, Department of Otolaryngology–Head & Neck Surgery, University of Pittsburgh Medical Center, 203 Lothrop St, Suite 500, Pittsburgh, PA 15213, USA.
Email: huyettpa@upmc.edu

general anesthesia and the influence of FNAB on surgical decision making.

Methods

Institutional review board approval was obtained from the University of Pittsburgh. Patients aged 0 to 21 years were retrospectively identified in a cytopathology database for having undergone FNAB of a HNM. Consecutive subjects from July 2007 to July 2014 were included, and there were no exclusion criteria. All patients were seen in the pediatric otolaryngology or endocrinology departments where the need for FNAB was determined and consent was obtained for the procedure.

The decision to proceed with nonthyroid FNAB was typically based on persistence of a neck mass beyond 4 weeks despite treatment with antibiotics. Cases atypical for benign lymphadenopathy were referred for FNAB sooner (eg, unusual location, rapid enlargement, weight loss, night sweats, skin changes, fixed/immobile mass). All nonthyroid FNABs were performed because the patient was considered a potential surgical candidate, the mass was atypical, and/or the family or medical team desired a pathologic diagnosis. Given the high rate of malignancy in pediatric thyroid nodules, patients with lesions greater than 1 cm or smaller with concerning ultrasonographic features (hypoechogenicity, irregular margins, or increased vascularity) were offered FNAB.

Fine-needle aspiration biopsies were subsequently performed in the otolaryngology clinic or inpatient ward by the cytopathologist, the interventional radiology suite (IR) by a radiologist, or the operating room (OR) by the surgeon or cytopathologist. Topical (4% lidocaine cream), general, or topical plus sedative anesthesia was used. As a standard practice at our institution, all biopsies performed in the IR suite used image guidance, and all others were performed by palpation. Most thyroid nodules were biopsied with ultrasound guidance, consistent with current recommendations.[6]

A 25- to 27-gauge needle was used, and approximately 3 to 5 passes were performed for each targeted site, representing a single FNAB. Patients with multiple FNABs therefore had more than 1 targeted HNM, multiple encounters, or both. Aspirated material was used for smear preparation, including air-dried slides stained with Diff-Quik and alcohol-fixed slides stained with the Papanicolaou stain. Residual material was submitted for ThinPrep (Hologic Inc, Marlborough, Massachusetts) processing, microbial cultures, molecular studies, flow cytometry, and/or cell block preparation, depending on the immediate interpretation. Cell block sections were stained with hematoxylin and eosin stain, and additional levels were used for immunostains, special stains, or other ancillary testing. The FNABs were interpreted by 1 of 9 cytopathologists, although most (88%) were interpreted by 1 of 2 cytopathologists with pediatric expertise. Nonthyroid cases received diagnoses with an adequacy interpretation (unsatisfactory, less than optimal, or satisfactory), a primary interpretation (nondiagnostic, negative for malignant cells, atypical cells present, suspicious for malignant cells, or positive for malignant cells), and a free text explanatory diagnosis. Thyroid cases received an adequacy interpretation, a primary interpretation using The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC),[4] and a free text explanatory diagnosis.

The determination of a nonsurgical (negative) vs surgical (positive) FNAB result was made for each patient. Final outcomes were then established either through correlation to surgical histopathology or clinical follow-up. Histopathology based on surgical biopsy (incisional or excisional) is considered the reference standard in the diagnosis of an HNM. Clinical follow-up is included as a secondary reference given that most pediatric HNMs are benign and do not undergo surgery and therefore histopathologic evaluation.

True positives were cytopathologic results that warranted surgical treatment and were confirmed as such histopathologically. True negatives were cytopathologic results that did not indicate a need for surgery and were confirmed histopathologically as such. Clinical true negatives were cytopathologically negative conditions that resolved or did not progress without surgical intervention. False positives were cytopathologic results that indicated a need for surgical treatment but histopathology demonstrated a nonsurgical condition. False negatives were cytopathologic results that did not indicate a need for surgery but were histopathologically proven to be conditions where surgery was indicated. Pathologists interpreting surgical histopathology were distinct from our cytopathologists and neither was blinded to clinical information or pathology results.

Certain conditions, such as atypical mycobacterial infection, cervicofacial abscess, lymphovenous malformations, and lymphoma, may warrant surgical diagnosis or treatment but may also appropriately proceed directly to medically therapy. These cases were all considered positive on the basis that surgery could be indicated. If surgery was pursued and histopathology confirmed the cytopathologic result, the case was a true positive. If the appropriate medical therapy was initiated and was effective, the result was a clinical true positive.

Individual diagnoses and demographic data such as age at first encounter and sex are presented on a patient level. Features unique to each encounter such as complications, FNAB venue, and level of anesthesia are presented on an encounter level. Specificity, sensitivity, and nondiagnostic results are presented on an FNAB level.

SPSS version 21 (SPSS, Inc, an IBM Company, Chicago, Illinois) was used to analyze the data. Sensitivity, specificity, and positive and negative predictive values were calculated using the definitions as detailed above. Nondiagnostic results were not included in these statistics, and no missing data were encountered. A P value $<.05$ was considered significant. Age at first encounter was compared between the high and low level of anesthesia and thyroid/nonthyroid groups using an independent sample t test. Age was compared between the thyroid/nonthyroid groups using Pearson's χ^2 test. Generalized estimating equations were used to compare the number of nondiagnostic results

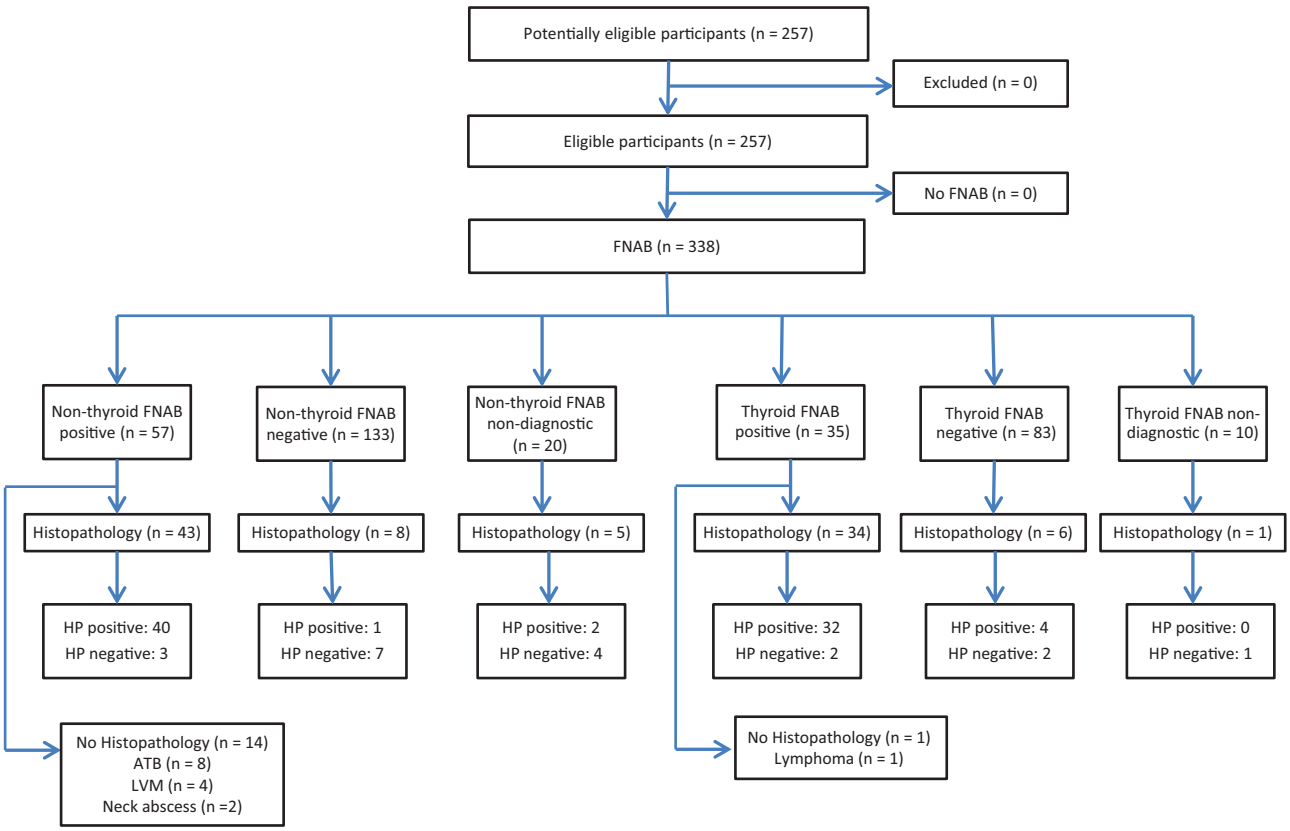

Figure 1. STARD flowchart of enrolled patients and FNAB. ATB, atypical tuberculosis; FNAB, fine-needle aspiration biopsy; HP, histopathology; LVM, lymphovenous malformation.

between the level of anesthesia groups. This method was used to account for the dependency of FNAB across encounters within patients.[17] The 2015 Standards for Reporting of Diagnostic Accuracy (STARD) guideline for reporting diagnostic accuracy studies was used.[18]

Results

Over the 7-year study period, 257 patients who underwent at least 1 FNAB were identified. By having multiple FNABs at 1 or multiple visits, there were 338 total FNABs, with 284 specific encounters (**Figure 1**). Baseline characteristics of the patients are shown in **Table 1**. The 169 patients in the nonthyroid group were younger (mean age, 7.1 vs 13.6 years, $P < .001$) and had a lower percentage of females (38.5% vs 77.3%, $P < .001$) than the 88 patients in the thyroid group. The mean (SD) size of the 189 masses with prebiopsy imaging was 2.4 (1.73) cm (range, 0.3-12.5 cm). The average time between FNAB and surgery was 73 days (range, 0-1183 days). The volume of FNABs performed per month steadily increased from 3.2 in 2007 to 7.2 in 2014 with no seasonal variation.

Diagnostic Accuracy

The overall pathologically confirmed sensitivity and specificity were 93.5% and 64.3%, respectively (**Table 2**). If clinically and pathologically confirmed results are combined, sensitivity was 94.6% and specificity was 97.7% (**Table 2**). When rapid on-site interpretation yielded a preliminary diagnosis, it correlated with final cytopathology 99.1% of the time (n = 106) and final surgical histopathology 93.3% of the time (n = 30). The false positives and false negatives are presented in **Table 3**.

The clinical nonthyroid HNM sensitivity and specificity were 98.2% and 97.7%, respectively, representing 190 total FNABs (**Table 2**). There were an additional 20 nondiagnostic specimens (9.5%). **Table 4** presents the final diagnoses, the most common of which was benign reactive lymphadenopathy (BLN), present in 99 patients. Malignancy was detected in 6 of the 169 patients (3.6%), including a metastatic medullary thyroid carcinoma that was not confirmed by thyroid FNAB prior to thyroidectomy.

There were 118 thyroid FNABs, with a clinical sensitivity of 88.6% and specificity of 97.6% (**Table 2**). There were 10 nondiagnostic results (7.8%). The most common diagnosis was benign colloid nodule, found in 31 children. Fifteen malignancies were detected in the 88 patients undergoing thyroid FNABs (17.0%), most commonly papillary thyroid carcinoma. The rates of malignancy by are presented TBSRTC[4] category in **Table 5** with comparisons to a large pediatric thyroid FNAB series.[19]

The overall FNAB nondiagnostic rate was 8.9% (n = 30). All 10 of the thyroid nondiagnostic results were performed with image guidance and under general anesthesia (GA) or sedation. Of the 20 nonthyroid nondiagnostic results, there

Table 1. Characteristic of Patients and FNABs.

Characteristic	No. (%)
Sex by patient (n = 257)	
Male	124 (48)
Female	133 (52)
Age (y) of patient at first encounter (n = 257)	
0-4	70 (27.2)
5-8	47 (18.3)
9-12	42 (16.3)
13-16	72 (28)
17-21	26 (10.1)
Location by encounter (n = 284)	
Clinic	66 (23.2)
OR	80 (28.2)
IR (US guided)	132 (46.5)
Ward	6 (2.1)
Anatomic site by FNAB (n = 338)	
Neck	136 (40.2)
Thyroid	128 (37.9)
Preauricular/parotid	36 (10.7)
Postauricular	32 (9.5)

Abbreviations: FNAB, fine-needle aspiration biopsy; IR, interventional radiology; OR, operating room; US, ultrasound.

was no difference in the number of nondiagnostic results by anesthesia group (8 in topical/no-anesthesia group vs 12 in GA/sedation, $P = .416$), but only 5 of these 20 used image guidance.

Safety Profile

The overall complication rate was 2.1%. All 6 of the complications occurred in nonthyroid HNM patients undergoing FNAB in the clinic with topical anesthesia only. Vasovagal response was seen in 2 patients after successful FNAB. Both patients were discharged home in good condition from the otolaryngology clinic. Two patients (aged 5 and 9 years) could not have all FNAB passes completed due to discomfort. One procedure was terminated due to equipment failure. One lesion was too small to be successfully targeted and has been followed clinically. Mild FNAB site ecchymosis was not considered a complication but rather an expected occurrence. In comparison, there was a 9.1% complication rate in the 77 surgeries performed, including hypertrophic scar/alopecia, neck abscess, neck seroma, incomplete resection, inadvertent pharyngotomy, and Horner's syndrome.

General Anesthesia

Of the FNABs, 73% were performed with GA or sedation. Overall, there was no statistically significant difference in the age of those requiring GA vs topical anesthesia alone (9.3 ± 5.5 vs 9.5 ± 5.6 years old, $P = .410$), but this finding is skewed by the use of GA for all but 3 thyroid FNABs. Excluding the thyroid and concurrent thyroid-lymph node FNAB, 66 (39%) FNAB encounters were performed with topical or no anesthesia and 105 (61%) with GA or sedation, and a younger average age was found in the heightened GA/sedation group (6.3 ± 4.8 vs 8.5 ± 5.4 years, $P = .006$).

Surgical Decision Making

Seventy-seven patients (27.0%) underwent surgery after an FNAB encounter, with 11.7% (n = 9) of these procedures following negative FNAB results. When combined with the nonsurgical cases, 9 of the 191 patients (4.7%) had a surgical intervention following FNAB results that did not indicate a need for surgery. Therefore, FNAB results assisted in the decision making to avoid surgery in 95.3% of patients in whom it was not considered appropriate.

Discussion

Pediatric HNMs are a commonly encountered finding with a broad differential diagnosis confronting pediatricians and otolaryngologists alike. The diagnostic challenge is distinct from the adult HNM in that only 4% to 11% of pediatric neck masses are found to be malignant, whereas in adults, this figure is over 60%.[20-24] Our overall incidence of malignancy in nonthyroid FNAB was 3.6%. This does, however, likely represent an overestimate of the true incidence of pediatric nonthyroid HNM malignancy, as typically only persistent or otherwise worrisome masses undergo FNAB or surgical excision, especially at a tertiary referral hospital. Furthermore, congenital lesions such as branchial cleft anomalies and lymphatic malformations tend to not undergo FNAB given characteristic physical exam and imaging findings.

The opposite scenario is seen in pediatric thyroid nodules—namely, they are far less common than in adults but more commonly malignant. Recent studies suggest that 16% to 26% (17% in this study) of pediatric thyroid nodules are malignant, which compares to 5% in adults.[6,25-27] Therefore, to ensure adequate sampling as well as increase patient comfort while undergoing a deeper FNAB, virtually all thyroid FNABs at our institution are performed under GA in the IR suite with ultrasound guidance.

Diagnostic Accuracy

Sensitivity reported in our study and others is dependent on surgical histopathologic results to validate true positives and false negatives. The overall sensitivity in this study (93.5%) is similar to previous studies, which have shown rates of 93.3% to 100%, indicating reliability in both small and large series as well as all head and neck locations.[10,14,15] Specificity, however, is more limited by the fact that most ''benign'' or negative FNAB results will not undergo surgery. Our pathologically confirmed specificity was 64.3% but represents only 14 cases. Working under the assumption that patients who have clinical resolution or nonprogression of disease confirms a negative FNAB, our specificity was 97.7%. Slightly higher overall sensitivity and specificity were seen in nonthyroid FNABs (**Table 2**), which is also seen in the adult population.[3]

Table 2. Sensitivity, Specificity, and Positive and Negative Predictive Values.

Characteristic	HP+, No.	HP–, No.	PPV/NPV, %	Sensitivity/Specificity, %
All, histopathologically proven only			93.5/64.3	93.5/64.3
FNAB positive	72	5		
FNAB negative	5	9		
Characteristic	HP and Clinically Positive, No.	HP and Clinically Negative, No.	PPV/NPV, %	Sensitivity/ Specificity, %
All, histopathological plus clinical follow-up			94.6/97.7	94.6/97.7
FNAB positive	87	5		
FNAB negative	5	211		
Nonthyroid			94.9/99.2	98.2/97.7
FNAB positive	56	3		
FNAB negative	1	130		
Thyroid			93.9/95.3	88.6/97.6
FNAB positive	31	2		
FNAB negative	4	81		

Abbreviations: FNAB, fine-needle aspiration biopsy; HP, histopathologically; NPV, negative predictive value; PPV, positive predictive value.

Table 3. False-Positive and False-Negative FNAB with Final Histopathologic Result, Explanation of Error, and/or Patient Outcome.

Error	FNAB	Histopathology	Outcome
False negative	BCN (×2)	Encapsulated follicular PTC	Sampling error (6.8 cm)[31]; surgery without delay, no complications
False negative	BCN	Follicular adenoma + papillary hyperplasia	Resolved with surgery, no complications
False negative	BLN	Hyaline variant of Castleman's disease	39 months between initial FNAB and surgery; resolved with surgery, no complications
False negative	Suspicious for PTC	FTC	Both are TBSRTC suspicious for malignancy[4]; surgery without delay, no complications
False positive	Suspicious for PTC	Nodular hyperplasia with 2 dominant nodules	Resolved with surgery, no complications
False positive	Heterogeneous lymphoid population with atypia	BLN	Resolved with surgery, no complications
False positive	Suspicious for lymphoproliferative disorder	Reactive primary follicular hyperplasia	Resolved with surgery, no complications
False positive	Follicular lesion or neoplasm	Hyperplastic colloid nodule	70%-85% of SFONs are expected to be benign[4]; resolved with surgery, no complications
False positive	Low-grade mucoepidermoid carcinoma	Kuttner tumor	Resolved with surgery, no complications

Abbreviations: BCN, benign colloid nodule; BLN, benign lymphadenopathy; FNAB, fine-needle aspiration biopsy; FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma; SFON, follicular neoplasm or suspicious for follicular neoplasm; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology.

The overall sensitivity and specificity of the thyroid FNAB was 88.6% and 97.6%, respectively, which is consistent with reports within both the general and pediatric populations.[19,28-30] The applicability of The Bethesda System (TBSRTC) to the pediatric population has been previously examined in the literature and is a recommendation of the 2015 American Thyroid Association (ATA) Guidelines for Pediatric Thyroid Nodules and Cancer.[6,19] We found the 128 thyroid FNABs to have excellent concordance with the rates of malignancy as described by TBSRTC[4] (**Table 5**). Similar to Lale et al,[19] there was an increased rate of malignancies in the indeterminate TBSRTC categories (III, IV, and V).

Table 4. Partial List of Patient Final Diagnoses.

	Nonthyroid (169 Patients, 210 FNABs)	Thyroid (88 Patients, 128 FNABs)
Malignant Neoplasms	T-cell lymphoblastic lymphoma	Papillary thyroid carcinoma (13)
	Diffuse large B-cell lymphoma	Medullary thyroid carcinoma
	Ganglioneuroblastoma	Follicular thyroid carcinoma
	Ewing's sarcoma	Burkitt's lymphoma
	Low-grade mucoepidermoid carcinoma (parotid)	
Benign Neoplasms	Pleomorphic adenoma (3)	Oncocytic adenoma (1)
	Lipoma (2)	Follicular adenoma (4)
	Lymphatic malformations (6)	
	Myofibroma	
	Pilomatrixoma	
	Desmoplastic fibroma	
Benign Lesions	Benign reactive lymphadenopathy (99)	Benign colloid nodule (31)
	Atypical tuberculosis (15)	Chronic lymphocytic thyroiditis (11)
	Branchial cleft cyst	Hyperplastic nodule (8)
	Cat scratch disease	Thyroid cyst (9)
	Castleman's disease	Multinodular goiter (2)
	Cervicofacial actinomyces	
	Kuttner tumor	
	Langerhans histiocytosis	
	Thymic cyst (2)	

Abbreviation: FNAB, fine-needle aspiration biopsy.

Table 5. Risk of Thyroid Malignancy as cited by TBSRTC,[4] Lale et al,[19] and This Study.[a]

		This Study		Lale et al.[19]	
TBSRTC Category	TBSRTC Risk of Malignancy, %	Rate of Malignancy, %	FNAB, No.	Rate of Malignancy, %	FNAB, No.
Nondiagnostic	1-4	0.0	9	0-25	59
Benign	0-3	2.6	77	0	136
FLUS	5-15	15.8	19	50	6
Follicular neoplasm	15-30	41.7	12	47.36	40
Suspicious for malignancy	60-75	80.0	5	100	6
Malignant	97-99	100.0	6	100	35

Abbreviations: FLUS, follicular lesion of undetermined significance; FNAB, fine-needle aspiration; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology.
[a]Rate of thyroid malignancy and number of FNABs are presented for each Bethesda System category. Rates according to TBSRTC and Lale et al[19] are presented for reference.

In addition to being highly accurate, FNAB offers the potential for a more rapid diagnosis when the cytopathologist can make an on-site judgment. Our study found that in the 106 instances when an initial diagnosis was offered, it correlated with final cytopathology 99.1% of the time—an improvement from 92% in the predecessor study from our institution.[14] Rapid on-site diagnosis correlated with 93.3% of histopathologic results. The ability to offer an accurate on-site diagnosis is not only helpful in treatment planning but also in alleviating patient and family anxiety.

The rate of nondiagnostic FNAB results is seemingly high (n = 30, 8.9%) but was found to be lower than in a large meta-analysis of adult HNM.[3] Current management of such a result consists of clinical follow-up with possible repeat FNAB or surgical excision. With these and all other results, it is critical to remember that neither the sensitivity nor the specificity of FNAB is 100%, and FNAB results must be taken in the context of clinical factors.

General Anesthesia

General anesthesia or sedation was used in a significant portion of the children in this study, thus nullifying one of main benefits of FNAB. Most of these cases were thyroid evaluations, where GA is employed routinely by policy at our institution. While a younger average age was seen in the nonthyroid patients undergoing FNAB with sedation or

GA (6.3 vs 8.5 years, P = .006), our experience was that many children of all ages were able to successfully undergo FNAB in the clinic with topical anesthesia alone. We therefore feel that general anesthesia is unnecessarily overused and that there is even the opportunity to perform thyroid FNAB with ultrasound guidance in an awake child or adolescent, as is common practice in adults. Nevertheless, parental preference, coordination with other procedures, or a perceived inability to tolerate an awake FNAB can drive the desire for a higher level of anesthesia in the OR or IR suite.

Surgical Decision Making

If the fundamental goal of FNAB is to provide a diagnosis that will influence management, there is a significant gain to be made in avoiding unnecessary surgery and associated complications in children with benign or nonsurgical conditions. Over the course of the 7-year study, surgery occurred only 9 times following the 191 negative FNAB results. Stated alternatively, negative FNAB results assisted in avoiding unnecessary surgery in 95.3% of patients in whom it was not indicated. In these 9 cases, the decision to proceed with surgery was guided by parental concern or the clinical judgment of the treating physician. Final histopathology concurred with the initial FNAB cytopathology in all 9 of these cases. Six of the cases occurred in the first 4 years of the study, whereas only 3 were in the last 3 years, indicating a possible increased clinician (and conceivably parental) confidence in FNAB results.

Aside from the avoided morbidity and mortality of surgery, the cost savings are potentially significant. For example, our institution charges $320.00 for an FNAB and $1203.00 for a simple excisional lymph node biopsy, excluding the cost of anesthesia ($550.00/hour), OR time ($740/hour), and a hospital room ($1017.10/day). The cost differences are obviously more pronounced when the surgery being considered is a total thyroidectomy or superficial parotidectomy.

Limitations

This study has several limitations that are inherent in its retrospective nature. First, the lack of standardization of the enrolled patients is reflective of both the diversity of pediatric HNM and the variable diagnostic and treatment approaches by different physicians. For example, in the routine lateral neck mass consistent with BLN, there was significant variation in the use, duration, and timing of antibiotic treatment, making uniform indications for FNAB challenging in the retrospective study. In these instances, FNAB was only offered once the child was deemed a potential surgical candidate, had an atypical presentation, or had an unclear diagnosis. Another limitation to this study is the lack of universal follow-up. All patients with negative FNAB results are instructed to follow up if the HNM persists or concerns remain. If no follow-up in our system was pursued, the child was assumed to have resolution and was counted as a clinical true negative. Even still, if these cases are excluded from the analysis, the overall specificity of FNAB is 96.2%. Despite these limitations, this study was able to demonstrate that FNAB in children is highly accurate and safe in a wide range of head and neck anatomic locations, diagnoses, and ages.

Conclusion

Fine-needle aspiration biopsy is a safe, well-tolerated, and accurate means of diagnosing pediatric HNM of thyroid and nonthyroid origin. Given that few nonthyroid pediatric HNMs are malignant, FNAB plays an important role in providing reassurance to obviate the need for unnecessary surgery in benign HNM. Pediatric thyroid malignancies, on the other hand, are not infrequent, and TBSRTC should be applied to the pediatric population with the caveat that a higher degree of suspicion should be present when FNAB result is indeterminate. When this triage or stratification of pediatric HNM is employed, it potentially reduces both surgical morbidity and the burden on health care resources.

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Author Contributions

Phillip Huyett, study design, data acquisition, analysis and interpretation, manuscript drafting, final manuscript approval; **Sara E. Monaco**, study design, data acquisition and interpretation, manuscript drafting and revisions, final manuscript approval; **Sukgi S. Choi**, data interpretation, manuscript drafting and revisions, final manuscript approval; **Jeffrey P. Simons**, study design, data interpretation, manuscript drafting and revisions, final manuscript approval.

Disclosures

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References

1. Rosa M. Fine-needle aspiration biopsy: a historical overview. *Diagn Cytopathol*. 2008;36:773-775.
2. Amedee RG, Dhurandhar NR. Fine-needle aspiration biopsy. *Laryngoscope*. 2001;111:1551-1557.
3. Tandon S, Shahab R, Benton JI, Ghosh SK, Sheard J, Jones TM. Fine-needle aspiration cytology in a regional head and neck cancer center: comparison with a systematic review and meta-analysis. *Head Neck*. 2008;30:1246-1252.
4. Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference. The Bethesda System for reporting thyroid cytopathology. *Am J Clin Pathol*. 2009;132:658-665.
5. The Canadian Pediatric Thyroid Nodule Study: an evaluation of current management practices. *J Pediatr Surg*. 2008;43:826-830.
6. Francis GL, Waguespack SG, Bauer AJ, et al. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2015;25:716-759.
7. Schaller RT Jr, Schaller JF, Buschmann C, Kiviat N. The usefulness of percutaneous fine-needle aspiration biopsy in infants and children. *J Pediatr Surg*. 1983;18:398-405.

8. Taylor SR, Nunez C. Fine-needle aspiration biopsy in a pediatric population: report of 64 consecutive cases. *Cancer*. 1984; 54:1449-1453.
9. Cohen MB, Bottles K, Ablin AR, Miller TR. The use of fine-needle aspiration biopsy in children. *West J Med*. 1989;150: 665-667.
10. Mobley DL, Wakely PE, Frable MA. Fine-needle aspiration biopsy: application to pediatric head and neck masses. *Laryngoscope*. 1991;101:469-472.
11. Tunkel DE, Baroody FM, Sherman ME. Fine-needle aspiration biopsy of cervicofacial masses in children. *Arch Otolaryngol Head Neck Surg*. 1995;121:533-536.
12. Ramadan HH, Wax MK, Boyd CB. Fine-needle aspiration of head and neck masses in children. *Am J Otolaryngol*. 1997;15: 400-404.
13. Liu ES, Bernstein JM, Sculerati N, Wu HC. Fine needle aspiration biopsy of pediatric head and neck masses. *Int J Pediatr Otorhinolaryngol*. 2001;50:135-140.
14. Anne S, Teot LA, Mandell DL. Fine needle aspiration biopsy: role in diagnosis of pediatric head and neck masses. *Int J Pediatr Otorhinolaryngol*. 2008;72:1547-1553.
15. Alam K, Khan R, Jain A, et al. The value of fine-needle aspiration cytology in the evaluation of pediatric head and neck tumors. *Int J Pediatr Otorhinolaryngol*. 2009;73:923-927.
16. Lee DH, Baek HJ, Kook H, Yoon TM, Lee JK, Lim SC. Clinical value of fine needle aspiration cytology in pediatric cervical lymphadenopathy patients under 12-years-of-age. *Int J Pediatr Otorhinolaryngol*. 2014;78:79-81.
17. Hardin JW. Generalized estimating equations (GEE). In: *Encyclopedia of Statistics in Behavioral Science*. New York, NY: John Wiley; 2005.
18. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;351:h5527.
19. Lale SA, Morgenstern NN, Chiara S, Wasserman P. Fine needle aspiration of thyroid nodules in the pediatric population: a 12-year cyto-histological correlation experience at North Shore-Long Island Jewish Health System. *Diagn Cytopathol*. 2015;43:598-604.
20. Brigger MT, Cunningham MJ. Malignant cervical masses in children. *Otolaryngol Clin North Am*. 2015;48:59-77.
21. Buchino JJ, Jones VF. Fine needle aspiration in the evaluation of children with lymphadenopathy. *Arch Pediatr Adolesc Med*. 1994;148:1327-1330.
22. Torsiglieri AJ Jr, Tom LW, Ross AJ III, Wetmore RF, Handler SD, Potsic WP. Pediatric neck masses: guidelines for evaluation. *Int J Pediatr Otorhinolaryngol*. 1988;16:199-210.
23. Johnson JT, Newman RK. The anatomic location of neck metastasis from occult squamous cell carcinoma. *Otolaryngol Head Neck Surg*. 1981;89:54-58.
24. Barakat M, Flood LM, Oswal VH, Ruckley RW. The management of a neck mass: presenting feature of an asymptomatic head and neck primary malignancy? *Ann R Coll Surg Engl*. 1987;69:181-184.
25. Corrias A, Mussa A. Thyroid nodules in pediatrics: which ones can be left alone, which ones must be investigated, when and how. *J Clin Res Pediatr Endocrinol*. 2013;5(suppl 1):57-69.
26. Bargren AE, Meyer-Rochow GY, Sywak MS, Delbridge LW, Chen H, Sidhu SB. Diagnostic utility of fine-needle aspiration cytology in pediatric differentiated thyroid cancer. *World J Surg*. 2010;34:1254-1260.
27. Niedziela M. Pathogenesis, diagnosis and management of thyroid nodules in children. *Endocr Relat Cancer*. 2006;13:427-453.
28. Gharib H, Papini E, Valcavi R, et al. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract*. 2006;12:63-102.
29. Izquierdo R, Shankar R, Kort K, Khurana K. Ultrasound-guided fine-needle aspiration in the management of thyroid nodules in children and adolescents. *Thyroid*. 2009;19:703-705.
30. Stevens C, Lee JK, Sadatsafavi M, Blair GK. Pediatric thyroid fine-needle aspiration cytology: a meta-analysis. *J Pediatr Surg*. 2009;44:2184-2191.
31. McCoy KL, Jabbour N, Ogilvie JB, Ohori NP, Carty SE, Yim JH. The incidence of cancer and rate of false-negative cytology in thyroid nodules greater than or equal to 4 cm in size. *Surgery*. 2007;142:837-844.

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ORIGINAL ARTICLE

A Randomized, Controlled Trial of Oral Propranolol in Infantile Hemangioma

C. Léauté-Labrèze, P. Hoeger, J. Mazereeuw-Hautier, L. Guibaud, E. Baselga, G. Posiunas, R.J. Phillips, H. Caceres, J.C. Lopez Gutierrez, R. Ballona, S.F. Friedlander, J. Powell, D. Perek, B. Metz, S. Barbarot, A. Maruani, Z.Z. Szalai, A. Krol, O. Boccara, R. Foelster-Holst, M.I. Febrer Bosch, J. Su, H. Buckova, A. Torrelo, F. Cambazard, R. Grantzow, O. Wargon, D. Wyrzykowski, J. Roessler, J. Bernabeu-Wittel, A.M. Valencia, P. Przewratil, S. Glick, E. Pope, N. Birchall, L. Benjamin, A.J. Mancini, P. Vabres, P. Souteyrand, I.J. Frieden, C.I. Berul, C.R. Mehta, S. Prey, F. Boralevi, C.C. Morgan, S. Heritier, A. Delarue, and J.-J. Voisard

ABSTRACT

BACKGROUND

Oral propranolol has been used to treat complicated infantile hemangiomas, although data from randomized, controlled trials to inform its use are limited.

METHODS

We performed a multicenter, randomized, double-blind, adaptive, phase 2–3 trial assessing the efficacy and safety of a pediatric-specific oral propranolol solution in infants 1 to 5 months of age with proliferating infantile hemangioma requiring systemic therapy. Infants were randomly assigned to receive placebo or one of four propranolol regimens (1 or 3 mg of propranolol base per kilogram of body weight per day for 3 or 6 months). A preplanned interim analysis was conducted to identify the regimen to study for the final efficacy analysis. The primary end point was success (complete or nearly complete resolution of the target hemangioma) or failure of trial treatment at week 24, as assessed by independent, centralized, blinded evaluations of standardized photographs.

RESULTS

Of 460 infants who underwent randomization, 456 received treatment. On the basis of an interim analysis of the first 188 patients who completed 24 weeks of trial treatment, the regimen of 3 mg of propranolol per kilogram per day for 6 months was selected for the final efficacy analysis. The frequency of successful treatment was higher with this regimen than with placebo (60% vs. 4%, P<0.001). A total of 88% of patients who received the selected propranolol regimen showed improvement by week 5, versus 5% of patients who received placebo. A total of 10% of patients in whom treatment with propranolol was successful required systemic retreatment during follow-up. Known adverse events associated with propranolol (hypoglycemia, hypotension, bradycardia, and bronchospasm) occurred infrequently, with no significant difference in frequency between the placebo group and the groups receiving propranolol.

CONCLUSIONS

This trial showed that propranolol was effective at a dose of 3 mg per kilogram per day for 6 months in the treatment of infantile hemangioma. (Funded by Pierre Fabre Dermatologie; ClinicalTrials.gov number, NCT01056341.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Léauté-Labrèze at Unité de Dermatologie Pédiatrique, Hôpital Pellegrin-Enfants, Pl. Amélie Raba Léon, 33 076 Bordeaux CEDEX, France, or at christine.labreze@chu-bordeaux.fr.

A complete list of the investigators who recruited patients for the trial is provided in the Supplementary Appendix, available at NEJM.org.

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Infantile hemangiomas are the most common soft-tissue tumors of childhood, occurring in 3 to 10% of infants.[1-4] Lesions are usually not developed at birth and are generally diagnosed during the first 4 to 6 weeks of life, with most growth during the first 5 months.[5] The characteristic evolution of nearly all infantile hemangiomas is proliferation, stabilization, and slow, spontaneous involution. Although most lesions follow an uncomplicated clinical course, approximately 12% result in complications requiring referral to a specialist.[6,7] Many infantile hemangiomas leave permanent sequelae, with potential psychological effects in the children and their parents.[8,9]

Historically, systemic glucocorticoids were the mainstay of treatment for complicated infantile hemangiomas,[10] with interferon alfa and vincristine used for lesions refractory to glucocorticoid therapy. The efficacy of these treatments is variable, and all have associated safety concerns.[9,11-14]

In 2008, several of the current authors reported cases of hemangioma regression in infants treated with oral propranolol, a nonselective β-adrenergic receptor–blocking agent.[15] Numerous retrospective studies and case reports[16-19] and two small, placebo-controlled trials[20,21] have subsequently supported the efficacy of this treatment (generally at a dose of 2 mg per kilogram of body weight per day). Propranolol is now widely considered to be first-line therapy for infantile hemangiomas, despite the paucity of randomized, controlled clinical trials and the previous lack of a pediatric formulation.[22] Here we report on a large, randomized, placebo-controlled trial involving patients treated for up to 24 weeks with a pediatric oral propranolol solution.

Methods

Participants

Eligible patients were 35 to 150 days of age, with a proliferating infantile hemangioma requiring systemic therapy (i.e., an evaluated lesion with a minimal diameter of 1.5 cm). Patients with life-threatening, function-threatening, or severely ulcerated hemangiomas were excluded for ethical reasons owing to the inclusion in the trial of a placebo control. Detailed eligibility criteria are presented in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Oversight

The trial was performed in accordance with Good Clinical Practice guidelines. The study protocol was approved by the local ethics committee at each participating center and is available with the statistical analysis plan at NEJM.org. Parents or guardians gave written informed consent according to national regulations.

The sponsor (Pierre Fabre Dermatologie) was involved in the study design in collaboration with three of the academic authors and was responsible for trial management, analysis and interpretation of data, and the decision to submit the manuscript for publication. A data confidentiality agreement existed between the sponsor and the investigators during the trial. The first, penultimate, and last authors vouch for the integrity and completeness of the data and analyses and for the fidelity of this report to the protocol.

Trial Design

This randomized, placebo-controlled, double-blind, phase 2–3 trial had a two-stage adaptive design, with selection of the propranolol regimen (dose and duration) at the end of stage 1 (interim analysis) and further evaluation of the selected regimen in stage 2.[23,24] Prespecified possible adaptations to be made after the interim analysis, as outlined in the protocol and statistical analysis plan, were selection of one or two regimens, sample-size reassessment, and nonbinding stopping for futility. The aim was to show superiority of propranolol over placebo and to document long-term efficacy and safety; 56 centers in 16 countries worldwide participated (see the Supplementary Appendix).

In stage 1, patients received either placebo twice daily for 6 months or one of four propranolol regimens (1 or 3 mg of propranolol base per kilogram per day, divided into two daily doses, for 3 or 6 months). Patients were assigned to treatment through an interactive voice-response system, with the use of block randomization stratified according to age group (35 to 90 days vs. 91 to 150 days) and hemangioma location (facial vs. nonfacial) and applied in a 2:2:2:2:1 ratio (propranolol at 1 mg per kilogram per day for 3 months, propranolol at 1 mg per kilogram per day for 6 months, propranolol at 3 mg per kilogram per day for 3 months, propranolol at 3 mg per kilogram per day for 6 months, and placebo, respectively).

Different concentrations of propranolol were used (1.25, 2.50, or 3.75 mg per milliliter) in order to administer the same volume to each patient and thereby maintain blinding; patients assigned to 3-month propranolol regimens received placebo for the second 3 months. Propranolol was administered in the morning and late afternoon, immediately before, during, or immediately after feeding. For patients assigned to a regimen of 3 mg of propranolol per kilogram per day, the doses of propranolol were adjusted as follows: 1 mg per kilogram per day on day 0, 2 mg per kilogram per day on day 7, and 3 mg per kilogram per day on day 14. Propranolol doses (1 and 3 mg per kilogram per day, spanning the range used in off-label practice) and durations (3 and 6 months) were determined in discussions with the regulatory agencies.

In stage 2, patients were to receive either the propranolol regimen selected after the interim analysis or placebo (in a 2:1 ratio). After the 6-month treatment period (or the premature end of treatment), patients were followed for 72 weeks (to week 96) and could receive another treatment for infantile hemangioma, at the investigators' discretion.

EFFICACY AND SAFETY ASSESSMENTS

Participation involved the following 15 visits: at screening; baseline (day 0); days 7, 14, and 21; and weeks 5, 8, 12, 16, 20, 24, 36, 48, 72, and 96. Primary efficacy was assessed by centralized evaluation of standardized digital photographs (taken by investigators at each visit) by two independent, trained, validated readers who were unaware of the study-group assignments, with adjudication for discrepancies; interreader and intrareader reliability were assessed (see the Supplementary Appendix for details of assessment). Complete or nearly complete resolution of the target hemangioma (with nearly complete resolution defined as a minimal degree of telangiectasis, erythema, skin thickening, soft-tissue swelling, and distortion of anatomical landmarks), hemangioma evolution (improvement, stabilization, or worsening), and change in hemangioma size and color were assessed centrally. At each visit, investigators assessed hemangioma evolution since the previous visit, complete resolution and complete or nearly complete resolution versus baseline, presence and extent of sequelae (e.g., telangiectasis) if complete resolution occurred, complications, and hemangioma appearance. Parents or guardians also assessed hemangioma evolution since the previous visit. Use of any other treatment for hemangioma was recorded through week 96.

Safety was assessed by analysis of adverse events (i.e., any adverse change in condition between the time of informed consent and the end of the trial or 5 days after the last trial treatment); laboratory investigations, including measurement of glucose levels from finger-prick blood samples; physical examination, including pulmonary auscultation, liver palpation, assessment of vital signs, and assessment of neurodevelopment (normal or abnormal); and electrocardiography (with findings assessed independently). All assessors were unaware of the study-group assignments. Patients were closely monitored for known important risks associated with propranolol therapy (hypoglycemia, hypotension, bradycardia, and bronchospasm) during the 4 hours after dose administration at initiation and at visits involving dosage increases; parents or guardians were informed of precautionary measures and warning signs (see the Supplementary Appendix).

OUTCOME MEASURES

The primary outcome was success (complete or nearly complete resolution of the target hemangioma) or failure of trial treatment at week 24 versus baseline according to centralized evaluation. Patients who were withdrawn from trial treatment or who used other hemangioma treatment before week 24 were considered to have had a failure of treatment. The key secondary outcome was success or failure of trial treatment according to onsite assessments by the investigator at week 48 versus baseline. Other prespecified secondary outcomes that were based on centralized, investigator, and parent or guardian assessments are presented in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size was calculated on the basis of conservative estimated success rates of 10% (placebo),[25,26] 20% (1 mg of propranolol per kilogram per day for 3 months), 30% (1 mg per kilogram per day for 6 months), 40% (3 mg per kilogram per day for 3 months), and 55% (3 mg per kilogram per day for 6 months) (see the Supplementary Appendix).[24] The planned sample size was 450 randomly assigned patients.

After the first 188 patients (stage 1) had completed 24 weeks of trial therapy (or had been withdrawn prematurely from trial therapy), an independent data and safety monitoring committee conducted the interim analysis. By this time, recruitment targets had been exceeded and the necessary sample size had been reached (460 patients). However, the sponsor decided, before unblinding, to maintain the interim analysis and the adaptive nature of the trial so that recruitment could continue if sample-size reassessment became necessary (this was important, since minimal data were available to estimate the success rates). Therefore, the prespecified week 24 analysis was maintained, and outcome data were collected for all regimens.

The superiority of the selected regimen versus placebo was tested with the use of the closed testing procedure and combination tests for all intersection hypotheses, with application of the Simes adjustment[24,27] (see the Supplementary Appendix). This testing method guaranteed that the familywise type I error rate was below the nominal and stringent one-sided significance level of 0.005. The week 24 analysis was performed, as planned, on the intention-to-treat population: all patients in stage 1 (regardless of regimen) plus patients in stage 2 who were randomly assigned to placebo or the selected propranolol regimen and who had received at least one dose of trial therapy. Sensitivity analyses with a broader definition of treatment failure were performed on the per-protocol population. Prespecified analyses of the primary end point with adjustment for stratification factors (age group and hemangioma location) and the randomization ratio (changed to aid recruitment) used an extension of the combination test for logistic regression.[24] Combination tests were used for an adaptive design in analyses of secondary end points. Unless otherwise specified, P values in the efficacy analyses are one-sided, as is common in adaptive-design methods.[23,24,28]

RESULTS

PATIENTS

Between February 2010 and November 2011, a total of 460 patients underwent randomization. Of those, 456 patients received treatment, 323 completed 24 weeks of trial treatment, 391 entered follow-up, and 343 completed follow-up to week 96 (last visit, November 2013) (Fig. 1). Demographic and baseline disease characteristics were similar across the study groups (Table 1).

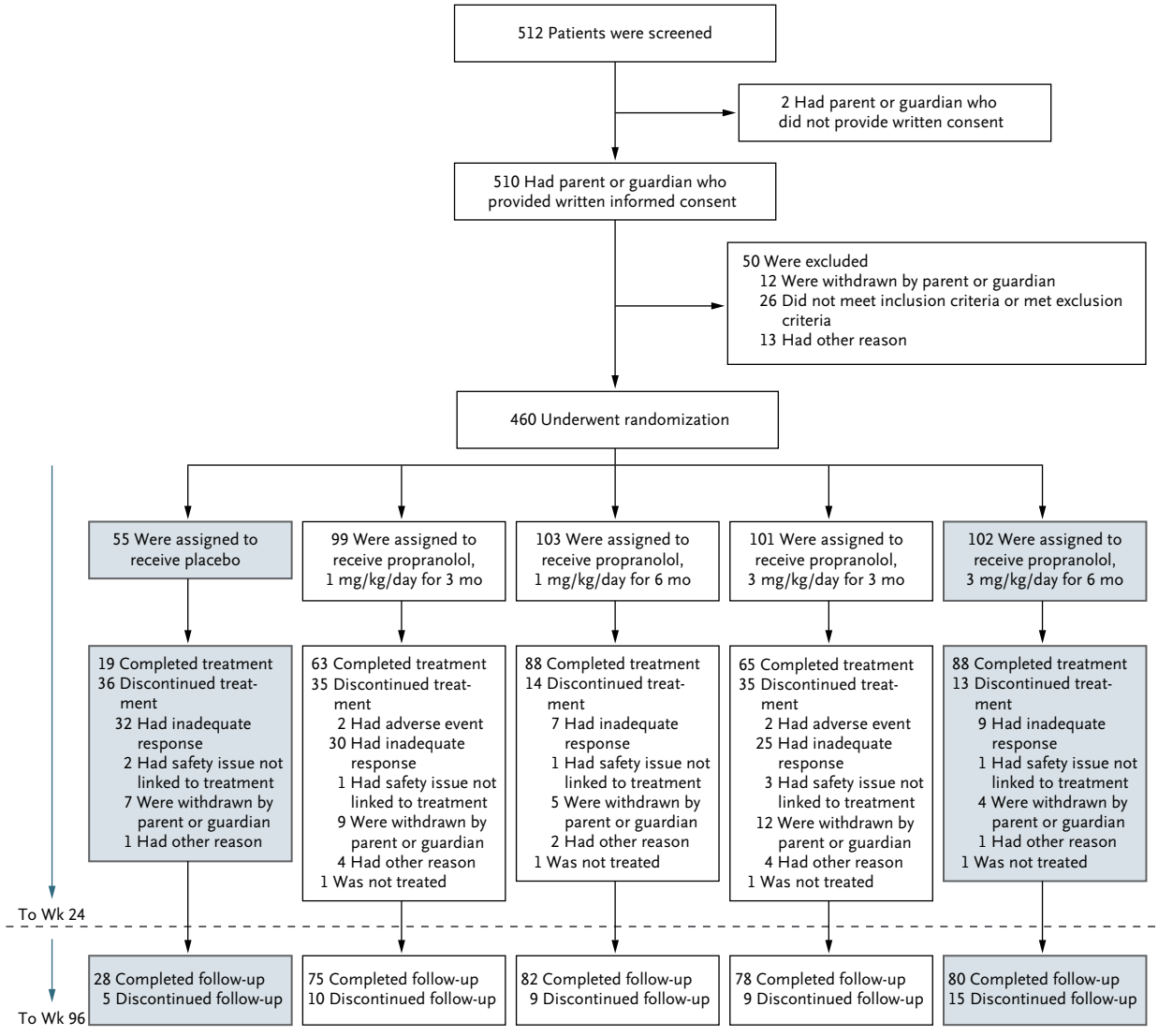
A total of 133 patients (29%) discontinued treatment prematurely, most frequently those receiving the 6-month placebo regimen (65%), with lower rates among those receiving the 3-month propranolol regimens (36% of patients receiving 1 mg per kilogram per day, and 35% of those receiving 3 mg per kilogram per day, mostly after the week-12 switch to placebo) and the lowest rates among those receiving the 6-month propranolol regimens (14% of patients receiving 1 mg per kilogram per day, and 13% of those receiving 3 mg per kilogram per day). Treatment inefficacy was the most frequent reason for discontinuation (Fig. S1 and Table S2 in the Supplementary Appendix).

EFFICACY

At the time of the interim analysis (January 2012), 2 of 25 patients (8%) receiving placebo had successful treatment at week 24, as compared with 4 of 41 patients (10%) receiving 1 mg of propranolol per kilogram per day for 3 months, 3 of 39 patients (8%) receiving 3 mg per kilogram per day for 3 months, 15 of 40 patients (38%) receiving 1 mg per kilogram per day for 6 months ($P=0.004$ for the comparison with placebo), and 27 of 43 patients (63%) receiving 3 mg per kilogram per day for 6 months ($P<0.001$ for the comparison with placebo) (Fig. 2A). The independent data and safety monitoring committee determined that the propranolol regimen with the highest benefit-to-risk ratio was 3 mg per kilogram per day for 6 months; the committee did not recommend adjusting the planned sample size. According to the prespecified plan, the week 24 efficacy analysis was conducted to test the superiority of the selected propranolol regimen over placebo.

Overall, 61 of 101 patients (60%) assigned to the selected propranolol regimen and 2 of 55 patients (4%) assigned to placebo had successful treatment at week 24 ($P<0.001$) (Fig. 2B). Results were consistent between trial stages, similar in the per-protocol population, and supported by sensitivity analysis (Tables S4 and S5 in the Supplementary Appendix).

The selected propranolol regimen remained



	Placebo	1 mg/kg/day for 3 Mo	1 mg/kg/day for 6 Mo	3 mg/kg/day for 3 Mo	3 mg/kg/day for 6 Mo	Total
			no. of patients			
Safety	55	98	102	100	101	456
Efficacy Stage 1 + Stage 2 — without Overrun (wk 24 analysis)						
Intention-to-Treat Population	55	41	40	39	101	276
Per-Protocol Population	53	38	38	37	93	259

Figure 1. Screening, Randomization, Treatment, and Follow-up of the Patients.

The safety population included all randomly assigned patients who received at least one dose of trial treatment. The intention-to-treat population included all randomly assigned patients in stage 1 (the phase 2 part of the trial, comparing each of the four propranolol regimens with placebo) plus all patients in stage 2 (the phase 3 part of the trial, comparing the selected regimen of propranolol [3 mg per kilogram per day for 6 months] with placebo) who received at least one dose of trial treatment. The per-protocol population included all patients in the intention-to-treat population with no major protocol deviation, except for prohibited treatments to treat infantile hemangiomas. "Overrun" indicates the subgroup of patients in stage 2 who were assigned to a regimen other than the selected regimen of propranolol or placebo. Patients could have more than one reason for study exclusion and for discontinuation of trial treatment. Shaded boxes indicate the week 24 efficacy analysis that was conducted to test the superiority of the selected propranolol regimen over placebo.

Table 1. Baseline Characteristics of Study Patients and Hemangiomas.*

Characteristic	Placebo (N=55)	Propranolol (N=401)				Total (N=456)
		1 mg/kg/day for 3 mo (N=98)	1 mg/kg/day for 6 mo (N=102)	3 mg/kg/day for 3 mo (N=100)	3 mg/kg/day for 6 mo (N=101)	
Patients						
Sex — no. (%)						
Male	17 (31)	30 (31)	32 (31)	21 (21)	31 (31)	131 (29)
Female	38 (69)	68 (69)	70 (69)	79 (79)	70 (69)	325 (71)
Age at inclusion						
Days	103.9±31.1	103.6±33.1	102.6±30.1	107.5±30.1	101.6±31.0	103.8±31.0
35–90 days — no. (%)	20 (36)	36 (37)	38 (37)	36 (36)	37 (37)	167 (37)
>90 days — no. (%)	35 (64)	62 (63)	64 (63)	64 (64)	64 (63)	289 (63)
Hemangiomas						
Location — no. of patients (%)						
Facial	40 (73)	71 (72)	72 (71)	64 (64)	71 (70)	318 (70)
Nonfacial	15 (27)	27 (28)	30 (29)	36 (36)	30 (30)	138 (30)
Morphologic classification — no. of patients (%)						
Segmental	2 (4)	4 (4)	7 (7)	7 (7)	5 (5)	25 (5)
Localized	48 (87)	89 (91)	90 (88)	88 (88)	91 (90)	406 (89)
Indeterminate	5 (9)	5 (5)	5 (5)	5 (5)	5 (5)	25 (5)
Superficial component — no. of patients (%)						
Flat	4 (7)	9 (9)	6 (6)	9 (9)	9 (9)	37 (8)
Elevated						
Slightly	19 (35)	22 (22)	22 (22)	29 (29)	22 (22)	114 (25)
Moderately	15 (27)	35 (36)	43 (42)	24 (24)	31 (31)	148 (32)
Markedly	17 (31)	32 (33)	31 (30)	38 (38)	39 (39)	157 (34)
Deep component — no. of patients (%)†	35 (64)	74 (76)	66 (65)	79 (79)‡	72 (71)	326 (71)

* Plus–minus values are means ±SD. There were no significant differences among the study groups unless otherwise indicated.
† Values are for a possible or a definite deep component.
‡ P=0.04 for the comparison with placebo.

superior to placebo in analyses adjusting for age group, hemangioma location, and randomization ratio (Table S6 in the Supplementary Appendix). Improvement between baseline and week 5 (according to centralized assessment) occurred in 88% of patients assigned to the selected regimen and 5% of patients assigned to placebo (P<0.001); sustained improvement (maintained at each subsequent visit until week 24) occurred from week 5 in 73% and 5% of patients, respectively. A significantly greater mean reduction in hemangioma surface area and color intensity was achieved with the selected propranolol regimen than with placebo (Table S8 in the Supplementary Appendix). Results of an exploratory analysis of the primary end point for all regimens are shown in Table 2 (and Table S7 in the Supplementary Appendix).

On-site investigators' assessments of complete resolution (Table S9 in the Supplementary Appendix) and complete or nearly complete resolution (Table S8 in the Supplementary Appendix) of the target hemangioma differed from centralized assessments; 40% of the cases

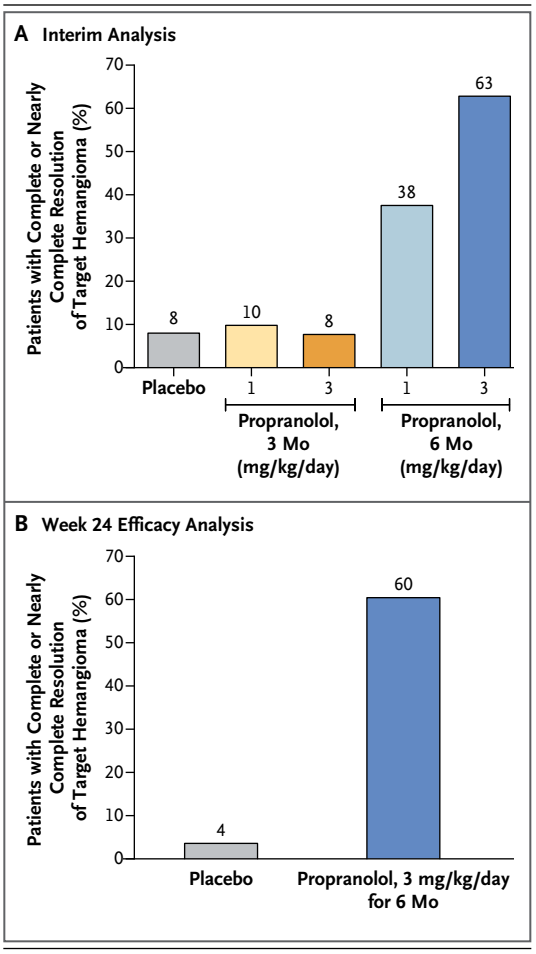


Figure 2. Interim Analysis and Week 24 Efficacy Analysis of Complete or Nearly Complete Resolution of the Target Hemangioma at Week 24 versus Baseline.

Nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft-tissue swelling, and distortion of anatomical landmarks. In the interim analysis (Panel A), differences in complete or nearly complete resolution between patients receiving propranolol and those receiving placebo were significant only for the 6-month regimens (1 mg per kilogram per day for 3 months, P=0.40; 3 mg per kilogram per day for 3 months, P=0.52; 1 mg per kilogram per day for 6 months, P=0.004; and 3 mg per kilogram per day for 6 months, P<0.001). In accordance with the protocol and the statistical analysis plan, the interim analysis involved the first 188 patients assigned to any of the five treatment regimens (corresponding to the patients in stage 1) who received at least one dose of trial treatment and who either had completed the week 24 visit or had been withdrawn prematurely from the trial treatment (i.e., the intention-to-treat population in stage 1). For the primary efficacy end point of complete or nearly complete resolution of the target hemangioma at week 24 according to centralized assessment, the P values for the four propranolol regimens (vs. placebo) were calculated with the use of a one-sided z-test for proportions with pooled variance estimates. In the week 24 efficacy analysis (Panel B), the difference in complete or nearly complete resolution between patients receiving propranolol at a dose of 3 mg per kilogram per day for 6 months and those receiving placebo was significant (P<0.001). This analysis involved the intention-to-treat population for the selected regimens at an interim analysis (i.e., all patients in stage 1 [regardless of regimen] and patients in stage 2 who were assigned to either placebo or the selected regimen of propranolol and who received at least one dose of trial treatment). The objective was to test the superiority of the selected regimen ($H0,sel:\theta sel \leq 0$ against the alternative $H1,sel:\theta sel > 0$) with the use of the method described by Heritier et al.,[24] for an adaptive confirmatory design with a single selection at an interim analysis, guaranteeing that the familywise type I error rate was maintained at the nominal level of 0.005.

judged centrally as having been treated successfully were assessed by local investigators as showing complete or nearly complete resolution (Table S10 in the Supplementary Appendix; see also examples of discrepancies and discussion). However, the rate of investigator-assessed sustained improvement from week 5 to week 24 (71%) (Table S8 in the Supplementary Appendix) was similar to the rate determined by centralized assessments.

Successful treatment at week 24 was sustained to week 96 in 35 of 54 patients assigned to the selected propranolol regimen (65%) and in 2 of 2 patients assigned to placebo, without any additional hemangioma treatment. Only 6 patients assigned to the selected propranolol regimen (10%) required reintroduction of systemic hemangioma treatment from week 24 to week 96 (7 patients [11%] required any additional hemangioma treatment).

SAFETY

Corresponding to rates of premature discontinuation of trial treatment, mean exposure was lowest for placebo (83 days), higher for 3-month propranolol treatment (143 days for 1 mg per kilogram per day and 147 days for 3 mg per kilogram per day), and highest for 6-month propranolol treatment (157 days for 1 mg per kilogram per day and 161 days for 3 mg per kilogram per day). During treatment, 33 serious adverse events occurred in 26 patients, with no significant difference overall or according to individual events between the placebo group and the group receiv-

Table 2. Exploratory Analysis of the Primary Efficacy Outcome in the Intention-to-Treat Population with Overrun.*

Variable	Placebo (N=55)	Propranolol (N=401)			
		1 mg/kg/day for 3 mo (N=98)	1 mg/kg/day for 6 mo (N=102)	3 mg/kg/day for 3 mo (N=100)	3 mg/kg/day for 6 mo (N=101)
Complete or nearly complete resolution of target hemangioma at wk 24 — no. (%)†					
Yes	2 (4)	8 (8)	50 (49)	12 (12)	61 (60)
No	53 (96)	90 (92)	52 (51)	88 (88)	40 (40)
P value‡		0.14	<0.001	0.04	<0.001

* "Overrun" indicates patients in stage 2 of the trial who were assigned to a regimen other than the selected regimen of propranolol or placebo.
† Nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft-tissue swelling, and distortion of anatomical landmarks.
‡ P values for the four propranolol regimens (vs. placebo) were calculated with the use of a one-sided z-test for proportions with pooled variance estimates.

ing the selected propranolol regimen (Table 3, and Tables S11 and S12 in the Supplementary Appendix).

The overall incidence of adverse events was higher among patients receiving the propranolol regimens (90% with 1 mg per kilogram per day for 6 months to 96% with 3 mg per kilogram per day for 6 months) than among patients receiving placebo (76%) (Table 3). The most common events were either expected in the infant population (e.g., nasopharyngitis, pyrexia, and teething) (Table S13 in the Supplementary Appendix) or known side effects of propranolol (e.g., diarrhea, sleep disorders, events potentially related to bronchial hyperreactivity, and cold hands and feet) (Table 3). Most events were classified as mild or moderate in severity, with onset within 3 months after treatment initiation. When events occurring only during propranolol treatment were considered (i.e., excluding events that occurred during the placebo phase of the 3-month propranolol regimens), infants receiving the 3-mg dose (vs. the 1-mg dose) appeared to have a higher incidence of diarrhea (22% vs. 14%) and of events potentially related to bronchial hyperreactivity (9% vs. 6%). Bronchospasm occurred in four patients (two receiving propranolol and two receiving placebo, including one who had previously received the regimen of 3 mg of propranolol per kilogram per day for 3 months), leading to temporary discontinuation of treatment in two patients (one receiving placebo).

In all propranolol groups during the 4 hours after the initial dose and after subsequent dose adjustments, the mean heart rate and mean systolic blood pressure decreased (by approximately 7 beats per minute and approximately 3 mm Hg across groups) and the PR interval increased, without appreciable differences between doses (Fig. S2, S4, and S5 in the Supplementary Appendix). Heart-rate decreases occurred within 1 hour after dose administration, with minimal changes thereafter. Overall differences observed in these variables as compared with placebo decreased between week 5 and week 8 and had disappeared by week 24. Bradycardia was reported in two patients assigned to propranolol during the dose-adjustment phase (one patient had a serious adverse event in the context of enterocolitis, and the other had no visible symptoms). One serious adverse event, second-degree atrioventricular block (with preexisting cardiac conditions later documented; see Tables S11 and S12 in the Supplementary Appendix), occurred after dose administration on day 0 (treatment was discontinued).

Hypotension (without apparent associated manifestations) occurred in seven patients (six of whom were receiving propranolol, four during the dose-adjustment phase). Mild hypoglycemia without visible manifestations occurred in two patients (both receiving propranolol during the dose-adjustment phase). No events of hypotension or hypoglycemia led to treatment discontinuation. During follow-up (Tables S14 and S15 in the Supplementary Appendix), no appreciable differences were noted between the propranolol groups and the placebo group in growth, neurodevelopment, or cardiovascular variables.

Table 3. Adverse and Serious Adverse Events with Propranolol or Placebo to Week 24 (Safety Population).*

Variable	Placebo (N=55)	Propranolol (N=401)			
		1 mg/kg/day for 3 mo (N=98)	1 mg/kg/day for 6 mo (N=102)	3 mg/kg/day for 3 mo (N=100)	3 mg/kg/day for 6 mo (N=101)
	number of patients (percent)				
Adverse-event summary†					
≥1 Serious adverse event	3 (5)	5 (5)	3 (3)	9 (9)	6 (6)
≥1 Adverse event that occurred during treatment	42 (76)	89 (91)	92 (90)	92 (92)	97 (96)
≥1 Adverse event that occurred during treatment, leading to definitive treatment discontinuation	6 (11)	4 (4)	2 (2)	6 (6)	3 (3)
Adverse events					
Known important risks associated with propranolol therapy					
Hypotension	1 (2)	2 (2)	1 (1)	3 (3)	0
Bronchospasm	1 (2)	0	0	2 (2)‡	1 (1)
Bradycardia	0	0	1 (1)	1 (1)	0
Hypoglycemia	0	0	1 (1)	0	1 (1)
Other risks associated with propranolol therapy§					
Diarrhea	4 (7)	16 (16)	14 (14)	17 (17)	28 (28)
Sleep disorder¶	7 (13)	28 (29)	14 (14)	19 (19)	22 (22)
Bronchitis	1 (2)	5 (5)	8 (8)	11 (11)	17 (17)
Vomiting	3 (5)	16 (16)	13 (13)	10 (10)	13 (13)
Bronchiolitis	3 (5)	6 (6)	7 (7)	6 (6)	10 (10)
Cold hands and feet	1 (2)	8 (8)	10 (10)	1 (1)	10 (10)
Agitation‖	6 (11)	12 (12)	18 (18)	8 (8)	7 (7)
Constipation	1 (2)	9 (9)	6 (6)	9 (9)	4 (4)
Decreased appetite	1 (2)	5 (5)	3 (3)	5 (5)	1 (1)
Somnolence	1 (2)	6 (6)	4 (4)	1 (1)	1 (1)

* The safety population included all randomly assigned patients who received at least one dose of trial therapy during stage 1 or 2. Adverse events were any events that occurred or worsened during trial treatment or up to 5 days after the last day of trial treatment; they were tabulated for each study group according to the preferred terms from the *Medical Dictionary for Regulatory Activities* (MedDRA).

† With regard to the 3-month propranolol regimens, the week 24 analysis did not separate events observed during the first 3 months (active-treatment phase) from those observed during the second 3 months (placebo phase).

‡ One event of bronchospasm occurred during the placebo phase, after the active-treatment phase had ended.

§ Shown are events observed in at least 5% of patients in any propranolol group, listed by decreasing order of incidence among patients who received 3 mg of propranolol per kilogram per day for 6 months.

¶ The term "sleep disorder" includes the following MedDRA preferred terms: sleep disorder, middle insomnia, hypersomnia, insomnia, poor quality sleep, initial insomnia, terminal insomnia, and nightmare.

‖ The term "agitation" includes the following MedDRA preferred terms: restlessness, agitation, anxiety, psychomotor hyperactivity, nervousness, stress, and irritability.

DISCUSSION

This large-scale, randomized, placebo-controlled trial showed that propranolol is effective in treating infantile hemangioma, with a favorable risk–benefit profile. Our adaptive design, involving an initial comparison of four propranolol regimens with placebo, allowed selection of a more effective dose (3 mg rather than 1 mg per kilogram per day) and treatment duration (6 months rather

than 3 months). Treatment with propranolol at a dose of 3 mg per kilogram per day for 6 months resulted in a significantly higher success rate (primary outcome) as compared with placebo (60% vs. 4%). Results were supported by a per-protocol analysis and a sensitivity analysis involving a broader definition of treatment failure.

The observed divergence between centralized and investigator evaluations of complete or nearly complete resolution of the target hemangioma after treatment with propranolol may be explained by limited investigator training and the lack of validation or monitoring (for logistic reasons) as compared with the training and validation of central readers. A review of the discrepant cases (see examples in the Supplementary Appendix) suggests that investigators applied a more stringent threshold for nearly complete resolution, especially regarding the presence of residual telangiectasis. Investigators' assessments of sustained improvement from week 5 to week 24 were highly concordant with the centralized assessments (both >70%).

Adverse events were more frequent among the patients who received propranolol than among those who received placebo; for some events, the greater frequency may be partly explained by the longer duration of treatment with propranolol than with placebo, largely owing to more frequent discontinuations for lack of efficacy in the placebo group. Important risks anticipated with the use of propranolol,[6] including bronchospasm, bradycardia, hypotension, and hypoglycemia, were infrequent but occurred more often in the propranolol groups than in the placebo group. With regard to these four risks, only one patient who received propranolol had a serious adverse event (bradycardia in the context of enterocolitis). Heart-rate decreases typically occurred within 1 hour after dose administration. The risk of hypoglycemia may be minimized with proper education of parents or guardians about the importance of administering propranolol as prescribed (i.e., during or right after feeding).

The current trial confirms and builds on the results of previous case series[16,18,19] and smaller placebo-controlled trials.[20,21] For example, one placebo-controlled trial involving 39 patients showed that the administration of propranolol (2 mg per kilogram per day) was associated with a 60.0% decrease in hemangioma volume at week 24, as compared with a 14.1% decrease with placebo.[20] In our study, only 10% of successfully treated hemangiomas required systemic retreatment within 72 weeks after the end of trial treatment. This finding is consistent with that of a prior report, in which 12% of the patients who had a response had relapses requiring retreatment.[29]

Limitations of this trial include the lack of a validated assessment for the evolution of infantile hemangiomas. However, assessment of our outcome involved standardized photographic procedures and independent, centralized, blinded, and validated reading. We did not include a group treated with 2 mg of propranolol per kilogram per day, a dose frequently used in practice, but the doses we studied (1 mg and 3 mg per kilogram per day) span the range used empirically in practice. Although patients with high-risk hemangiomas were excluded owing to the placebo control, other case series support the efficacy of oral propranolol in high-risk cases.[30-37]

In conclusion, this trial shows that oral propranolol at a dose of 3 mg per kilogram per day for 6 months is effective in the treatment of infantile hemangioma.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Christine Léauté-Labrèze, M.D., Peter Hoeger, M.D., Juliette Mazereeuw-Hautier, M.D., Laurent Guibaud, M.D., Eulalia Baselga, M.D., Gintas Posiunas, M.D., Ph.D., Roderic J. Phillips, M.D., Hector Caceres, M.D., Juan Carlos Lopez Gutierrez, M.D., Rosalia Ballona, M.D., Sheila Fallon Friedlander, M.D., Julie Powell, M.D., Danuta Perek, M.D., Brandie Metz, M.D., Sébastien Barbarot, M.D., Annabel Maruani, M.D., Ph.D., Zsuzsanna Zsófia Szalai, M.D., Ph.D., Alfons Krol, M.D., Olivia Boccara, M.D., Regina Foelster-Holst, M.D., Maria Isabel Febrer Bosch, M.D., John Su, M.D., Hana Buckova, M.D., Ph.D., Antonio Torrelo, M.D., Frédéric Cambazard, M.D., Rainer Grantzow, M.D., Orli Wargon, M.D., Dariusz Wyrzykowski, M.D., Jochen Roessler, M.D., José Bernabeu-Wittel, M.D., Adriana M. Valencia, M.D., Przemyslaw Przewratil, M.D., Sharon Glick, M.D., Elena Pope, M.D., Nicholas Birchall, M.D., Latanya Benjamin, M.D., Anthony J. Mancini, M.D., Pierre Vabres, M.D., Pierre Souteyrand, M.D., Ilona J. Frieden, M.D., Charles I. Berul, M.D., Cyrus R. Mehta, Ph.D., Sorilla Prey, M.D., Franck Boralevi, M.D., Caroline C. Morgan, D.Phil., Stephane Heritier, Ph.D., Alain Delarue, M.D., and Jean-Jacques Voisard, M.D.

The authors' affiliations are as follows: Hôpital Pellegrin–Enfants, Centre Hospitalier Universitaire (CHU), Bordeaux (C.L.-L., S.P., F.B.), Hôpital des Enfants, Toulouse (J.M.-H.), Hôpital Femme–Mère–Enfant, CHU Lyon Est, Lyon (L.G.), CHU Nantes and INSERM

Centre d'Investigation Clinique (CIC) 004, Nantes (S.B.), Université François Rabelais Tours, Centre Hospitalier Régional Universitaire (CHRU) Tours, INSERM CIC 1415, Tours (A.M.), Hôpital Necker–Enfants Malades (O.B.) and Cardinal Systems (C.C.M.), Paris, CHU Saint Etienne, Hôpital Nord, Saint Etienne (F.C.), Hôpital du Bocage, CHU Dijon, Dijon (P.V.), Hôtel-Dieu, CHRU Clermont-Ferrand, Clermont-Ferrand (P.S.), and Pierre Fabre Dermatologie, Lavaur (A.D., J.-J.V.) — all in France; Kinderkrankenhaus Wilhelmstift, Hamburg (P.H.), Universitätsklinikum Schleswig-Holstein, Kiel (R.F.-H.), Kinderchirurgische Klinik Ludwig-Maximilians-Universität, Munich (R.G.), and Universitätsklinikum Freiburg, Zentrum für Kinderheilkunde und Jugendmedizin, Freiburg (J.R.) — all in Germany; Hospital de la Santa Creu i Sant Pau, Barcelona (E.B.), Hospital La Paz (J.C.L.G.) and Hospital del Niño Jesús (A.T.), Madrid, Hospital General Universitario de Valencia, Valencia (M.I.F.B.), and Hospital Universitario Virgen del Rocio, Seville (J.B.-W.) — all in Spain; Hospital Infantil de Mexico Federico Gomez, Mexico City (A.M.V.); Children's Hospital, Vilnius University Hospital, Vilnius, Lithuania (G.P.); Royal Children's Hospital (R.J.P.), Box Hill Hospital (J.S.), and the School of Public Health and Preventive Medicine (S.H.), Monash University, Melbourne, VIC, and Sydney Children's Hospital, Sydney (O.W.) — both in Australia; Pediatric Clinic of the Faculty, Hospital Brno, Brno, Czech Republic (H.B.); Clinica Internacional (R.B.) and Instituto Nacional de Salud del Niño (H.C.), Lima, Peru; Rady Children's Hospital, San Diego, CA (S.F.F.); CHU Sainte Justine, Montreal (J.P.); Instytut Pomnik–Centrum Zdrowia Dziecka, Warsaw (D.P.), Copernicus Hospital, Gdansk Medical University, Gdansk (D.W.), and Szpital Kliniczny, M. Komopnickiej Uniwersytetu, Lodz (P.P.) — all in Poland; University of California–Irvine, Irvine (B.M.); Heim Pál Gyermekkórház, Borgyogyaszati Ozrtaly, Budapest, Hungary (Z.Z.S.); Oregon Health Sciences University, Portland (A.K.); SUNY Downstate Medical Center, Brooklyn, NY (S.G.); Hospital for Sick Children, Toronto (E.P.); Auckland Dermatology, Auckland, New Zealand (N.B.); Lucile Packard Children's Hospital, Stanford University School of Medicine, Stanford, CA (L.B.); Ann and Robert H. Lurie Children's Hospital, Chicago (A.J.M.); University of California–San Francisco, San Francisco (I.J.F.); Children's National Medical Center, Washington, DC (C.I.B.); and Cytel, Cambridge, MA (C.R.M.).

REFERENCES

1. Frieden IJ, Eichenfield LF, Esterly NB, Geronemus R, Mallory SB. Guidelines of care for hemangiomas of infancy: American Academy of Dermatology Guidelines/Outcomes Committee. J Am Acad Dermatol 1997;37:631-7.
2. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatr Dermatol 2008;25:168-73.
3. Hoornweg MJ, Smeulders MJ, van der Horst CM. Prevalence and characteristics of haemangiomas in young children. Ned Tijdschr Geneeskd 2005;149:2455-8. (In Dutch.)
4. Munden A, Butschek R, Tom WL, et al. Prospective study of infantile haemangiomas: incidence, clinical characteristics and association with placental anomalies. Br J Dermatol 2014;170:907-13.
5. Chang LC, Haggstrom AN, Drolet BA, et al. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics 2008;122:360-7.
6. Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics 2013;131:128-40.
7. Hemangioma Investigator Group. Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. J Pediatr 2007;150:291-4.
8. Bauland CG, Lüning TH, Smit JM, Zeebregts CJ, Spauwen PH. Untreated hemangiomas: growth pattern and residual lesions. Plast Reconstr Surg 2011;127:1643-8.
9. Frieden IJ, Haggstrom AN, Drolet BA, et al. Infantile hemangiomas: current knowledge, future directions — proceedings of a research workshop on infantile hemangiomas, April 7-9, 2005, Bethesda, Maryland, USA. Pediatr Dermatol 2005;22:383-406.
10. Zarem HA, Edgerton MT. Induced resolution of cavernous hemangiomas following prednisolone therapy. Plast Reconstr Surg 1967;39:76-83.
11. Enjolras O, Riche MC, Merland JJ, Escande JP. Management of alarming hemangiomas in infancy: a review of 25 cases. Pediatrics 1990;85:491-8.
12. Barrio VR, Drolet BA. Treatment of hemangiomas of infancy. Dermatol Ther 2005;18:151-9.
13. Ezekowitz RA, Mulliken JB, Folkman J. Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. N Engl J Med 1992;326:1456-63. [Errata, N Engl J Med 1994;330:300, 1995;333:595-6.]
14. Enjolras O, Brevière GM, Roger G, et al. Vincristine treatment for function- and life-threatening infantile hemangioma. Arch Pediatr 2004;11:99-107. (In French.)
15. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008;358:2649-51.
16. Sans V, de la Roque ED, Berge J, et al. Propranolol for severe infantile hemangiomas: follow-up report. Pediatrics 2009;124:e423-31.
17. Izadpanah A, Izadpanah A, Kanevsky J, Belzile E, Schwarz K. Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. Plast Reconstr Surg 2013;131:601-13.
18. Price CJ, Lattouf C, Baum B, et al. Propranolol vs corticosteroids for infantile hemangiomas: a multicenter retrospective analysis. Arch Dermatol 2011;147:1371-6.
19. Bertrand J, McCuaig C, Dubois J, Hatami A, Ondrejchak S, Powell J. Propranolol versus prednisone in the treatment of infantile hemangiomas: a retrospective comparative study. Pediatr Dermatol 2011;28:649-54.
20. Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics 2011;128:e259-66.
21. Léauté-Labrèze C, Dumas de la Roque E, Nacka F, et al. Double-blind randomized pilot trial evaluating the efficacy of oral propranolol on infantile haemangiomas in infants <4 months of age. Br J Dermatol 2013;169:181-3.
22. Mabeta P, Pepper MS. Hemangiomas — current therapeutic strategies. Int J Dev Biol 2011;55:431-7.
23. Posch M, Koenig F, Branson M, Brannath W, Dunger-Baldauf C, Bauer P. Testing and estimation in flexible group sequential designs with adaptive treatment selection. Stat Med 2005;24:3697-714.
24. Heritier S, Lô SN, Morgan CC. An adaptive confirmatory trial with interim treatment selection: practical experiences and unbalanced randomization. Stat Med 2011;30:1541-54.
25. Bowers RE, Graham EA, Tomlinson KM. The natural history of the strawberry nevus. Arch Dermatol 1960;82:667-80.
26. Lister WA. The natural history of strawberry naevi. Lancet 1938;1:1429-34.
27. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. Biometrika 1986;73:751-4.
28. Jennison C, Turnbull BW. Adaptive seamless designs: selection and prospective testing of hypotheses. J Biopharm Stat 2007;17:1135-61.
29. Ahogo CK, Ezzedine K, Prey S, et al. Factors associated with the relapse of infantile haemangiomas in children treated with oral propranolol. Br J Dermatol 2013;169:1252-6.
30. Hermans DJ, van Beynum IM, Schultze Kool LJ, van de Kerkhof PC, Wijnen MH, van der Vleuten CJ. Propranolol, a very promising treatment for ulceration in infantile hemangiomas: a study of 20 cases with matched historical controls. J Am Acad Dermatol 2011;64:833-8.
31. Saint-Jean M, Léauté-Labrèze C, Mazereeuw-Hautier J, et al. Propranolol for treatment of ulcerated infantile hemangiomas. J Am Acad Dermatol 2011;64:827-32.
32. Haider KM, Plager DA, Neely DE, Eikenberry J, Haggstrom A. Outpatient

treatment of periocular infantile hemangiomas with oral propranolol. J AAPOS 2010;14:251-6.
33. Snir M, Reich U, Siegel R, et al. Refractive and structural changes in infantile periocular capillary haemangioma treated with propranolol. Eye (Lond) 2011; 25:1627-34.
34. Fuchsmann C, Quintal MC, Giguere C, et al. Propranolol as first-line treatment of head and neck hemangiomas. Arch Otolaryngol Head Neck Surg 2011;137: 471-8.
35. Mazereeuw-Hautier J, Hoeger PH, Benlahrech S, et al. Efficacy of propranolol in hepatic infantile hemangiomas with diffuse neonatal hemangiomatosis. J Pediatr 2010;157:340-2.
36. Metry D, Frieden IJ, Hess C, et al. Propranolol use in PHACE syndrome with cervical and intracranial arterial anomalies: collective experience in 32 infants. Pediatr Dermatol 2013;30:71-89.
37. Phillips RJ, Penington AJ, Bekhor PS, Crock CM. Use of propranolol for treatment of infantile haemangiomas in an outpatient setting. J Paediatr Child Health 2012;48:902-6.

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