THE
HOME STUDY COURSE
IN
OTOLARYNGOLOGY — HEAD AND NECK SURGERY

SECTION 1

Congenital and Pediatric Problems

September 2015

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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:

Airway, Bronchoesophagology, and Laryngology

1) Recognize the societal costs of airway foreign bodies, including potential serious complications that might affect these patients.
2) Apply a possible method to more effectively wean sedation following laryngotracheal reconstruction, and the potential advantages and disadvantages of different protocols.
3) Decribe the changes in vocal fold structure and pathologic findings such as nodules in children as they mature, and how these changes affect treatment decisions.
4) Define mechanisms of swallowing dysfunction following laryngeal cleft repair.

Craniofacial Abnormalities and Trauma

1) Recognize common patterns of craniosynostosis, and be able to understand the etiology and treatment options.
2) Describe the manifestations of obstructive sleep apnea in the cleft population, including risk factors for airway obstruction and potential complications of treatment.
3) Identify the indications for mandibular distraction in micrognathic patients, and potential costs as well as success rates for surgical repair.
4) Recognize common patterns of facial fractures in children, as well as unique characteristics in this patient population which guide management.

Adenotonsillar Disease and Sleep Disorders

1) Weigh the advantages and disadvantages of treatment with perioperative dexamethasone.
2) Apply medical treatment options for children with mild obstructive sleep apnea.
3) Interpret common practice guidelines for obtaining a polysomnogram in children prior to consideration of undergoing an adenotonsillectomy.
4) Consider the implications of using common anti-inflammatory medications for pain control following an adenotonsillectomy, including possible complications requiring trips to the emergency department.
5) Recognize the possibilities regarding weight gain following an adenotonsillectomy.

Rhinology

1) Communicate in a coordinated manner regarding common manifestations of pediatric chronic rhinosinusitis.
2) Recognize the implications of anti-Pneumococcal vaccines on the prevalence and complications of pediatric sinusitis.
3) Describe the advantages and disadvantages of different surgical approaches for treatment of juvenile nasopharyngeal angiofibroma.
4) Understand long term implications in patients undergoing sinus surgery for complications of acute sinusitis.

Otology

1) Recognize the long term costs to individuals and society of pediatric cochlear implantation.
2) Define the indications for cochlear implantation in children, particularly as it relates to the hearing loss identified on auditory brainstem response testing.
3) Use the clinical practice guidelines regarding tympanostomy tube placement in children.
4) Recognize the indications of a canal wall up vs. canal wall down mastoidectomy in children.
5) Describe surgical treatment options of cochlear nerve deficiency.

Head and Neck

1) Compare different diagnostic imaging modalities in the management of pediatric patients with lateral neck abscesses.
2) Compare potential genetic etiologies of thyroid carcinoma in pediatric patients.
3) Describe common etiologies of pediatric neck masses, including diagnostic and therapeutic modalities.
4) Apply guidelines for use of Propranolol in the treatment of infants with hemangiomas
5) Recognize the classification of vascular anomalies in children.

Medium Used

The Home Study Course is available as printed text. 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 a maximum of 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 record the amount of credit claimed based on the number of hours actually spent in this activity. Indicate this amount in the appropriate section of the exam in order to either receive *Credit* or to have exam results provided to the Training Program Director.

PHYSICIANS ONLY: In order to receive *Credit* for this activity **a post-test score of 70% or higher is required**. Credit will not automatically be awarded. Only when you achieve a score of 70% or higher on the post-test will you be awarded *Credit.* A one-time retest opportunity will be available with a retest fee.

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.**

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This 2015 Home Study Course Section 1does not include discussions of any drugs and devices that have not been approved by the United States Food and Drug Administration.

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June 10, 2016: Deadline for all 2015-16 exams to be received without late score fee**.**

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.

CONGENITAL AND PEDIATRIC PROBLEMS
Section 1 September 2015
Outline

I. Airway, Bronchoesophagology, and Laryngology

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CONGENITAL AND PEDIATRIC PROBLEMS
SELECTED RECENT MATERIALS—REPRODUCED IN THIS STUDY GUIDE

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. EBM level 1.....74-79

Summary: This is a multicenter, prospective, randomized placebo-controlled trial of perioperative dexamethasone as a risk factor for postoperative bleeding following tonsillectomy. Using a noninferiority study design, perioperative dexamethasone was not associated with excessive clinically significant bleeding requiring hospital admission or reoperation, but increased mild, self-reported bleeding events could not be excluded.

Katz ES, Moore RH, Rosen CL, et al. Growth after adenotonsillectomy for obstructive sleep apnea: an RCT. *Pediatrics*. 2014; 134(2):282-289. EBM level 1.....80-87

Summary: This article describes secondary outcomes from a multicenter, randomized controlled trial of adenotonsillectomy in children for treatment of obstructive sleep apnea evaluating anthropometric changes. The adenotonsillectomy children demonstrated significantly greater weight increases in all weight categories at the 7-month follow up compared to the children in the watchful waiting group. This occurred in both overweight and non-overweight children, but overweight children were more likely to be obese at follow up.

Kheirandish-Gozal L, Bhattacharjee R, Bandla HP, Gozal D. Antiinflammatory therapy outcomes for mild OSA in children. *Chest*. 2014; 146(1):88-95. EBM level 4.....88-95

Summary: This is a retrospective review of 836 children with mild obstructive sleep apnea treated with a combination of 12 weeks of an intranasal steroid and oral montelukast to determine polysomnography outcomes. A beneficial response was found in >80% of children. The authors recommend implementation of a multicenter randomized trial to further establish the role of anti-inflammatory therapy for children with mild OSA.

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. EBM level 1.....96-110

Summary: This is a clinical practice guideline produced for otolaryngologists by the American Academy of Otolaryngology–Head and Neck Surgery Foundation to provide evidence-based recommendations for using polysomnography to assess sleep-disordered breathing prior to tonsillectomy in children aged 2 to 18 years. Specific action statements were formulated regarding the indications for polysomnography, advocating for polysomnography, communication with the anesthesiologist, inpatient admission for children with obstructive sleep apnea, and the use of unattended polysomnography.

IV. Rhinology

Summary: This article presents a systematic review of English-language articles reporting on results of surgical management of juvenile nasopharyngeal angiofibroma published between 1990 and 2012. The authors separately analyze those studies reporting individual patient data (mainly case reports and small case series) and aggregate patient data (larger case series and prospective studies).

Summary: This article is a summary of an expert panel consensus which was convened to help optimize the diagnosis and management of pediatric chronic rhinosinusitis (PCRS). The conclusions were assembled after using a Delphi method survey of nine experts and can be categorized as topics relevant to the definition and diagnosis of PCRS, medical management, adenoiditis/adenoidectomy, and endoscopic sinus surgery and turbinate surgery.

Summary: This is a population study examining the risk of hospitalization for pneumonia, sinusitis, and empyema following vaccination with pneumococcal conjugate vaccines PCV7 and PCV13. This study shows reduced risk of hospitalization for pneumonia in children under age 5 years and sinusitis in children under 2 years.

Summary: This is a retrospective study of 91 pediatric patients who underwent endoscopic sinus surgery and *S. pneumoniae* was identified via intraoperative culture. Comparison was made of the serotype of *S. pneumoniae* identified before and after 13-valent pneumococcal conjugate vaccine (PCV13) vaccinations were implemented. Following the introduction of PCV13, the rate of isolation of *S. pneumoniae* decreased, particularly of serotype 19A.

Summary: This is a retrospective study of 86 pediatric patients who were hospitalized and treated for complications of acute sinusitis. Overall, these patients, whether they were initially treated medically or surgically, were unlikely to require secondary endoscopic sinus surgery in the future.

V. Otology

Summary: This is an excellent article presenting the largest case series on auditory brainstem implants for children with cochlear nerve deficiency. Speech and language results and reasonable expectations from both cochlear implantation and auditory brainstem implantation are discussed.

Summary: This article provides a review of clinical outcomes of children who had "no response" diagnostic auditory brainstem responses, which was highly predictive of receiving a cochlear implant in the vast majority of children (a few children did not receive cochlear implants for various reasons but not due to residual hearing). Sound recommendations regarding caregiver counseling and treatment planning are outlined.

Summary: This article presents a large case series of canal wall-up and canal wall-down mastoidectomy in children with cholesteatoma. The authors present compelling reasoning for choosing either procedure depending upon the clinical scenario and a variety of other factors. Reasonable expectations for outcomes, both with respect to recidivism and hearing, are presented.

Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children. *Otolaryngol Head Neck Surg*. 2013; 149(1S):S1-S35. EBM level 1.....170-204

Summary: Rosenfeld et al provide an excellent, state-of-the-art review and clinical practice guideline regarding tympanostomy tubes in children that makes very clear recommendations for this extremely common surgical procedure.

Semenov YR, Yeh ST, Seshamani M, et al. Age-dependent cost-utility of pediatric cochlear implantation. *Ear Hear*. 2013; 34(4):402-412. EBM level 2.....205-215

Summary: An excellent, multi-center NIH funded study yielded this analysis of the effect of age at the time of cochlear implantation on educational placement, quality of life, and cost to society amongst many other findings. Early implantation (patient age <18 months) is shown to be clearly beneficial to individuals and society. Some barriers to early implantation are exposed along with the difficulties in overcoming these barriers.

VI. Head and Neck

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. EBM level 4.....216-219

Summary: This article investigates the utility of ultrasound vs computed tomography (CT) in the diagnosis of pediatric lateral neck abscesses. This retrospective study compares ultrasound and CT accuracy to diagnose lateral neck abscesses which were confirmed by incision and drainage procedures. Ultrasound imaging was found to have similar sensitivity and positive predictive value and higher specificity as compared to CT imaging for the diagnosis of lateral neck abscesses.

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. EBM level 2.....220-232

Summary: This article summarizes the report of the multidisciplinary consensus conference on the initiation and use of propranolol for infantile hemangiomas (IH). The pharmacologic properties and adverse events of propranolol in the pediatric population were reviewed. Recommendations were made regarding when to treat IH; contraindications to treatment with propranolol; pretreatment ECG; propranolol use in PHACE syndrome; formulation, target dose, and frequency of propranolol; initiation of propranolol; and monitoring during treatment.

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. EBM level 4.....233-237

Summary: This article investigates the BRAF V600E mutation in pediatric papillary thyroid carcinoma (PTC). In adult papillary thyroid carcinoma, the BRAF V600E mutation predicts more aggressive disease. This study reveals that the BRAF V600E mutation is more prevalent than previously reported in pediatric PTC patients, but the mutation was not associated with aggressive clinical features in the pediatric population.

Meier JD, Grimmer JF. Evaluation and management of neck masses in children. *Am Fam Physician*. 2014; 89(5):353-358. EBM level 5.....238-243

Summary: This article summarizes the evaluation and management of neck masses in children. Neck masses are divided into three categories: developmental/ congenital, inflammatory/reactive, and neoplastic. Depending on the history of the neck mass, laboratory or imaging studies may be indicated. Management depends on what category the neck mass falls in and ranges from watchful waiting to antibiotic therapy, incision and drainage, or surgical excision.

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. EBM level 5.....244-258

Summary: This article provides an algorithm for the diagnosis, management, and treatment for vascular anomalies. The algorithm utilizes the classification system established by the International Society for the Study of Vascular Anomalies (ISSVA) separating the vascular tumors and vascular malformations along with the use of radiological studies to guide practitioners.

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The Laryngoscope

The National Cost Burden of Bronchial Foreign Body Aspiration in Children

Irene A. Kim, MD; Nina Shapiro, MD; Neil Bhattacharyya, MD

Objectives/Hypothesis: Foreign body aspiration (FBA) continues to be a concerning pediatric problem, accounting for thousands of emergency room visits and more than 100 deaths each year in the United States. The costs incurred with hospitalizations and procedures following these events are the focus of this study.

Study Design: Retrospective review.

Methods: The Nationwide Inpatient Sample from 2009 to 2011 was analyzed, and all cases with pediatric bronchial foreign body aspirations (International Classification of Diseases-9 codes: 934.0, 934.1, 934.8, and 934.9) were reviewed. Cases were analyzed to determine type of foreign body aspiration, procedural interventions performed, duration of inpatient stay, mortality rate, complications, and posthospitalization disposition. The median length of hospital stay and total costs associated with aspiration events were determined.

Results: An estimated 1,908 $\pm$ 273 pediatric bronchial FBA patients were admitted annually over the 3-year period (mean age, 3.6 $\pm$ 0.3 years; 61.3% $\pm$ 1.9% male). The ratio of foreign object aspiration to food aspiration was 5:3. Overall, 56%.0 $\pm$ 3.6% of the patients underwent a bronchoscopic procedure for foreign body removal; of those, 41.5% $\pm$ 2.5% had a foreign body removed at the time of the endoscopy. The hospital mortality rate associated with bronchial aspiration was 1.8% $\pm$ 0.4%; and 2.2% $\pm$ 0.5% of patients were diagnosed with anoxic brain injury. The median length of stay was 3 days (25th–75th interquartile range, 1–7 days).The median charges and actual costs per case were $20,820 ($10,800–$53,453) and $6,720 ($3,628–$16,723), respectively.

Conclusion: The annual overall inpatient cost associated with pediatric bronchial foreign-body aspiration is approximately $12.8 million. Combined, the rate of death or anoxic brain injury associated with pediatric foreign body is approximately 4%.

Key Words: Foreign body, aspiration, choking, bronchial, national, cost.

Level of Evidence: 2C.

***Laryngoscope*, 00:000–000, 2014**

INTRODUCTION

Foreign body aspiration poses a significant public health issue because it accounts for thousands of emergency room visits and more than 100 deaths each year in the United States alone. In fact, according to the Centers for Disease Control and Prevention, pediatric FBA accounted for more than 17,500 emergency room visits in 2001.[1–3]

The pediatric population is globally more affected than older patient cohorts by FBA of both food and nonfood objects, given the inherent characteristics of this group. Young children are more likely to explore their environment by placing objects into their mouths and unfortunately have underdeveloped swallowing and coughing mechanisms. Thus, the majority of patients with FBA are younger than 5 years old.[1] When these patients present to the emergency room with a witnessed choking event—or concerning symptoms such as shortness of breath, cough, or wheezing—the patients' history, clinical examination, and radiographic studies usually prompt the healthcare provider to consult an otolaryngologist who is equipped to perform a bronchoscopy in the operating room. The patients are then typically admitted following these procedures, or for observation if a procedure is not performed.

Bronchial FBAs lead to numerous hospital admissions and procedures each year, but related hospital charges and costs to the healthcare system have not been objectively delineated previously. The aim of this study was to review and examine FBA cases gathered from the 2009 to 2011 Nationwide Inpatient Sample (NIS) to determine the type of foreign body involved, procedural interventions performed, duration of inpatient stay, mortality rate, complications, posthospitalization disposition, and the overall healthcare costs of FBA in the United States.

MATERIALS AND METHODS

The data source for this study consisted of the NIS for the calendar years 2009 to 2011. This study was reviewed by our

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TABLE I.
Quartile Stratification and Overall Mean Length of Stay, Actual Costs, and Total Charges per Hospital Admission.

Quartile	Mean Length of Stay	Actual Costs ($)	Total Charges ($)
First	0.80 ± 0.02 days	2,306 ± 52	6,518 ± 173
Second	2.00 ± 0.01 days	5,046 ± 57	15,371 ± 171
Third	4.12 ± 0.07 days	10,648 ± 211	33,118 ± 699
Fourth	21.0 ± 1.13 days	68,475 ± 3831	209,537 ± 14,207
Overall mean	7.08 ± 0.96 days	21,479 ± 2,432	65,590 ±7,819

hospital institutional review board and deemed exempt from review. For each of these calendar years, all admissions with a pediatric (age ≤ 16 years) foreign-body aspiration diagnosis code (International Classification of Diseases [ICD]-9 diagnosis codes: 934.0, 934.1, 934.8, and 934.9) were extracted. The data were then imported into SPSS (version 21.0, Chicago, Illinois) for analysis.

Standard descriptive demographic information was computed for the admission population. The incidence of food versus object aspiration, the airway procedure intervention rate (ICD-9 procedure codes—bronchoscopy: 33.22, 33.23, and 33.24; bronchoscopy with foreign body removal: 98.15; laryngoscopy or tracheoscopy: 31.42; foreign body removal from larynx, pharynx, or site not otherwise specified: 98.13, 98.14 and 98.20) were determined. Data for length of stay, total charges, and actual costs were extracted and divided into quartiles because they were not normally distributed. The mean values for length of stay, total charges, and actual costs were computed for each quartile.

Finally, disposition status for the population including inpatient death and the incidence of anoxic brain injury (ICD-9 code 348.1) was also tabulated. Data were analyzed using the complex sample algorithm, which takes into account survey design variables contained within the NIS that allow for estimation of these variables at the national level. In accordance with published analyses from the Agency for Healthcare Research and Quality, data were considered reliable as a national estimate if the relative standard error of the estimate was less than 30%.[4]

RESULTS

An estimated 1,908 ± 273 pediatric bronchial foreign-body aspiration patients were admitted annually over a 3-year period. Of this group, 61.3% ± 1.9% were male, with an average age at presentation of 3.6 ± 0.25 years. The ratio of nonfood foreign object aspiration to food aspiration was 5:3. Approximately half of the patients (56.0 ± 3.6%) underwent an airway endoscopic procedure (1068 ± 117 cases, annually) for diagnostic and/or therapeutic purposes. Among those children undergoing airway endoscopy, 41.5% ± 2.5% had a foreign body removed at the time of the endoscopy. Following their hospital stay, 86.6% ± 2.0% of patients were discharged to home without nursing care; 5.3% + 1.6% were discharged to home with home healthcare; 3.5% + 0.7% were transferred to another hospital; and 2.6% + 0.5% were transferred to a skilled care facility. Forty-one patients (2.2% ± 0.5%) suffered anoxic brain injury and 34 patients died, representing a hospital mortality rate of 1.8% ± 0.4%.

Data for length of stay, total charges, and actual costs were extracted and divided into quartiles because they were not normally distributed. The median length of stay was 3 days (25th–75th interquartile range, 1–7 days). The median charges and actual costs per case were $20,820 ($10,800–$53,453) and $6,720 ($3,628–16,723), respectively. Table I presents the means for length of stay, charges, and actual costs for each quartile, as well as the overall means for these values.

DISCUSSION

Bronchial FBA continues to pose a significant healthcare concern in the pediatric population. Although the vast majority of these events are nonfatal, thousands of patients present to the emergency room for evaluation, procedures, and admissions. Our study, which included aggregated 2009 to 2011 data from the NIS, included information from nearly 1,149 (unweighted N) admissions. Incorporating sample weights and the structured survey design variables from the NIS allows for extrapolation to an overall national estimate of 1,908 ± 273 pediatric airway foreign bodies, with approximately $41.0 million in inpatient healthcare expenditures annually.

There exists some heterogeneity in the literature regarding the most common type of foreign body aspirated among pediatric patients; a recent study reviewing 72 articles showed that 94% of studies reported food foreign bodies as the most frequently aspirated items.[1] In our study, the ratio of nonfood object aspiration to food object aspiration in the study was 5:3. Regardless of whether an aspirated object is edible or not, its size and shape are important considerations. Various cylindrical and spherical objects (nuts, hard candies, grapes, marbles) are capable of occluding the pediatric airway.[1] What remains constant and perpetually concerning is the morbidity of these events, as well as the nonnegligible incidence of anoxic brain injury and death (2.2% and 1.8%, respectively, in this study). This is the first study to quantify the incidence of anoxic brain injury with bronchial foreign body aspiration. Clearly, these rates for anoxic brain injury and mortality are concerning in and of themselves.

Currently, to our knowledge, no studies reviewing data regarding only airway FBA admissions have been performed. There does exist a study of patient admissions for both airway and esophageal foreign bodies from the Kids' Inpatient Database 2003 performed by Shah et al.; there was a 3.4% mortality rate among patients and the average length of stay was 11.7 days.[5] The mean total charges were $34,652.[5] Our study, which focused on bronchial foreign body aspirations alone, showed a $20,820 charge for each hospital admission and an annual overall inpatient cost associated with pediatric bronchial FBA to be approximately $12.8 million. One notable difference between our study and that of Shah et al. concerns the sampled hospitals. Shah et al. examined foreign body admissions in a database of

primarily pediatric hospitals, whereas our study analyzed data from a wider selection of hospitals in the United States. Therefore, these data should be viewed as complementary.

Bronchial FBA contributes to nonlethal events that can cause significant medical morbidity and produce a considerable socioeconomic burden. For purposes of comparison with respect to hospital charges, a pediatric intensive care unit admission for an intubated patient in status asthmaticus who suffers a complication is $117,184, and average length of intensive care unit stay is 10 days.[6] Pediatric firearm-related injuries show an average inpatient admission charge of $70,164, whereas the total annual charges for the entire United States is $371 million.[7] Thus, although the charges for foreign body aspiration-related admissions are relatively small on an individual patient basis in comparison to those of other acute pediatric conditions, they remain significant.

Studies also reveal that up to 20% of children who suffer FBA can be misdiagnosed and treated incorrectly for more than a month before the correct diagnosis is made.[8,9] When patients present with vague symptoms, and chest radiographs are normal in the first hours to weeks following an event,[10] a diagnosis of a FBA may not even be considered initially by the healthcare professional. Children whose symptoms subside soon after an FBA event may have several visits to a healthcare provider and be given several medical therapies before being referred for specialty care.[11] Missing such a diagnosis can lead to long-term pulmonary complications such as bronchiectasis, pulmonary abscesses, and irreversible damage of the lung parenchyma—all of which can ultimately require treatment with surgical resection.[8,12] Thus, total healthcare costs related to the workup and treatment of these more chronic conditions have yet to be clearly defined.

Generally, a witnessed choking episode prior to the onset of symptoms has been positively associated with the presence of a true FBA event. Additionally, the presence of a choking event remains important when considering FBA in patients who present with pulmonary symptoms weeks to months after a remote choking episode; an endoscopy can prove to be therapeutic even months after the event. [1] In our study, nearly half of the patients underwent an immediate rigid bronchoscopy for diagnosis and/or therapeutic interventions. Approximately 40% of those patients had a foreign body removed. Our reported negative bronchoscopy rate of approximately 60% is higher than the reported range in the literature of 11% to 46%.[13] Data from the NIS encompasses a wider range of bronchoscopy outcomes because they account for rates across a wider selection of hospitals across the United States and do not selectively reflect those among pediatric otolaryngology subspecialty centers. Academic medical centers reporting lower negative rates may have received referrals from outside hospitals for evaluation of possible airway foreign bodies, perhaps leading to increased positive findings.

Rigid bronchoscopy is considered the safest and most preferred method of airway foreign body removal in children.[8] Interestingly, in cases of low suspicion of FBA, some authors support the cost-effectiveness of an initial flexible fiberoptic bronchoscopy before going straight to a rigid bronchoscopy. In one study, for example, data showed that $1,400 was saved per patient by initially resorting to flexible bronchoscopy. These patients were spared general anesthesia as well; flexible bronchoscopy requires premedication with intrarectal midazolam and can be performed through a facial mask under continuous anesthetic inhalation.[13]

General guidelines suggest that findings of asphyxia, a radio-opaque foreign body on chest X-ray, or unilaterally decreased breath sounds normally warrant an initial rigid bronchoscopy. In other cases, a flexible bronchoscopy can be attempted first.[14] Rhigini et al. presented a "decisional algorithm" to perform a flexible bronchoscopy when patients present with vague symptoms, do not have obvious pulmonary abnormalities on physical examination, and do not show concerning radiographic findings.[13] Martinot et al. performed a cost analysis study that showed both decreased procedural charges ($1,100 rigid bronchoscopy versus $287 flexible bronchoscopy), hospital stay charges, and days of hospitalization when children suspected of having an FB had undergone a flexible bronchoscopy instead of a rigid bronchoscopy first.[14]

Rhigini et al. noted that among their eight patients who did not have a foreign body detected on rigid bronchoscopy, five would have been spared the procedure (and general anesthesia) if their decisional algorithm had been followed and flexible bronchoscopies were performed initially.[13] Perhaps relating patient symptoms to studies analyzing the rates of identifying a foreign body versus the number of procedures done will help guide the healthcare provider into performing the appropriate procedures based on the probability of a true FBA.

However, although some contend flexible bronchoscopy to be a safe and cost-saving diagnostic procedure, there is the risk of FB dislodgement at the time of evaluation. This necessitates that use of flexible bronchoscopy be performed by a senior pediatrician near an operating room in the presence of an otorhinolaryngologist. If an FB is found, rigid bronchoscopy most often needs to be performed anyway; the success of object extraction with flexible bronchoscopy is widely variable and ranges from 10% to 90%.[15] At this time, despite increased costs and need for general anesthesia, rigid bronchoscopy still remains the first technique of choice for pediatric airway foreign body extraction.[15]

The potential consequences of nonlethal airway obstruction secondary to bronchial FBA events are variable, ranging from temporary sequelae to permanent anoxic brain damage or even death. Pulmonary complications include persistent cough, pneumonia, emphysema, and bronchial stenosis[16]; these can persist for months to years. Looking forward, it may be important to investigate the types of complications that our patients may have experienced and stratify them according to incidence and costs incurred. Additionally, it may be helpful to analyze the data further to know what other procedures (tracheostomy, other surgeries) may have been performed secondary to these complications.

Both food and nonfood items pose choking hazards in the pediatric population secondary to this cohort's underdeveloped anatomy and swallowing function. With regard to nonfood products, formal legislation to help prevent FBAs has been established through the Federal Hazardous Substances Act to regulate the packaging, labeling, and manufacturing of these items.[1] The Consumer Product Safety Commission regulates the manufacturing and labeling of toys, helping to decrease the dangers associated with bronchial aspiration of toy parts. Similar guidelines do not exist for food products, although there has been work directed to establish such measures.

To date, there is no official federal legislation regulating the production and labeling of food products. Lobbying efforts have resulted in the Food Choking Prevention Act (introduced to Congress in 2005) requiring the Commissioner of Food and Drugs to educate parents of young children and to designate a week of increased dissemination of choking information to the public. The American Academy of Pediatrics released a policy statement (Prevention of Choking Among Children) in 2010 with recommendations for government agencies, manufacturers, parents, teachers, and healthcare professionals to help prevent FBA.[17] Some of these include placing warning labels on high-risk foods, recall of foods that are known to be potentially hazardous, education of cardiopulmonary resuscitation and choking first-aid techniques to parents and child care providers, and redesigning of existing foods to minimize their choking risk.[17] Standardized safety guidelines for the production and packaging of commonly implicated objects, as well as developing public health initiatives to raise awareness about the dangers of bronchial FBA, will help protect children from potentially catastrophic events.

CONCLUSION

Foreign body aspiration events affect thousands of pediatric patients and their families annually, and the incurred charges contribute to the socioeconomic burden.[5] Preventative measures are key.[1,11] Currently, increasing efforts are underway to promote public health initiatives and government legislation that help regulate the manufacturing and labeling of both food and nonfood objects that pose potential aspiration risks. [1] Educating primary care physicians, caregivers, and parents about appropriate eating habits, as well as the risks associated with particular foods, can help prevent many of these events. Because most deaths due to FBAs occur in the home environment, parents and caregivers should be educated about the signs and symptoms of aspiration, as well as the importance in taking swift action to present their children to healthcare professionals for timely evaluation.[16] While most children are successfully discharged to home in good condition, a small but nonnegligible number of patients suffer catastrophic anoxic brain injury and death.

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Original Investigation

Systemwide Change of Sedation Wean Protocol Following Pediatric Laryngotracheal Reconstruction

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IMPORTANCE Pediatric laryngotracheal reconstruction (LTR) remains the standard surgical technique for expanding a stenotic airway and necessitates a multidisciplinary team. Sedation wean following LTR is a critical component of perioperative care. We identified variation and communications deficiencies with our sedation wean practice and describe our experience implementing a standardized sedation wean protocol.

OBJECTIVE To standardize and decrease length of sedation wean in pediatric patients undergoing LTR.

DESIGN, SETTING, AND PARTICIPANTS Using Institute for Healthcare Improvement (IHI) methodology, we implemented systemwide change at a tertiary care center with the goal of improving care based on best practice guidelines. We created a standardized electronic sedation wean communication document and retrospectively examined our experience in 29 consecutive patients who underwent LTR before (n = 16, prewean group) and after (n = 13, postwean group) wean document implementation.

INTERVENTIONS Implementation of a standardized sedation protocol.

MAIN OUTCOMES AND MEASURES Presence of sedation wean document in the electronic medical record, length of sedation wean, and need for continued wean after discharge.

RESULTS The sedation wean document was used in 92.3% patients in the postwean group. With the new process, the mean (SD) length of sedation wean was reduced from 16.19 (11.56) days in the prewean group to 8.92 (3.37) days in the postwean group (P = .045). Fewer patients in the postwean group required continued wean after discharge (81.3% vs 33.3%; P = .02).

CONCLUSIONS AND RELEVANCE We implemented a systemwide process change with the goal of improving care based on best practice guidelines, which significantly decreased the time required for sedation wean following LTR. Our methodological approach may have implications for other heterogeneous patient populations requiring a sedation wean.

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Laryngotracheal stenosis remains a significant issue in the pediatric population.[1-3] Originally introduced in 1972, laryngotracheal reconstruction (LTR) has evolved to include a variety of techniques for expanding a stenotic airway, including airway reconstruction with a rib cartilage graft.[4,5] Through open surgical techniques, success rates in achieving decannulation and avoiding tracheotomy approached 90%.[6] Perioperative management involving a multidisciplinary team is vital to the success of airway reconstruction.[7-12]

During the postoperative period in the pediatric intensive care unit (PICU), the patient is usually nasotracheally intubated, requiring sedation and analgesia with or without neuromuscular blockade. The physical and pharmacologic precautions minimize excessive neck movement that could place tension on the newly repaired airway and decrease movement of the endotracheal tube that could disrupt suture lines and cartilage grafts, cause repeated trauma to the airway mucosa, or result in accidental extubation. Pharmacologic restraints and mechanical ventilation in the PICU typically are necessary for 3 to 7 days, depending on the type of airway reconstruction.[5] Following extubation, tapering of sedative medications becomes the primary focus of postoperative care with the goal of avoiding sedative medication withdrawal syndromes.[13] Ineffective tapering may result in analgesia-related complications, prolonged hospital stay, increased hospital costs, and family dissatisfaction.[14] Research on the best pharmacologic approaches to sedation, neuromuscular blockade, and withdrawal monitoring is ongoing.[15-17]

Similar to other airway centers around the world, at our tertiary care center, sedation wean is recognized as a major postoperative concern in the LTR patient population. While a suggested sedation wean protocol exists in the PICU based on best practice guidelines, actual provider practice varies and the wean approach often changes on transfer to the ward, as implementation of standardized approaches to sedation weaning algorithms in all locations has proven difficult. Furthermore, there is no standardized approach to communication of the sedation wean algorithm during the transfer of LTR patients from the PICU to the ward. Consequently, systemwide variability has resulted in avoidable complications, including oversedation, prolonged weans, and miscommunication among health care practitioners (ie, otolaryngologists, intensivists, hospitalists, residents, pharmacists, nurses, and social workers) in our LTR patient population.

To address systemwide issues in implementing a commonly accepted sedation wean protocol, we turned to the Institute for Healthcare Improvement (IHI) methodology.[18] Herein, we describe our experience in applying the IHI methodology to (1) identify key issues regarding transitions of care, and (2) implement a standardized sedation wean protocol. Given the relatively few patients, as well as similar patient demographics and medical backgrounds, the LTR population represents an ideal patient population to trial a rigorous approach to standardize sedation weans.

Methods

Ethical Concerns and Study Setting

The institutional review board of the Massachusetts Eye and Ear Infirmary (MEEI) approved the retrospective review of patient data. As specific pharmacologic approaches to sedation wean guidelines had previously been established at Massachusetts General Hospital for Children (MGHfC), these guidelines served as a basis for patient management and implementation, ensuring equivalent standard of care to all patients.

The study took place at MGHfC and MEEI. MGHfC is a pediatric tertiary care academic hospital that is physically integrated within the Massachusetts General Hospital (MGH). MGHfC has a dedicated PICU, neonatal ICU, pediatric operating rooms, and pediatric patient wards. MGHfC patient wards are managed by pediatricians and associated pediatric specialists. MEEI is an adjacent tertiary care academic medical hospital that treats both adult and pediatric patients. MEEI has a dedicated space for pediatric outpatient visits, operating rooms, and inpatient rooms that are largely managed by pediatric otolaryngologists and pediatric consultant subspecialists. The 2 hospitals share academic affiliations, some physician and resident coverage, and an electronic health record (EHR) system. MGHfC and MEEI are otherwise distinct facilities in terms of space, support staff, management, and hospital policies.

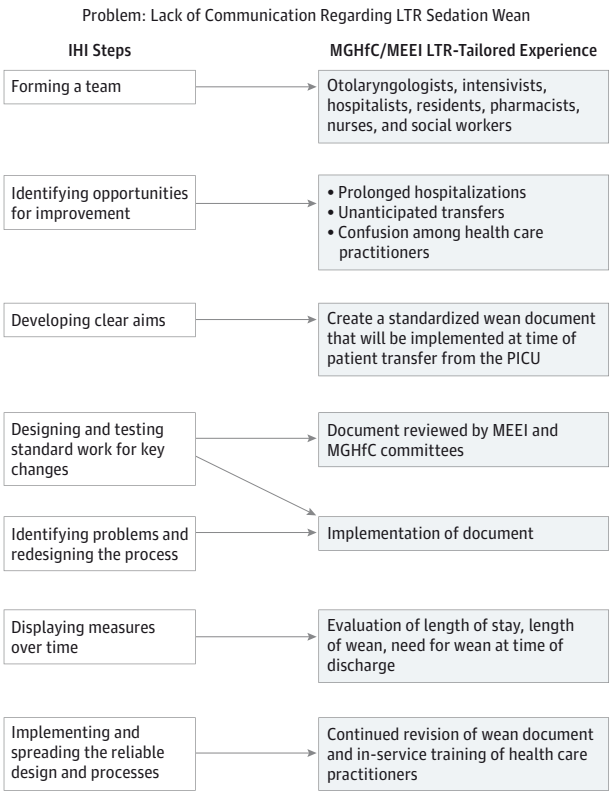
The Pediatric Airway, Swallowing and Voice Center is an unique collaboration between the MEEI and MGHfC. Patients who require intensive care are transferred from the MEEI operating room to the MGHfC PICU. Pediatric airway reconstruction patients, such as those undergoing LTR, constitute most of these transfers. Following postoperative care in the PICU, patients are either transferred to the floor at MGHfC or MEEI, depending on individual patient needs. The physically and organizationally unique MEEI-MGHfC relationship potentially exposes our patients to risk for communication breakdown between the health care practitioners within each institution.

Planning the Intervention

The Institute for Healthcare Improvement is a recognized health care quality improvement organization that provides resources, such as white papers and "Field Guides," for implementing systemwide change. We used the IHI Field Guide's 7 steps to implement change across 2 institutions.[18] The 7 steps comprise forming a team, identifying opportunities for improvement, developing clear aims, designing and testing standard work for key changes, identifying failures or problems and redesigning the process, displaying measures over time to assess progress, and implementing and spreading the reliable design and processes (**Figure 1**).

The first step, building a team, is a challenging task, especially with multiple physician subspecialists and other health care practitioners across hospital systems. One strategy to engage health care practitioners in safety efforts is to focus on projects that are important to the entire medical staff. At the onset, we organized a focus group led by a senior otolaryngology attending physician (C.J.H.). In IHI terms, this individual was the "physician champion." Focus group participants con-

Figure 1. Institute of Healthcare (IHI) Improvement Algorithm Adapted to Improve Pediatric Sedation Wean in Postoperative LTR Patients



IHI Field Guide's 7 steps used to improve outcomes related to sedation wean. LTR indicates laryngotracheal reconstruction; MEEI, Massachusetts Eye and Ear Infirmary; MGHfC, Massachusetts General Hospital for Children; and PICU, pediatric intensive care unit.

vened in August 2012 and included attending pediatric otolaryngologists, pediatric intensivists, hospitalists, fellows, residents, nurses, pharmacists and social workers. The multidisciplinary focus group reviewed our center's experience for all LTR patients in 2011 and 2012. Three issues stood out among LTR patients related to sedation wean: (1) prolonged and disparate wean protocols, (2) unanticipated transfer from floor to ICU-level care because of oversedation, and (3) confusion among health care practitioners regarding sedation wean protocol.

The focus group identified key communication breakdowns typically occurred during transfer of care from the PICU to the MGHfC ward or MEEI ward. The group identified that existing hospital documents, in the PICU and on patient transfer notes to the ward, did not routinely convey a plan for weaning sedation, arguably the main reasons for continued postoperative inpatient status. Sedation wean approaches, which typically consists of methadone and lorazepam tapered at regular intervals, were communicated from physicians to physicians or nurses to nurses, in inconsistent fashion. In addition, sedation weans typically required management on MGHfC wards instead of MEEI wards due to lack of existing wean protocols at MEEI and training.

On the basis of information gathered at the focus group, we formulated an IHI-based action plan and developed a "sedation wean document" that contained essential information about the postoperative sedation wean, including dates, times, and dosages of key medications, that was readily comprehensible to all team members. The document was based on previously established MGHfC sedation wean medication calculations and documents; original documents were authored by the MGHfC PICU Withdrawal Committee and adapted from published literature.[19] Because we previously determined that transfer from the PICU to the ward was the most likely time for communication breakdown, it was determined that the document should be placed in the EHR as a stand-alone document at the time of patient transfer. Because the intensivists and associated pediatric residents in the PICU are in charge of the sedation wean medications, it was agreed that they would be the authors of the document and communicate its information to other health care practitioners, including otolaryngology and nursing staff.

Methods of Evaluation and Statistical Analysis

We compared the primary outcome of sedation wean length in LTRs from baseline period of 2011 through 2012 (prewean group) and after implementation of the sedation wean document (LTR in 2013-2014; postwean group). Additional outcomes included presence of sedation wean document at time of transfer to the floor and discharge (process measure), location of discharge, hospital length of stay (LOS), and need for continued wean at time of discharge (balance measures). A statistical process control run chart of sedation wean length with baseline data and 99% confidence intervals was constructed with an XmR chart and then reanalyzed following new process using Minitab version 17.1 (Minitab Inc). Descriptive statistics were used with parametric data presented as mean and standard deviation. The *t* test (unpaired) and Fisher exact test were used for study arm comparisons. Statistical analyses were performed by Stata version 12.1 (StataCorp). Results were considered statistically significant at $P < .05$.

Results

Implementation of New Process

The sedation wean document was revised several times by stakeholders, with the final form completed in February 2013 (**Figure 2**). The document was converted into an EHR template titled "MGH/MEEI Sedation Wean Plan," accessible by health care practitioners at both hospitals and all 3 locations. Physicians and nurses at all locations received in-service training for its implementation as a new standard communication tool.

Figure 3 provides a run chart of 29 consecutive LTR patients over 3.5 years, with a baseline period (prewean, n = 16) and postprocess implementation (postwean, n = 13). The process measure of an electronic sedation wean plan was adopted in 12 of 13 eligible patients (92%). There are 2 notable patient outliers in the prewean group, with length of wean longer than others in the study cohort. These patients had pro-

Figure 2. MGH/MEEI Sedation Wean Document

Post LTR Transition from PICU Suggested Sedation Wean Communication Form
Date of Operation:
Type of Operation:
Date Admitted to PICU:

Assessment
Type and Duration of Continuous Sedation While Intubated:
Midazolam
Morphine
Fentanyl
Propofol
Dexmedetomidine
Other

Approach to Wean Plan (refer to chart below):
***The following is an illustrative approach, individual patients will vary and clinicians must interpret accordingly**
Consult pain team if concerns or further tailored therapy needed.
Original Dose (OD) of opiate replacement (methadone/morphine) was calculated at ____ mg
Original Dose (OD) of benzodiazepine replacement was calculated at ____ mg

Day/Date	Infusions for 7-14 days **SHORT-TERM THERAPY PROTOCOL**	Infusions > 14 days **LONG-TERM THERAPY PROTOCOL**	Plan following, doses as below:
Day 1 ___	Dose "Original Dose (OD)" every 6 hours for 24 hours	Dose "Original Dose (OD)" every 6 hours for 24 hours	
Day 2	Consider change to PO (no dose change) for 24 hours	Consider change to PO (no dose change) for 24 hours	
Day 3	Decrease OD 20%, every 8 hours for 24 hours	Decrease OD 20%, every 6 hours for 48 hours	
Day 4	Decrease OD 20%, every 8 hours for 24 hours	No change	
Day 5	Decrease OD 20%, every 12 hours for 24 hours	Decrease OD 20%, every 8 hours for 48 hours	
Day 6	Decrease dose 20%, every 24 hours for 24 hours	No change	
Day 7	Discontinue	Decrease OD 20%, every 12 hours for 48 hours	
Day 8		No change	
Day 9		Decrease OD 20%, every 24 hours for 48 hours	
Day 10		No change	
Day 11		Discontinue	

Rescue: If symptoms appear through weaning, consider providing additional dose of medications to treat. Dose that captured patient in PICU was:
Morphine __ mg
Lorazepam __mg
Consider patient condition has changed and expert consultation (pain team) is needed.

Patient Transferred out of PICU on day __ of planned __ day wean. See chart for further dose adjustments.

Contact Information:
PICU and PICU pharmacist for prior wean information
Pain team for new patient withdrawal concerns

Wean document based on best practice guidelines. LTR indicates laryngotracheal reconstruction; MGH/MEEI, Massachusetts General Hospital/Massachusetts Eye and Ear Infirmary; and PICU, pediatric intensive care unit.

longed length of wean because of communication breakdown between health care practitioners, resulting in sedation withdrawal syndromes, transfers to the ICU from the floor, and prolonged hospital stays. The first patient in the postintervention period did not have the formal electronic sedation document placed in the EHR. The multidisciplinary team noted the failure and recognized education gaps in pediatric house staff rotating in the PICU and subsequent training was provided. Assurance of the presence of the wean document at the time of transfer from the PICU became the responsibility of 2 physician leaders, a pediatric intensivist (B.M.C.) and otolaryngology resident (B.L.). Because the first postwean implementation period patient did not have a standardized wean document, the patient was excluded from subsequent outcome analyses of the process.

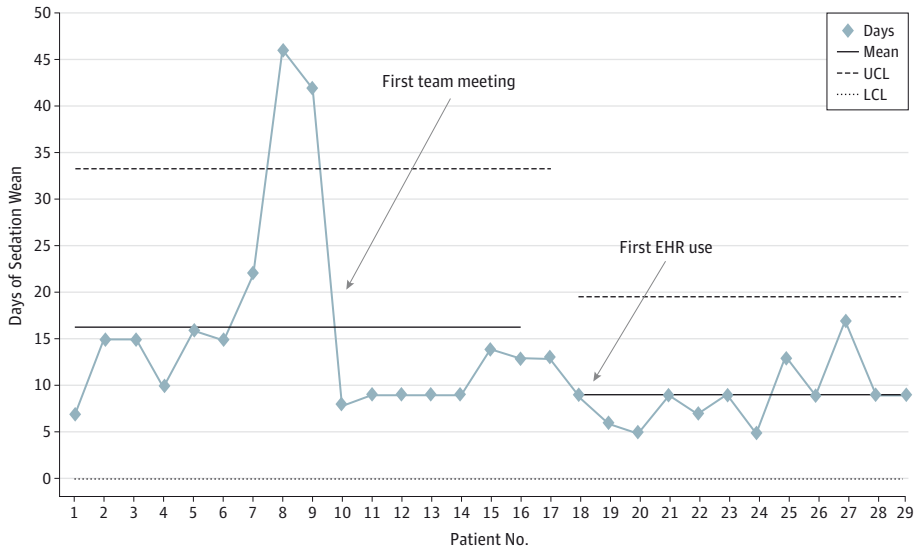
Patient Demographics Before and After Implementation of Sedation Wean Document

Basic demographic information of the baseline prewean and postwean patients were similar. There were no statistical differences between mean (SD) age (2.55 [1.42] vs 1.89 [1.29] years; $P = .22$), female sex (50% vs 17%, $P = .11$), mean (SD) continuous sedation infusion duration (8.94 [3.47] vs 9.17 [3.13] days; $P = .86$), mean (SD) length of mechanical ventilation (10.56 [4.59] vs 10.25 [3.41] days; $P = .84$), mean (SD) PICU LOS (13.44 [5.37] vs 13.75 [4.07]; $P = .87$), and patients with rib cartilage graft (68.8% vs 91.7%; $P = .20$).

Outcomes Following Implementation of Sedation Wean

The **Table** summarizes outcomes between the baseline group and patients following the new process. For the primary out-

Figure 3. Length of Sedation Wean Run Chart



XmR run chart (X stands for observation, and mR, moving range) of consecutive patient sedation wean days with baseline process and new process (P = .01). Dashed lines represent 99% confidence intervals. EHR indicates electronic health record communication form; LCL, lower confidence interval; and UCL, upper confidence interval. Note: patient 17 was excluded from the analysis because this patient did not have a standardized wean document.

come, mean (SD) length of sedation wean was 16.19 (11.56) days in prewean group compared with 8.92 (3.37) days in the postwean group (P = .045). Less variation in sedation wean length was also noted with the new process (Figure 3). Fewer patients postwean process required continued sedation wean after hospital discharge (81.3% vs 33.3%; P = .02). In terms of discharge location, there was a decrease in the number of patients discharged from the MGHfC ward (87.5% prewean vs 41.6% postwean; P = .02), representing an increase in discharge from the PICU and MEEI ward.

In terms of other balance measures, mean (SD) hospital LOS was 17.9 (5.5) vs 16.9 (4.0) days (P = .62) in prewean and postwean group, respectively. Mean length of days spent on the ward was also similar (5.27 days prewean vs 4.3 days postwean; P = .47) (Table). In the prewean baseline, 1 patient was required to be transferred from the MEEI ward to PICU because of oversedation during the sedation wean. No patients required return to PICU because of sedation wean failure or oversedation in the postintervention group.

Discussion

Our quality improvement project using IHI methodology demonstrates a significant impact on length of sedation wean following LTR, a critical aspect of postoperative patient care. The new process was well accepted and used in 92% of eligible patients. Like all process improvement, implementation at the user level is paramount, and we quickly responded to our first missed opportunity, dedicating process champions that likely ensured its use. Our primary outcome of sedation wean length demonstrated a nearly 50% decrease in duration, and fewer patients were discharged requiring a narcotics prescription for continued sedation wean, putting less burden on families. Another beneficial impact to the new process was streamlined care, with fewer patients requiring MGHfC ward care. Prior to the new process, patients would often be transferred to the MGHfC ward for sedation weaning because nursing and physician staff at MEEI did not have a robust policies of sedation wean practice. The sedation wean multidisciplinary process change enabled PICU and MEEI health care practitioners to better manage LTR patients and streamline discharges and location management.

The 2 groups, prewean and postwean, were well matched. We had an equivalent patient population between the prewean and postwean groups in terms of age, sex, and need for a rib graft, which may be considered a general proxy for extent of surgery and potential source of considerable postoperative pain. It is important to account for potential differences in the study population in terms of length of mechanical ventilation and continuous sedation because this may be associated with potential increased sedation wean duration. For example, a patient on mechanical ventilation and continuous sedation for 3 days has a much lower risk for dependence and need for sedation wean compared with a patient receiving mechanical ventilation and continuous sedation for 8 days. We found there was no difference in length of continuous sedation or number of days of mechanical ventilation, which could have a potential impact on duration needed for sedation wean since longer exposure worsens risk for withdrawal.

In terms of LOS outcomes, including PICU, ward, and total LOS, we did not identify any differences between the prewean and postwean study groups. This result was expected, and there are several possible explanations. Principally, LOS depends more on the timing of the postoperative bronchoscopies than the sedation wean. At our institution, the LTR is followed by 2 bronchoscopies, the first at the time of extubation when patient is admitted to the PICU and a second around the time of discharge when the patient is on the ward, ensuring the continued patency of the airway. The exact timing for the first "second look" bronchoscopy is based on both historic and contemporary LTR studies and typically occurs at our institu-

Table. Primary Study Outcomes Between the Baseline Group and Patients Following the New Process

Outcome	Prewean Document (n = 16)	Postwean Document (n = 12)	*P* Value[a]
Length of wean, mean (SD), d	16.19 (11.56)	8.92 (3.37)	**.045**
Total LOS, mean (SD), d	17.88 (5.51)	16.92 (4.01)	.62
LOS on ward, mean (SD), d[b]	5.27 (3.56)	4.33 (1.58)	.47
Continue wean on discharge (yes), No. (%)	13 (81.3)	4 (33.33)	**.02**
Discharge location, No. (%)			
MGHfC floor	14 (87.5)	5 (41.7)	**.02**
Non-MGHfC floor[c]	2 (12.5)	7 (58.3)	

Abbreviations: LOS, length of stay; MGHfC, Massachusetts General Hospital for Children.

[a] Values in boldface are statistically significant.

[b] Patients discharged directly from PICU excluded from analysis (1 patient excluded prewean; 3 patients excluded postwean).

[c] Non-MGHfC floor locations include the pediatric intensive care unit and the Massachusetts Eye and Ear Infirmary floor.

tion around postoperative day 7. In contrast, the timing of the second bronchoscopy typically depends on when the patient is considered safe for discharge and incorporates multiple factors: wound healing, sedation wean length, swallowing function, physical therapy needs, and family readiness. Therefore, while LOS in the PICU is relatively fixed, the LOS on the wards is multifactorial, including sedation wean. The findings of our study are important because they may indicate that at least 1 of these major factors necessitating hospitalization on the wards, the sedation wean can be reduced. Because sedation wean is only 1 factor, it is conceivable that with a larger sample size, one may be able to identify small differences in LOS on the ward. Moreover, given our findings, one could envision performing the bronchoscopy prior to discharge at an earlier time point during the postoperative period, since the patient may be ready for discharge home sooner. With the advent of new LTR techniques such as the "1.5-stage LTR," where an endotracheal tube is inserted through the tracheostoma to stent it open in the immediate postoperative period, it may be argued that an earlier second bronchoscopy would be safe since these patients generally have stable airways.[20] Future studies will need to address safety and outcomes of an earlier "second look" bronchoscopy. Nevertheless, our data suggest that improvements in sedation wean may theoretically lead to an overall shift in the postoperative timeline of patients undergoing LTR.

In this study, we did not examine the efficacy of our weaning protocol in terms of medications or dosages, but rather examined how changing the process of communication among health care practitioners with an initial standardized plan could have an impact on discrete outcomes. We acknowledge that recommendations vary and controversy exists regarding sedation wean best practices.[21] At our hospital, specific sedative mediations and dosages were adapted from recommendations of a large pediatric research network.[19] Furthermore, as part of our sedation wean protocol, we assess withdrawal symptoms every 6 hours to ensure weaning is tolerated. We did not study scoring systems or changes in weaning based on patient symptoms. Because all our patients had similar continuous infusion exposures, our study is more uniform than previous heterogeneous studies in withdrawal care. Compliance with the actual recommendations is a potential area for further improvement. Of note, our length of sedation wean is shorter than achieved with a pharmacy managed methadone tapering protocol, which reduced the mean length of weaning from 24 to 15 days.[22]

Our study fits into the intersection of research on best clinical practices, checklists, and patient handoffs. In terms of best practices, there is often a discrepancy between hospital policy or published guidelines and actual practice patterns. Previous studies have both investigated the implementation of best practices, as well as examined checklists for implementation with positive results.[23-29] Furthermore, numerous studies have identified the need for improved communication at the time of patient handoff.[30-32] Our sedation wean document was designed to address actively all of these issues simultaneously: implement a systemwide best practice recommendations, provision of a checklist-style document readily available to all health care practitioners, and focus on communication of the document at time of patient transfer and handoff.

The question arises, "Can IHI methodology be used in other more common procedures in otolaryngology, such as tonsillectomy, tracheostomy, or tympanostomy tube placement?" IHI methodology was used to implement systemwide change for the transfer of airway reconstruction patients from the operating room to the PICU[28] and has been used in the anesthesia literature as well.[33] In the case of tracheostomy, one can envision generating a uniform electronic form easily interpretable by physicians, nurses, and other health care practitioners that would provide standard information, eg, date of tube placement, type and size of tube, dates of first tracheostomy tube change, and anatomy details, that would travel with the patient during the hospital stay. This type of document would help facilitate communication of critical aspects of patient care, and procedure-specific outcomes may be studied. Furthermore, previous studies in the otolaryngology literature have addressed patient safety initiatives, such as checklists and wrong-sided surgery.[34-36] IHI methodology may be used to identify systemwide patient safety issues and implement change.

Several potential limitations exist in our study. Our findings may be related to the Hawthorne effect, a phenomenon whereby an individual improves or changes an aspect of his or her behavior in response to a change in the environment. There may have been improvement in postoperative care owing to a change in attitudes and behaviors regarding communication spurred by the sedation wean multidisciplinary effort. In terms of transfers to MEEI, it is clear that implementation of the sedation wean document set into place new hospital policies that facilitated patient transfers from the PICU. Also, our small cohort limits our ability to draw statistical conclusions of our secondary outcome end points. The LTR, while readily performed and well studied, it is not a common procedure. Several years of data may be necessary to detect changes in hospital LOS.

Conclusions

We identified variability in sedation wean practices and opportunities for communication improvement. We implemented systemwide process change using IHI methodology with the goal of improving care based on best practice guidelines, which significantly decreased the time required for sedation wean. Our approach to a sedation wean communication in the LTR patient population may be potentially studied in other more heterogeneous patient populations requiring standardized sedation wean protocols.

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Study concept and design: Kozin, Cummings, Rogers, Noviski.
Acquisition, analysis, or interpretation of data: Kozin, Cummings, Lin, Sethi, Noviski, Hartnick.
Drafting of the manuscript: Kozin, Cummings, Noviski.
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Original Investigation

A Retrospective Review of the Progression of Pediatric Vocal Fold Nodules

Heather C. Nardone, MD; Thomas Recko, BA; Lin Huang, PhD; Roger C. Nuss, MD

IMPORTANCE To our knowledge, the rate of change in the size of pediatric vocal fold nodules (VFNs) has not been investigated. Improved understanding of the factors that affect change in VFN size may help to better guide treatment decisions and counselling of families.

OBJECTIVE To characterize the rate of change in the size of pediatric VFNs over time and to identify which factors affect increased rates of improvement.

DESIGN, SETTING, AND PARTICIPANTS Retrospective review of 67 children evaluated in a voice clinic between 2002 and 2011 with a primary diagnosis of VFNs.

EXPOSURE No treatment or behavioral modification only (n = 19) vs targeted voice therapy with or without the treatment of associated conditions (gastroesophageal reflux and allergic rhinitis) (n = 45) vs surgical intervention (n = 3).

MAIN OUTCOMES AND MEASURES Change in VFN grade (graded according to a previously validated scale based on size) over time.

RESULTS Sixty-seven patients with a median (range) age of 6.0 (3.8-20.6) years were analyzed. Median (range) follow-up was 25 (1-119) months. The rate of change in VFN grade over time was significantly associated with large baseline VFN size ($P < .001$) and targeted voice therapy with or without the management of associated conditions or surgery ($P = .01$); the association with postpubescent age was not significant ($P = .09$). The rate of change in VFN grade was not significantly different at 1 and 3 years postbaseline ($P = .33$).

CONCLUSIONS AND RELEVANCE Baseline VFN size, treatment, and patient age are important in predicting the rate of improvement in nodule size over time. Rate of change in VFN size is a gradual decrease that is steady over time. This information can be used to help guide treatment decisions and counsel families of children with VFNs regarding expectations for improvement. Additional study is needed to evaluate whether the same factors that influence nodule size similarly influence parental perception of voice and expert perceptual voice analysis.

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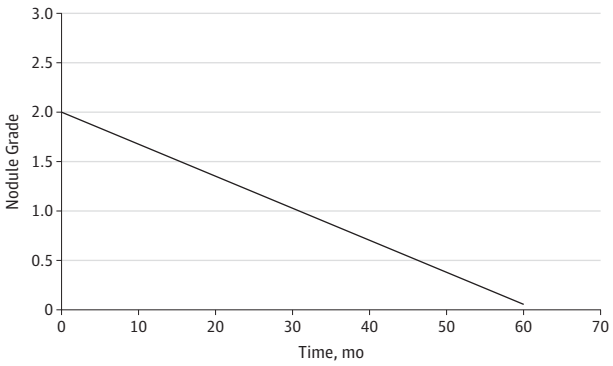
Vocal fold nodules (VFNs) are benign lesions that appear at the junction of the anterior and middle thirds of the vocal fold. They develop as a result of trauma arising from contact between the opposing surfaces of the vocal folds, generally related to voice overuse or to repetitive vocal abuse and vocal strain. Multiple factors may act to create an environment more conducive to VFN formation, including gastroesophageal reflux, allergy, sinusitis, postnasal drip, and chronic cough. There may be a genetic predisposition toward the development of nodules as well.[1]

Among hoarse pediatric patients, VFNs are the most frequently found pathological condition of the larynx.[2] Their prevalence among school-aged children is high, estimated at 16.9%.[3] Commonly used treatments for pediatric VFNs include (1) behavioral management to guide children toward improved vocal hygiene, (2) direct voice therapy, and (3) treatment of exacerbating factors such as allergic rhinitis or gastroesophageal reflux. Surgery to remove VFNs is generally reserved for patients with severe cases and those whose VFNs do not respond to more conservative treatment.

Many clinicians advocate for conservative treatments initially because VFNs resolve spontaneously at puberty in the majority of children, particularly in boys.[1,4] Vocal behaviors including excessive or aggressive voice use that may lead to

Figure 1. Expected Resolution of Vocal Fold Nodules Over Time for Entire Study Population



Extrapolation showing the expected decrease over time for all children (N = 67).

VFN formation often subside as a child matures. However, it has been shown that pediatric hoarseness can have an adverse effect on how others perceive a child and on the child's self-perception.[5] Thus, although many cases eventually resolve without treatment, it is important to have effective treatment options for children who are more severely affected.

There remains little in the literature about the evolution of pediatric VFNs over time. This study was designed to investigate the rate of change in pediatric VFN size over time and to identify which factors influence increased rates of improvement in VFN size.

Methods

This retrospective study was approved by the institutional review board at Boston Children's Hospital. The requirement for patient consent was waived by the institutional review board as a result of the retrospective nature of the study. Children evaluated from 2002 to 2011 in the Voice Clinic at Boston Children's Hospital with a primary diagnosis of VFNs were studied. Transnasal videostroboscopic examination was performed for all patients. An FNL-10RP3 fiberoptic nasolaryngoscope (KayPENTAX) was used to capture video and still images in children aged 13 years and older; a KayPENTAX FNL-7RP3 fiberoptic nasolaryngoscope was used in children 3 to 12 years of age.

The nodules were reviewed on the still images, as well as on video clips, by one of us (R.C.N.) and graded according to a previously validated, published scale.[2,6] Specifically, nodules were graded 1, 2, or 3. A grade 1 nodule protruded less than 0.5 mm from the vibratory edge, allowing for complete adduction of the glottis; a grade 2 nodule protruded 0.5 to 1.0 mm from the vibratory edge, often resulting in an anterior glottic gap on adduction; a grade 3 nodule protruded more than 1.0 mm from the vibratory edge, resulting in an hourglass formation of the glottis on adduction.

Vocal fold nodule grade was analyzed by means of a 2-step method described by Feldman.[7] First, for each patient who had at least 2 time-linked data points for nodule grade, the earlier nodule grade was set as baseline. A simple linear regression was performed to each child's nodule grades and time since baseline, generating a slope. The slope then represents the change in nodule grade per month.

The slopes were then analyzed in relation to several factors, including sex, baseline nodule size, treatment, and patient age, to evaluate for a potential effect on the slope. Treatment groups included group 1, no treatment or behavioral modification only; group 2, targeted voice therapy with or without the treatment of associated conditions (gastroesophageal reflux and allergic rhinitis); and group 3, surgical intervention. A 2-sided type I error level of $\alpha = .05$ was used for all analysis. All the analyses were conducted in SAS, version 9.3 (SAS Institute).

Results

Sixty-seven patients with a median (range) age of 6.0 (3.8-20.6) years were analyzed. The male to female ratio was 2.35:1. Median (range) follow-up was 25 (1-119) months.

The mean (SD) slope (change in grade/time [months]) was −0.03 (0.12), with a median (range) of −0.01 (−0.94 to 0.06) (**Figure 1**). The median (range) slope was not significantly different between boys (−0.01 [−0.94 to 0.05]) and girls (0.00 [−0.20 to 0.06]; $P = .63$). The slope was significantly associated with baseline VFN size ($P < .001$), with an increased rate of improvement in VFN size observed for those children with larger baseline VFN size. In particular, the median (range) slope for those with VFNs of grade 3 (n = 28) was −0.04 (−0.94 to 0.00) vs 0.00 (−0.20 to 0.06) for those with VFNs of grade 1 or 2 (n = 39). Considering this monthly change in grade, we extrapolated that for children with baseline VFN grade 3, it would take approximately 2 years (25 months) to observe a decrease from grade 3 to grade 2. In contrast, minimal change is expected over time for those children with a baseline VFN grade of 1 or 2 (**Figure 2**A).

The rate of change in VFN size was significantly associated with treatment, with a greater rate of improvement seen in those children receiving voice therapy with or without the management of associated conditions or those undergoing surgery. Those whose treatment consisted of observation or behavioral modification (n = 19) had a median (range) slope of 0.00 (−0.08 to 0.06) vs those receiving targeted voice therapy with or without the treatment of associated conditions (n = 45) with a median (range) slope of −0.03 (−0.94 to 0.05) ($P = .01$) vs those undergoing surgery (n = 3) with a median (range) slope of −0.08 (−0.09 to 0.00). In this way, it could be expected to take approximately 3 years (33.3 months) to observe 1 full grade decrease in VFN size for those children undergoing voice therapy with or without the treatment of associated conditions. In those undergoing surgery, it could be extrapolated to take approximately 1 year (12.5 months) to observe 1 full grade decrease in VFN size. Finally, minimal change in VFN size could be expected for those children who are observed or receive instruction regarding behavioral modification (Figure 2B).

Finally, there was an increased rate of improvement in VFN size seen in the postpubescent age group, those older than 13 years (n = 7), with a median (range) slope of −0.06 (−0.20 to 0.00) vs those 13 years or younger (n = 60), with a median (range) slope of 0.00 (−0.94 to 0.06) (P = .09). Extrapolation of these slopes suggests that for those in the postpubescent age group, it would take approximately 1.5 years (16.7 months) to observe a decrease in VFN size by 1 full grade. Conversely, in the prepubescent age group, very small increments of improvement could be expected (Figure 2C).

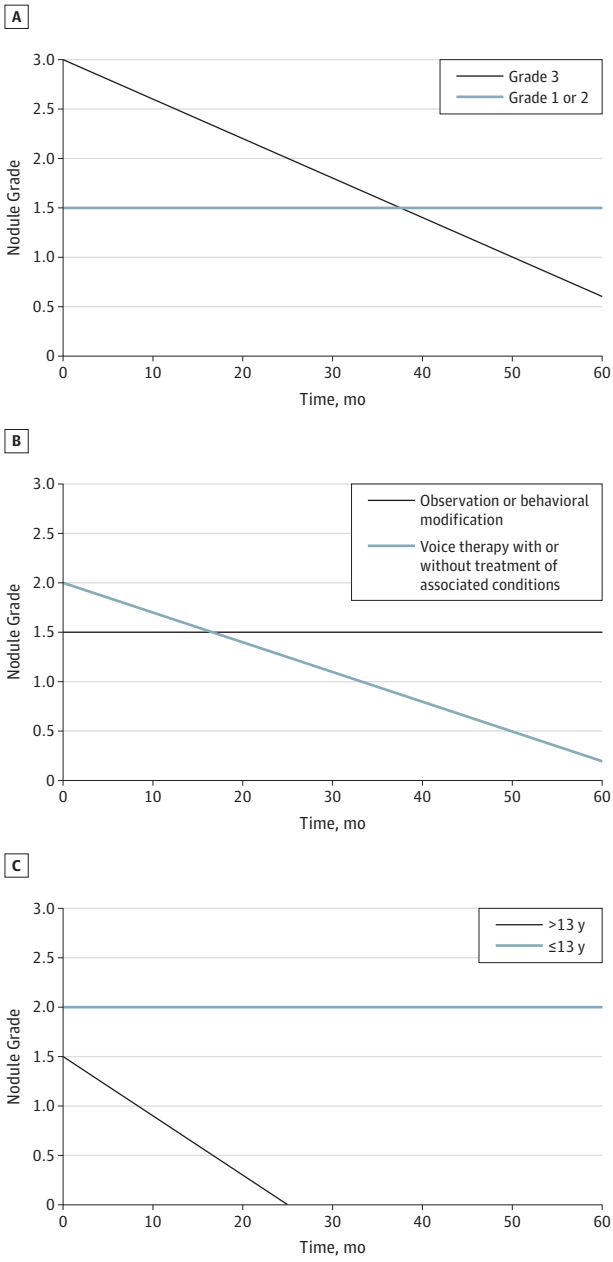
Change in the grade of the VFN size during periods of 1 and 3 years was next examined. The rate of change in size of the VFNs was not significantly different at 1 and 3 years (P = .33). For years 1 and 3, the median (range) slope was −0.01 (−0.94 to 0.04) and 0.00 (−0.08 to 0.04), respectively.

Discussion

To our knowledge, this study is unique in providing longitudinal information regarding the rate at which pediatric VFNs evolve and the factors that influence this change. Baseline VFN size, treatment, and patient age were found to be important factors in predicting the rate of improvement in nodule size over time. In addition, the rate of change in VFN size observed was a gradual decrease that was steady over periods of 1 and 3 years. An increased rate of improvement was observed for those children with larger baseline VFN size. It is postulated that larger nodules may show increased effect from voice therapy, vocal hygiene, or treatment of associated medical conditions (a relatively more "inducible change"), whereas the change from moderate to small nodules required more effort.

In terms of treatment, those children participating in voice therapy with or without the treatment of associated conditions experienced an increased rate of improvement in VFN size, as compared with those who were observed or received instruction regarding behavioral modification. Possible reasons for the increased rate of improvement in those undergoing voice therapy with or without the treatment of associated conditions are several. First and foremost, the improvement could be due to use of the techniques learned and reinforced during voice therapy sessions and/or the control of exacerbating conditions such as allergy or reflux. This group may also represent children who are more severely affected in terms of voice quality or families who are more motivated to adhere to treatment recommendations. Other studies have examined how treatment influences change in pediatric VFNs. These studies have measured progress via perceptual voice measures. Mori[8] examined the effects of treatment, namely, vocal hygiene, voice therapy, and surgery, on VFNs using either parental or self-perception of voice. Overall, 16% of children using vocal hygiene advice, 52% of those receiving voice therapy, and 89% of those who underwent microsurgery showed some improvement in overall voice quality. For the prepubertal subgroup, no significant differences were found among the vocal hygiene, voice therapy, and no treatment groups, whereas surgery was found to consistently result in improvement. In contrast, no significant difference was found in the postpubertal subgroup among the 4 treatment modalities, with almost all patients improving. De Bodt et al[4] found similar outcomes, with no correlation between voice complaints after puberty and the type of therapy previously received in childhood. We observed an overall increased rate of improvement in VFN size in the postpubescent age group, in

Figure 2. Expected Effect of Baseline Vocal Fold Nodule (VFN) Grade, Treatment, and Age on Resolution of VFNs Over Time



Extrapolation comparing the expected decrease in VFN grade over time for children with large (grade 3; n = 39) and small (grade 1 or 2; n = 28) baseline VFNs (A), for children who were observed or underwent behavioral modification (n = 19) or received targeted voice therapy with or without the treatment of associated conditions (n = 45) (B), and for prepubescent (n = 60) and postpubescent (n = 7) age groups (C).

which it was extrapolated to take approximately 1.5 years to observe a decrease in VFN size by 1 full grade. In contrast, in the prepubescent age group, very small increments of improvement were observed over time. Possible explanations for the increased rate of improvement in the postpubertal age group include hormonal changes related to puberty, improvement in vocal hygiene with maturation, or improved adherence to treatment recommendations. In addition, the increased rate of growth of the vocal folds during adolescence may result in a change in the location of maximal shear stresses during phonation. In effect, this moving target of phonation-related vocal trauma may help decrease trauma to previously formed nodules, with a subsequent decrease in their size. As a next step, we plan to examine prepubertal and postpubertal subgroups, evaluating for whether the aforementioned treatment effects persist for both subgroups.

De Bodt et al[4] examined the evolution of VFNs from childhood into adolescence and found a significant sex difference. Overall, 21% of the study group reported voice complaints that persisted into adolescence; this included 37% of the girls and 8% of the boys. Objective data were found to correlate with the perceptual data, with VFNs persisting in 47% of girls and 7% of boys. In the present study, sex was not significantly correlated with the rate of change of VFN size. However, the median age of our patient population was young (6 years); thus, a sex difference may have become more apparent with an older patient population.

A shortcoming of the present study is that measures of voice analysis were not available for all patients, making it impossible to analyze perceptual assessment of voice quality or acoustic measures over time. It may be hypothesized that improvement in laryngoscopic findings does not translate into improved voice quality. Prior studies are conflicting in terms of whether there is a direct correlation between the size of VFNs and voice quality. Shah et al[9] did not find a significant correlation between VFN size and objective voice measures but noted that laryngoscopic findings correlated only with pitch reduction. In many other categories, both acoustic and perceptual, interesting although statistically insignificant differences were noted, with voice measures worsening as nodule size increased. That study, however, had limitations in that a validated instrument for the perceptual assessment of voice quality was not used. In a study by Nuss et al,[10] a significant correlation was found between nodule size and measures including roughness, strain, pitch, loudness, and overall severity. Additional study is needed to evaluate whether the same factors that influenced a greater rate of improvement in VFN size similarly result in improved acoustic measures, as well as parental and professional perception of voice quality.

Conclusions

The treatment plan for children with VFNs is an individualized one. In formulating a plan, one must take into account the age of the patient, the patient's motivation and ability to adhere to therapy, and the degree of dysphonia and its impact on daily functioning. The present study provides information that may help to better guide treatment decisions and to better educate patients' families in setting reasonable expectations and time course for improvement. Additional investigation is needed to look into whether the findings in the present study persist regardless of prepubertal or postpubertal patient age and to determine whether the same factors that affect an increased rate of improvement in the size of the VFN also result in improved measures on acoustic and perceptual voice analyses.

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Acquisition of data: Nardone, Recko, Nuss.
Analysis and interpretation of data: Nardone, Huang, Nuss.
Drafting of the manuscript: Nardone.
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The Laryngoscope

Swallowing Function After Laryngeal Cleft Repair: More Than Just Fixing the Cleft

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Objectives/Hypothesis: To evaluate and describe the swallowing function in children after laryngeal cleft repair.

Study Design: Ten-year (2002–2012) retrospective chart review. Setting: Academic tertiary care pediatric otolaryngology practice.

Methods: Records of 60 children who had surgical repair of laryngeal cleft (ages 2 weeks–14 years) and postoperative functional endoscopic evaluation of swallowing or videofluoroscopic swallow studies were examined retrospectively.

Results: Twenty-nine children had one postoperative swallow evaluation, 19 children had two, 4 children had three, 5 children had four, and 3 children had five. Median time to the first evaluation was 10.8 weeks (interquartile range [IQR]: 36.5, 231). On the final swallow evaluation, 34 (57%) children demonstrated normal swallowing parameters, 12 (20%) children showed penetration, and 14 (23%) children showed aspiration. Forty-three (72%) children were able to take everything by mouth normally or with minor behavioral modifications, 11 (18%) children required thickened fluids, and six (10%) children were kept nil per os (NPO). Mean improvement on the penetration-aspiration (pen-asp) scale was 2.13. On multivariable analysis, neurodevelopmental issues and gastronomy tube use were associated with the need for NPO status.

Conclusion: Despite a high rate of surgical success, a substantial minority of children have persistent swallowing dysfunction after laryngeal cleft repair. Swallowing dysfunction after repair is multifactorial and arises from concomitant neurologic, anatomic, or other comorbidities that contribute to oropharyngeal and pharyngeal dysphagia. Based on our results, we recommend a testing schedule for postoperative swallowing evaluations after cleft repair.

Key Words: Laryngeal cleft, swallowing, FEES, VSS, VFSS.

Level of Evidence: 4.

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INTRODUCTION

Laryngeal cleft is a rare congenital anomaly in which there is incomplete separation of the aerodigestive tract due to a midline defect in the common wall between the laryngotracheal and esophageal lumens. Clefts range from deep interarytenoid notches to those that extend below the vocal cords, through the cricoid, and into the trachea. Benjamin and Inglis[1] developed the most commonly used classification scheme for laryngeal clefts, and cleft grade correlates with symptom intensity.[2] Common presenting symptoms include hoarseness, stridor, chronic cough, aspiration with feeding, recurrent pneumonia, and respiratory distress.[3] Diagnosis of a laryngeal cleft requires a high index of suspicion—and typically direct laryngoscopy.

Small clefts (type I and II) can remain clinically silent, causing no symptoms at all. Even when symptoms are present, almost half of children with type I and type II clefts can be treated conservatively with medical and feeding modifications.[4] The remainder of small clefts and virtually all type III and IV clefts require surgery to close the cleft and to prevent aspiration and life-threatening pulmonary compromise. Studies of patients with laryngeal clefts have focused largely on indication for surgery, surgical methodology, and surgical success rates.[4–7] A detailed characterization of swallowing function in children who have had laryngeal cleft repair is missing from the literature.

Although the laryngeal cleft itself can lead to aspiration through incomplete separation of the respiratory and digestive tracts, dysfunctional swallowing in children with clefts is often multifactorial. Laryngeal clefts can be associated with other airway abnormalities or syndromes with craniofacial, aerodigestive, or neurological effects that contribute to oral motor and pharyngeal swallowing dysfunction. Furthermore, even otherwise normal children with laryngeal clefts may require prolonged periods of gastronomy tube (g-tube) feeding and nil per os (NPO) status, during which the complex oral

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and oropharyngeal motor patterns required for normal feeding and swallowing may regress or fail to develop. Additionally, decreased oral feeding over a prolonged time period is associated with the development of oral aversion and the lack of progression with oral feeding.[8] With these points in mind, we examined the postoperative swallowing function of children in our practice who underwent laryngeal cleft repair.

MATERIALS AND METHODS

Study approval was granted by the Cincinnati Children's Hospital Medical Center (CCHMC, Cincinnati, OH) Institutional Review Board (study number 2012–2035). Ten years (July 2002–June 2012) of records from the Otolaryngology–Head and Neck Surgery Clinic and the Aerodigestive and Esophageal Center (ADEC) were searched for children less than 18 years of age with a diagnosis of laryngeal cleft confirmed by direct laryngoscopy in the operating room. All children who underwent surgical repair of their cleft and who had postoperative evaluation of swallowing were included in our analysis.

We collected information on demographics, Benjamin and Inglis cleft grade (3 "deep interarytenoid groove" patients were included in the type I group), type of repair, other airway findings, neurologic comorbidities, syndromic associations, and swallowing outcomes (see Supplementary Information for a complete list).

Cleft repair was decided upon by the interdisciplinary aerodigestive and esophageal center group. Symptoms such as recurrent pneumonia and choking during feeds, as well as data from bronchioalveolar lavage, computed tomography, or preoperative swallow studies were used to guide this decision. Closure techniques were endoscopic or open, layered or simple, and with or without cartilage or periosteal graft—at the discretion of the operating surgeon. Revision was performed if breakdown was seen on surveillance endoscopy and if symptoms or laboratory data suggested continued aspiration.

Functional endoscopic evaluation of swallowing (FEES) or videofluoroscopic swallowing study (VSS/VFSS) was performed at the discretion of the ADEC physicians and speech pathologists. The airway protection ability of each child was rated using the penetration-aspiration scale (pen-asp scale) previously described.[9] Children are scored on a scale of 1 to 8: 1 = normal; 2 to 5 = penetration; 6 to 8 = aspiration. Occasionally, children with tracheostomies were evaluated with dye testing. These were graded in a binary fashion (aspiration or no aspiration) by the presence or absence of dye in the tracheal aspirate. The recommendations of the speech pathologist were grouped as follows: 1) safe for oral feeding with all consistencies; 2) safe for oral feeding with all consistencies with minor feeding modifications such as slow bolus presentation, limited volume boluses, or positional adaptations; 3) safe for oral feeding with altered fluid viscosity; and 4) unsafe for oral feeding. In revision cases, only swallowing evaluations performed after the last revision for a persistent cleft or fistula that was causing aspiration were considered. Standard clinical signs of aspiration (or the resolution thereof), such as choking or coughing with feeds, recurrent respiratory infections, and parental suspicion served as indications for repeated postoperative swallow evaluations.

Descriptive statistics including frequencies and proportions or medians with interquartile ranges (IQR) were calculated on all variables. Chi-square or Fisher's exact tests were used to examine relationships between categorical predictors and feeding recommendations. Logistic regression was used to examine multivariable relationships between predictors and swallowing outcomes and feeding modifications. An alpha level of 0.05 was considered significant. SAS (Version 9.3, Cary, NC) was used to conduct the analysis.

RESULTS

We found 115 children with laryngeal clefts seen in our practice over the study period. Of these, 89 children had surgery to repair the cleft and 60 children had postoperative swallowing evaluation (35 [58%] males and 25 [42%] females). Forty-four patients had one surgery to repair the cleft, 10 patients had one revision, and six patients had two revisions. The median ages at the first and last surgery were 27.5 and 37.1 months, respectively (ranges 1 week–14.1 years and 2 weeks–18.11 years, respectively). There were 21 (35%) grade I clefts, 21 (35%) grade II clefts, 17 (28%) grade III clefts, and one (2%) grade IV cleft. Twenty-nine patients who underwent surgery did not have a postoperative swallow evaluation, either due to an extremely encouraging clinical picture or because they returned to their referring center for ongoing care.

Twenty-nine patients had one postoperative swallowing evaluation; 19 patients had two; four patients had three; five patients had four; and three patients had five evaluations. Of these 114 studies, 28 (24.5%) studies were FEES; 77 (67.5%) studies were VFSS; and nine (7.9%) studies were clinical/dye tests in patients with tracheotomy. The median time between surgery and first postoperative swallowing evaluation was 9.9 weeks (IQR: 1.7, 6.1 years). In those children who had multiple swallow studies (n = 31), the median time between surgery and the last swallow evaluation was 8 months (IQR: 1.9, 28.4 months).

On final swallowing evaluation, 34 children had normal swallowing parameters, 12 demonstrated some degree of penetration, and 14 demonstrated some degree of aspiration (Fig. 1). Forty-three children were ultimately able to take all consistencies by mouth with minor or no feeding modifications, 11 children required modified consistencies, and six children remained unsafe for oral intake (Fig. 2).

Of the six children who were unsafe for oral intake, two children had a persistent cleft or fistula through which they aspirated. One child had a recurrent type II cleft, which is scheduled for revision. The second child had a type III cleft that was repaired but had a small tracheoesophageal fistula near the apex of the repair. This patient visited our center, did not remain under our care to have this fistula addressed, and was thus lost to follow-up. Interestingly, three children with normal swallowing parameters also had some degree of persistent clefting on follow-up direct laryngoscopy. These children were not revised because of their normal swallowing parameters.

Criteria for proceeding to cleft repair without a preoperative swallow evaluation at our institution included type III or IV cleft, strongly suggestive clinical symptoms of aspiration, or a swallow evaluation at the patient's home institution (which may not have been scored by our speech pathologists). Given those limitations, 41 children in the current study had preoperative

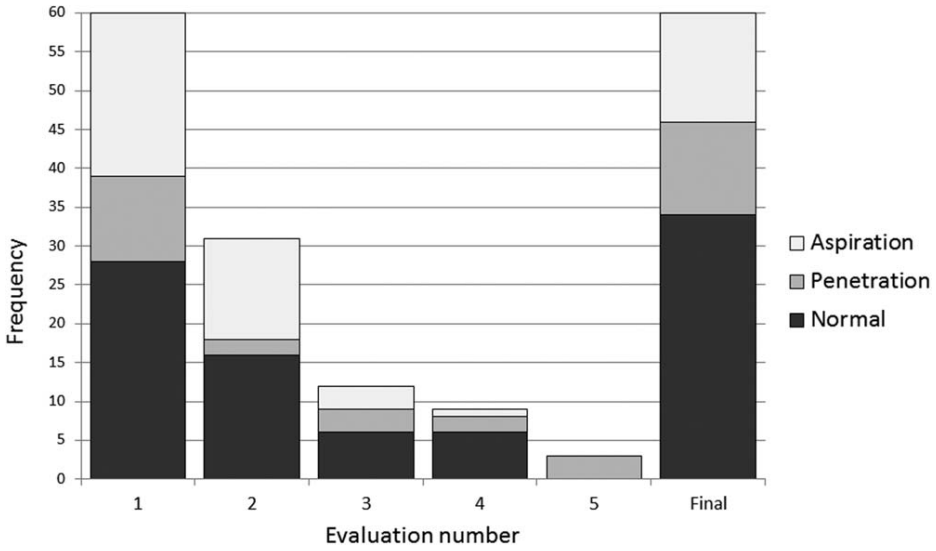

Fig. 1. Results of swallowing evaluations of children after laryngeal cleft repair. The results describing the degree of airway protection seen during swallowing evaluations after laryngeal cleft repair are shown. Proportions of children falling into each category are shown.

swallow evaluations that we could score. Preoperative and postoperative evaluations are compared in Table I. Children with normal swallow studies demonstrated clinical symptoms that warranted repair of the cleft in the opinion of the treating physician. The mean score on the pen-asp scale decreased from 5.33 to 3.2 ($P < 0.05$, paired t test).

When we examined potential predictors of feeding modifications, there was no association detected between cleft grade and final feeding recommendations (Fig. 3). We considered other factors that might influence the ability to gain functional swallowing, such as g-tube use prior to surgery, neurologic comorbidities, syndromic associations, age at repair, method of repair (endoscopic vs. open), and additional airway findings. Upon multivariable analysis, the presence of neurologic comorbidities (Coloboma Heart abnormalities, choanal Atresia, growth Retardation, Genitourinary abnormalities, and Ear abnormalities (CHARGE) syndrome, Opitz syndrome, trisomy 21, cerebral palsy, and global developmental delay) and g-tube use predicted the need to modify diet (minor feeding modifications, thickeners, or NPO status). Children with neurodevelopmental issues had 6 times greater odds of having modified feeding recommendations compared to those without neurodevelopmental issues (95% CI 1.4–26.6). Those with g-tubes had 3.6 times greater odds of diet modification (95% CI: 1.02–13.0). Although feeding modifications are a restriction, they do not represent the same lifestyle impact and burden of care that the use of thickeners and NPO status represent. Accordingly, we separated children into two groups: those children who could take a normal diet without modifications or with slight modifications and those children who required the use of thickeners or NPO status. When these alternative groups were considered, only neurodevelopmental issues remained as a predictor of the need for thickeners or NPO status (OR: 5.8, 95% CI: 1.5–22.7).

Taking those 43 children who were ultimately cleared for per os (PO) intake of all consistencies with no or only minor behavioral modifications, 20 (45%) of the children

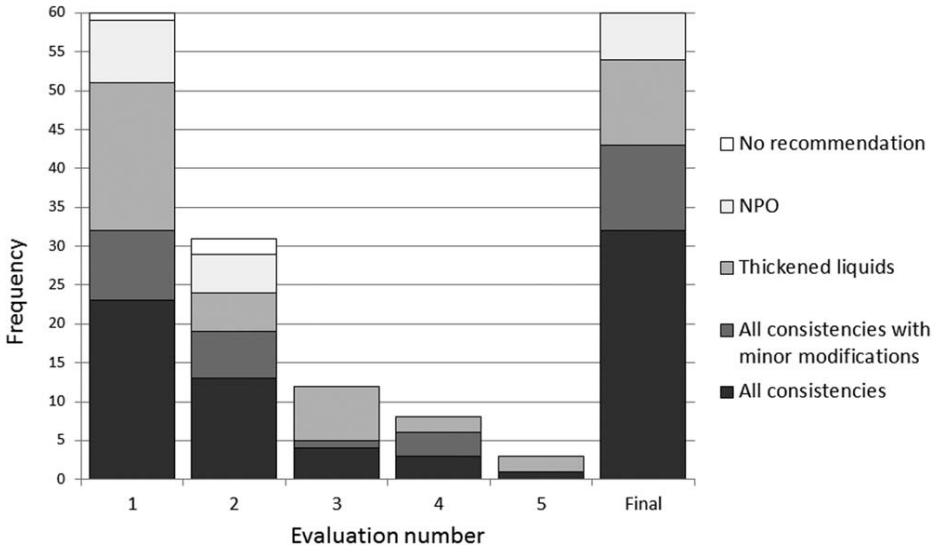

Fig. 2. Speech pathologist's recommendations following swallowing evaluations after laryngeal cleft repair. The recommendations regarding per os intake based on the swallowing evaluations after laryngeal cleft surgery are described, and proportions of children falling into each category are shown. In rare instances, the child was evaluated using the penetration-aspiration scale, but no formal recommendation by the speech pathologist was recorded in the chart on how to proceed with feeding. These studies are represented as "no recommendation."

TABLE I.
Comparison of Preoperative and Postoperative Swallow Studies.

	Normal	Penetration	Aspiration
Preoperative	13	2	26
Postoperative	25	7	9

had evaluations within the first 3 months after their final surgery that demonstrated safety for intake of all consistencies (Fig. 4). Cumulatively, 32 (74%) children were cleared for PO intake of all consistencies within the first year, and 11 children took more than 1 year. Of those individuals who took more than 2 years to be cleared for all consistencies (n = 7), two patients did not have their first evaluation until more than 5 years after surgery; however, the remaining patients had regular swallow studies at roughly 1-year intervals until they were cleared for all consistencies. Thus, a small number of individuals (in this case 5 out of 43 [11%]) can truly take many months to achieve normal swallowing after cleft repair.

DISCUSSION

We present the first detailed analysis of swallowing function after laryngeal cleft repair. Thirty-four (57%) children ultimately achieved normal swallowing as confirmed by FEES, VFSS, or dye testing; and 43 (72%) children were cleared for a normal diet with no or only minor feeding modifications. Some children who demonstrated penetration or aspiration did so only under certain circumstances such as rapid chain swallows or with large volumes. These children can often take thin liquids safely with adequate pacing of intake or with changes in positioning. We feel that there is a natural distinction between children who are given a final recommendation for normal PO diet or normal diet with minor feeding modifications and those children who require the use of thickened liquids or are kept NPO. Both NPO status and the need for thickened fluids present a large impact on quality of life for children and their caretakers, while minor feeding modifications are easily adopted, develop naturally, or are sometimes ignored—essentially placing the child on a normal PO diet without modifications.

We anticipated that more severe cleft grade, later age at surgical repair, use of a g-tube, method of repair, and the presence of other medical comorbidities or aerodigestive findings would influence the chance of acquiring normal swallowing. Only g-tube use and neurodevelopmental comorbidities predicted the need for feeding modifications; and neurodevelopmental compromise was the strongest predictor. That neurodevelopmental abnormalities predict the need for NPO status or the use of thickeners is expected. The relationship between neurodevelopmental disorders and dysphagia has been extensively studied.[10–12] We included children with Trisomy 21, CHARGE syndrome, and Opitz syndrome in our group of children with neurodevelopmental disorders. Despite the fact that these syndromes may have comparatively mild neurodevelopmental defects compared to cerebral palsy or severe global developmental delay, a significant portion of these children had difficulty gaining normal swallowing after cleft repair. Thus, the complex oral and oropharyngeal motor patterns of safe swallowing in these individuals may be sensitive to moderate perturbations brought about by laryngeal surgery and developmental delay. Additionally, it is difficult to separate the effects of neurodevelopmental delay from the concomitant craniofacial abnormalities that are present in some of these children. The true picture of dysphagia in these cases is likely a combination of neurologic, anatomic, and medical factors.[13]

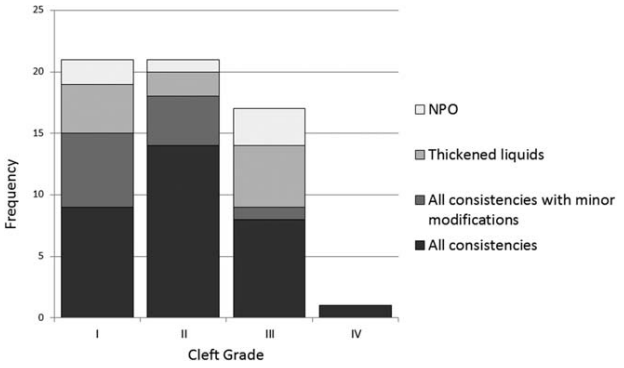

Fig. 3. Final speech pathologist recommendation shown with respect to initial cleft grade.

It is not surprising that g-tube use might predict worse swallowing function postoperatively. Many children with type I or II clefts can partially or entirely compensate for the cleft to prevent aspiration. If a g-tube is needed, it might indicate that the child had worse compensatory mechanisms to begin with. Additionally, evidence suggests a critical window of neuromotor development for the coordination of swallowing and breathing, which can be disrupted if the infant engages in nonnutrative sucking alone.[14] Thus, reliance on a g-tube early in life might impair development and hinder postrepair swallowing. In our study, even children who were ultimately cleared for a normal diet with no or minor modifications demonstrated a high rate of oral and oropharyngeal dyscoordination, highlighting the sensitivity of these motor patterns to disruption.

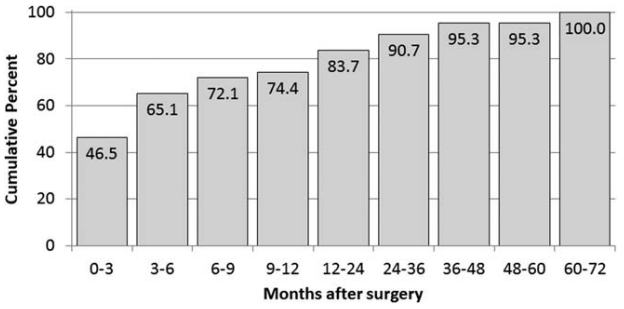

Fig. 4. Time to clearance for a normal per os diet with no or minor feeding modifications after repair of laryngeal cleft. For those children who were ultimately cleared for a full diet with no or only minor behavioral modifications (n = 43), the cumulative frequency of those cleared is displayed as a function of time after cleft repair.

Almost half of the children who were ultimately cleared for a normal diet with no or minor modifications were so cleared within the first 3 months after surgery. In the second 3 months after surgery, another 18% of patients were cleared for a normal diet. Approximately 10% of patients were cleared in the next 6 months, after which the rate of clearance fell dramatically. Given these rates, we recommend swallow evaluation at 3 months after surgery. Those with persistent swallowing problems should have evaluations at 6 and 12 months and then annually, while problems persist. Although most children do recover normal swallowing within 24 months of surgery, a small minority of children recover normal swallowing after this time. This raises the question of when to stop the evaluation of swallowing in the child who persistently aspirates after cleft repair. It is here that the clinicians must exercise their judgment. The degree of dysfunction, neurologic status, and other factors such as progress with the speech therapist and parental reports must be considered. If children undergo multiple swallowing evaluations, nonirradiating studies should be used when appropriate.

Interpretation of the above results is hindered by the most obvious limitation of our study, namely that there was no set protocol for the timing or indications for postoperative swallowing evaluations. Some children in our study had their first swallowing evaluation many months after surgery. This artificially inflated the postsurgical time to normal swallowing, and many children likely recovered normal swallowing earlier than indicated in Figure 4. This strengthens the argument for less frequent swallow evaluations after the first 6 months; even fewer children would be expected to recover normal swallowing after this time if evaluated regularly. Despite the lack of a strict protocol, the current study does allow broad guidelines to be established for the timing of postoperative swallowing evaluation of patients after laryngeal cleft repair.

A set protocol would ideally clearly delineate clinical indications for repeat studies. In the current series, the timing of and indications for a repeat swallowing evaluation was decided by the managing physician and speech therapist, with standard clinical signs of aspiration such as choking or coughing with feeds, recurrent respiratory infections, and parental suspicion serving as guiding factors. Additionally, the choice of which test was performed was made partially subjectively. Although VFSS was our preferred means of evaluation, if patients were unable to take significant amounts of contrast or if they had already had a number of irradiating VFSS evaluations, then FEES was performed. Although we have pooled the data from VFSS and FEES studies, little correlation exists between VFSS and FEES scores.[15] This underscores the importance of taking into account clinical, laboratory, and temporal data when assembling a picture of aspiration.

CONCLUSION

We have performed a retrospective analysis of swallowing function after laryngeal cleft repair. A substantial minority of children (28%) remained NPO or required the use of thickeners to achieve airway protection during swallowing after surgery, and neurodevelopmental delay was the best predictor of falling into this category. Based on our analysis of children who ultimately regained normal swallowing, we recommend swallow evaluations at 3, 6, 12, and 24 months after surgery, until normal swallowing is observed. The chance of recovering normal swallowing more than 24 months after surgery is small, so the physician must balance patient factors, the availability and quality of swallowing therapy, and parental wishes when deciding how long to follow swallowing function after surgery.

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Study data were collected and managed using research electronic data capture (REDCap (developed by Vanderbilt University, Nashville TN), CCHMC) electronic data capture tools hosted at CCHMC.[16] REDCap is a secure, Web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Institutional guidelines as well as our license agreement for REDCap usage mandate this precise text be used in all papers published in which REDCap was used. REDCap is made possible at CCHMC by the Center for Clinical and Translational Science and Training grant support (UL1-RR026314).

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Evaluation of True Vocal Fold Growth as a Function of Age

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Abstract

Objective. To evaluate change in true vocal fold length as a function of age.

Study Design. Prospective study.

Setting. Tertiary aerodigestive center.

Subjects and Methods. In total, 205 patients (aged 1 month to 20 years), of whom 87 (42.4%) were female and 118 (57.6%) male, were included. Lengths of the total vocal fold (TVFL), membranous vocal fold (MVFL), and cartilaginous vocal fold (CVFL) were measured during direct laryngoscopy. Membranous-to-cartilaginous (M/C) ratios were calculated.

Results.For patients younger than 1 year, mean (SD) MVFL was 4.4 (1.3) mm for females and 4.9 (1.8) mm for males. At age 17 years, mean (SD) MVFL was 12.3 (2.1) mm for females and 14.0 (1.4) mm for males. Mean TVFL, MVFL, and CVFL increased an average of 0.7 mm, 0.5 mm, and 0.2 mm per year in linear fashion, respectively (linear regression, $P < .0001$). The M/C ratio did not significantly change with age ($P = .33$). Mean TVFL, MVFL, and CVFL showed no statistical difference between males and females ($P = .27$, .11, and .75, respectively).

Conclusion. This is the largest longitudinal pediatric study specifically examining vocal fold length as a function of age. Each length of the true vocal fold appeared to linearly increase for both females and males. The M/C ratio remained relatively constant, unlike previously reported data, possibly due to in vivo vs cadaveric measurements. These findings suggest that critical periods of development in females and males are not explainable by changes in vocal fold length alone, and other factors such as vocal fold layers need further exploration.

Keywords

vocal fold length, pediatric voice, pediatric laryngology

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Understanding the anatomic development of the pediatric vocal fold and how changes in anatomy affect acoustic and aerodynamic properties remains paramount to the evolving field of pediatric laryngology. As vocal tasks become more sophisticated throughout development, the length of the true vocal fold increases,[1] and the composition of the lamina propria changes.[2] It remains unclear whether the increase in vocal fold length or the number of layers in the lamina propria is responsible for changes in fundamental frequency.

The first step to increase our understanding of the pediatric voice was to establish normative pediatric voice data. Campisi et al[3] developed the first normative pediatric voice database, which suggested that prepubescent females and males share a similar vocal profile until the fundamental frequency of males dramatically decreases at age 12 years. However, this study derived the normative data from only 100 patients. Maturo et al[4] established a more comprehensive database by recording 335 children sustaining the phrase ''ah'' to develop an age- and sex-based growth chart to track the pediatric voice as it changes with maturation. Unlike the study by Campisi et al, this study found that discrete fundamental frequency changes occurred at ages 11 and 14 years in girls and ages 12 and 16 years in boys. Hill et al[5] then evaluated the consistency of sustained utterances in measuring pediatric voice frequency and perturbation with the Voice Evaluation Suite (VES) and Multi-Dimensional Voice Program (MDVP). They found that fundamental

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Table 1. Summary of Vocal Fold Measurements from Hirano et al.[1]

Age	Total Vocal Fold Length, mm	Membranous Vocal Fold Length, mm	Cartilaginous Vocal Fold Length, mm	Membranous-to-Cartilaginous Ratio
Newborn	2.5-3.0	1.3-2.0	1.0-1.4	1.1-1.8
Adult female	11-15	8.5-12	2.0-3.0	3.3-4.5
Adult male	17-21	14.5-18	2.5-3.5	4.7-6.2

frequency had excellent reliability in both VES and MDVP, but jitter, shimmer, and noise-to-harmonic ratio were poorly reliable in the MDVP and more reliable in the VES. Next, Diercks et al[6] found that fundamental frequency and frequency-based analyses demonstrated excellent reliability for continuous speech across 2 time points, suggesting that frequency-based analysis of continuous speech may be more representative of a child's actual voice. We are currently repeating the study by Maturo et al by using continued speech sampling to analyze whether similar discrete fundamental frequency changes occur. Further work by Maturo et al[7] resulted in a normative database of pediatric laryngeal diadochokinetic rates, which suggested that neurolaryngeal development approaches adult maturation during early adolescence.

Now that normative pediatric voice data have been established that suggest critical periods of development, a more thorough knowledge of the anatomic maturation of the pediatric larynx and how these changes in anatomy affect the acoustic and aerodynamic qualities remains imperative. Most theories of vocal mechanics have been transferred from adult studies with minimal data arising from the first 20 years of life. Although it has been recognized that the vocal folds lengthen with age, little is known regarding the details of these changes. Moreover, the impact of the change in the microstructure of the vocal fold lamina propria on acoustic and aerodynamic measurements remains to be elucidated.

Our current understanding of the changes in both vocal fold length and layers in the lamina propria hinges on the seminal work of Hirano. In 1983, Hirano et al[1] reported changes in the length and the inner structure of the true vocal fold as a function of age in 88 normal Japanese larynges (**Table 1**). However, the data came from cadaveric larynges, most of which were fixed in 10% formalin between the 7th and 10th days postmortem. Furthermore, only 39 (44%) of the larynges were from subjects younger than 20 years. Eckel et al[8] studied the development of 43 larynges from children aged 1 to 60 months, but these were cadaveric specimens treated via plastination before measurements were taken. The plastination process involved freezing the specimens, treating them with multiple chemicals, and then slicing the specimens with a diamond band-saw, which presumably caused alterations in the delicate vocal fold tissue.

The objective of this study was to further evaluate the change in true vocal length as a function of age. By specifically focusing on ages younger than 20 years and obtaining data in vivo, we hope to more accurately characterize the changes in true vocal fold length as we age. Our hypothesis is that this study will help explain the critical periods of development in females and males and lead to a better anatomic laryngeal model in which to correlate the changes seen in acoustic and aerodynamic vocal properties.

Methods

Patients

This study was approved by the institutional review board of the Massachusetts Eye and Ear Infirmary. Written, informed consent was obtained for each patient before enrollment in this study. Patients were gathered consecutively and were included if they were aged 20 years and younger and required a direct laryngoscopy as part of their operative procedure. Exclusion criteria consisted of age older than 20 years, vocal fold pathology such as a mass or paralysis, prior laryngeal or tracheal surgery, and presence of a known syndrome.

Measurement Technique

After informed consent, the patients were brought to the operating room and placed supine on the operating table. Anesthesia was induced with inhalational sevoflurane and transitioned to intravenous propofol and remifentanil. Direct laryngoscopy was performed with a Miller blade as long as a view of the entire glottis was possible. Otherwise, a Lindholm laryngoscope was inserted and placed on suspension. Approximately 5 patients required suspension laryngoscopy. A metal vocal fold measuring stick was then used to measure the membranous vocal fold length (MVFL) and cartilaginous vocal fold length (CVFL) of one of the true vocal folds (**Figure 1**). The measuring sticks were sized 5.0 mm, 7.5 mm, 10 mm, and 15 mm (**Figure 2**). The appropriate-sized measuring stick was selected based on the size of the patient's glottis. The MVFL was measured from the vocal process of the arytenoid to the anterior commissure and the CVFL from the vocal process of the arytenoid to the presumed posterior insertion point. The actual vocal fold lengths were estimated, beginning with the size of the measuring stick.

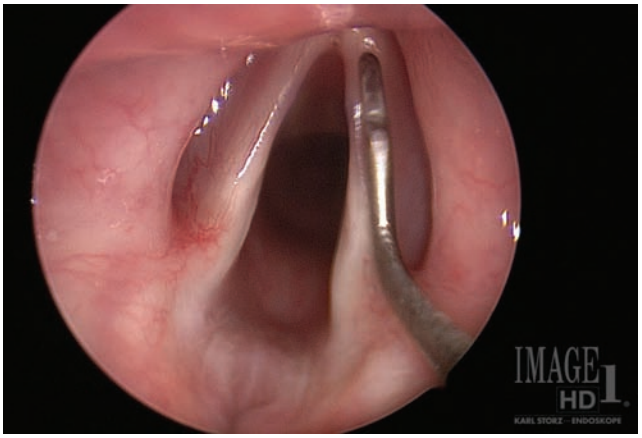

Figure 1. Intraoperative photo of vocal fold measurement process.

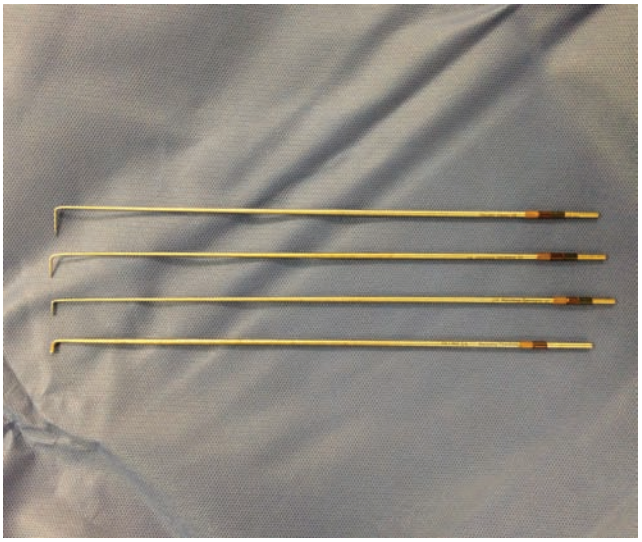

Figure 2. Vocal fold measuring sticks.

Statistical Analysis

Total vocal fold length (TVFL), MVFL, and CVFL were recorded for all patients. The TVFL was calculated by adding the MVFL and CVFL. The membranous-to-cartilaginous (M/C) ratio was determined for each patient by dividing the MVFL by the CVFL. Mean TVFL, MVFL, CVFL, and M/C ratio were calculated for each age group. These data were plotted with error bars for initial visual inspection. Simple linear regression appeared to be an accurate fit for each vocal fold length. A nonparametric smoothing, or LOESS fit, was performed on the data for MVFL, which confirmed that the linear regression model was a good fit over the entire age range. Multiple linear regressions were performed for each vocal fold length (TVFL, MVFL, and CVFL) and the M/C ratio, including age, sex, and interaction between age and sex. The Bonferroni correction was applied, and a reduced P value of .0125 was considered statistically significant. All statistical analyses were conducted using SAS version 9.2 statistical software (SAS Institute, Cary, North Carolina).

Results

A total of 205 patients were included in this study. Eighty-seven (42.4%) were female, and 118 (57.6%) were male. Ages ranged from 1 month to 20 years. Mean TVFL, MVFL, CVFL, and M/C ratio for each sex and age group are presented in Supplemental Tables S1 and S2 (available at otojournal.org).

Linear regressions were performed on the data for TVFL, MVFL, CVFL, and M/C ratio (**Figure 3** and **Table 2**). Mean TVFL increased by an average of 0.7 mm each year ($P < .0001$) and showed no statistical difference between females and males ($P = .27$). Mean MVFL increased by an average of 0.5 mm each year ($P < .0001$) and demonstrated no statistical difference between females and males ($P = .11$). Mean CVFL increased by an average of 0.2 mm each year ($P < .0001$). Once again, no statistical difference was detected between males and females ($P = .75$). The mean M/C ratio did not significantly change with age ($P = .33$). Furthermore, no significant difference was found in the M/C ratio between males and females ($P = .27$).

Discussion

Although our understanding of pediatric dysphonia continues to evolve, pediatric laryngology remains in its nascency. Developing a normative pediatric voice database marked a considerable advancement in this field.[4] However, the next step is to determine what is responsible anatomically for these different critical periods of vocal development in both females and males.

To address this fundamental question, one must be familiar with the physics of vocal fold vibration. Traditionally, it was thought that vocal fold length, thickness, and mass were the key variables involved, and the equations were inferred from the formula for a mass coupled to a spring or the formula for a vibrating string.[9-11] However, the most recent theory deduced by Titze[9] provides the following equation for fundamental frequency, or F_0:

$$F_0 = \frac{1}{2L_m}\sqrt{\frac{\sigma_p}{\rho}}\left(1+\frac{d_a}{d}\frac{\sigma_{am}}{\sigma_p}a_{TA}\right)^{\frac{1}{2}}.$$

L_m represents membranous vocal fold length; σ_p, passive (noncontractile) tissue stress; ρ, tissue density; d, medial-lateral depth of vibration; d_a, depth of vibration of the thyroarytenoid muscle; σ_{am}, maximum active stress; and a_{TA}, the activation level in the thyroarytenoid muscle. In the above equation, Titze[9] stated that soft tissue density, ρ, remains constant at 1.04 g/cm^2.

This study specifically assessed changes in true vocal fold length as we age. Titze's equation[9] assumed that the primary oscillator contributing to fundamental frequency is the membranous vocal fold and that the contribution from the cartilaginous vocal fold is negligible. We evaluated TVFL, MVFL, CVFL, and the M/C ratio as a function of

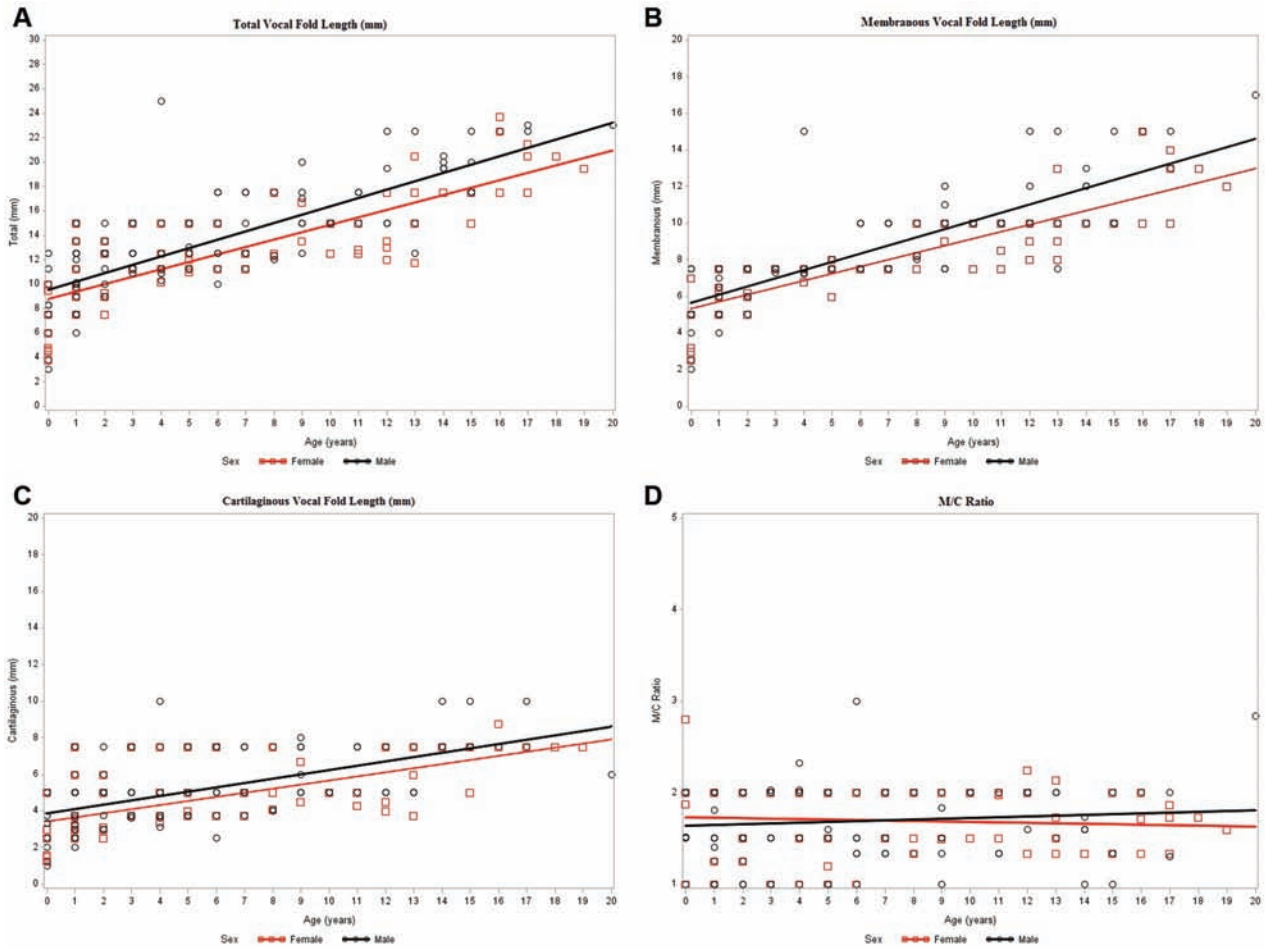

Figure 3. Linear regressions for each portion of the true vocal fold and M/C ratio. *P* value was <.0001 for the total vocal fold length (TVFL), membranous vocal fold length (MVFL), and cartilaginous vocal fold length (CVFL) and <0.33 for the membranous-to-cartilaginous (M/C) ratio. Correlation coefficient (*R*) was 0.79, 0.82, 0.62, and 0.10 for the TVFL, MVFL, CVFL, and M/C ratio, respectively.

age in case the growth pattern of any portion of the true vocal fold suggested it may correlate with changes in fundamental frequency.

Various methods have been used in the past to measure true vocal fold length. Several studies used cadaveric larynges to measure vocal fold dimensions, but each of these often used a fixation or plastination process for their specimens.[1,12-14] A few studies have attempted to measure true vocal fold length in living individuals. The methods used include photography,[15] plain films,[16] ultrasound,[17] and laser.[18] We chose to acquire our measurements in vivo using vocal fold measuring sticks. This ensured that all individuals were in a similar physiologic state (under the same type of anesthetic and spontaneously ventilating) and allowed direct visualization of the vocal folds during the measuring process.

Our data revealed some interesting results compared with previously published data. Mean MVFL for females in our study was 4.4 mm (2.5-7.0 mm) for those younger than 1 year and 12.3 mm (10.0-14.0 mm) at age 17 years; for males, it was 4.9 mm (2.0-7.5 mm) for those younger than 1 year and 14.0 mm (13.0-15.0 mm) at age 17 years. This compares well to the data by Hirano et al[1] presented in **Table 1**. For subjects younger than 1 year, Eckel et al[8] found a mean MVFL of 2.9 mm (2.6-4.7 mm) in 24 male and female cadaveric specimens, and for their 4 oldest subjects aged 49 to 60 months, they reported a mean MVFL of 5.9 mm (5.3-6.7 mm). These measurements were shorter than ours at both of these age groups, possibly due to loss of elasticity during their measurement process.

Mean CVFL for females in our study was 2.8 mm (1.3-5.0 mm) for those younger than 1 year and 7.5 mm (7.5-7.5 mm) at age 17 years; for males, it was 3.0 mm (1.0-5.0 mm) for those younger than 1 year and 8.8 mm (7.5-10.0 mm) at age 17 years. These values are approximately twice as long as those reported by Hirano et al.[1] Eckel et al[8] reported a mean CVFL of 4.1 mm (2.9-5.1 mm) in children younger than 1 year and 4.8 mm (4.2-5.2 mm) in children aged 49 to 60 months. Our mean CVFL was about 1 mm shorter in children younger than 1 year compared with these data, but it was quite similar for patients aged 4 to 5 years.

The mean M/C ratio for females in our study was 1.7 (1.0-2.8) for those younger than 1 year and 1.6 (1.3-1.9) at

Table 2. Summary of Multiple Regression Analyses.

Variable	b	SE b	*P* Value
Total vocal fold length			
Intercept	9.52	0.37	<.0001
Age	0.69	0.05	<.0001
Sex (female vs male)	–0.77	0.57	.1778
Age × sex	–0.08	0.07	.2746
R^2	0.62		
F statistics	111.07		
P value	<.0001		
Membranous vocal fold length			
Intercept	5.65	0.21	<.0001
Age	0.45	0.03	<.0001
Sex (female vs male)	–0.32	0.32	.3130
Age × sex	–0.06	0.04	.1068
R^2	0.68		
F statistics	145.50		
P value	<.0001		
Cartilaginous vocal fold length			
Intercept	3.87	0.22	<.0001
Age	0.24	0.03	<.0001
Sex (female vs male)	–0.45	0.33	.1778
Age × sex	–0.01	0.04	.7479
R^2	0.39		
F statistics	42.39		
P value	<.0001		
Membranous-to-cartilaginous ratio			
Intercept	1.64	0.06	<.0001
Age	0.01	0.01	.3287
Sex (female vs male)	–0.09	0.10	.3419
Age × sex	–0.01	0.01	.2715
R^2	0.01		
F statistics	0.45		
P value	.7192		

age 17 years; for males, it was 1.8 (1.0-2.0) for those younger than 1 year and 1.7 (1.3-2.0) at age 17 years. Compared with the data from Hirano et al,[1] these values are similar for children younger than 1 year, but they are approximately half as large when comparing 17-year-olds in our study with adults in Hirano et al. The mean M/C ratio in our study did not increase significantly with age as opposed to the data reported by Hirano et al. We found that the cartilaginous vocal fold was not only longer but also continued to grow enough along with the membranous vocal fold to keep the M/C ratio relatively constant.

A few factors may be responsible for the difference in our data compared with previously published data. First, we obtained our measurements in vivo under the same type of anesthetic for each patient. As noted earlier, Hirano et al[1] and Eckel et al[8] both used cadaveric larynges, preparing them with formalin and a plastination process, respectively. Our method likely resulted in a more physiologic state of the larynx during the measurements. Second, we had to estimate the posterior insertion point of the cartilaginous vocal fold in our patients. No clear demarcation exists along the arytenoid mucosa to delineate this exact location. Last, using a Miller or Lindholm laryngoscope might have placed some tension on the glottis during the measurement process, possibly resulting in slight lengthening of the true vocal folds.

When looking at the growth patterns for each vocal fold length in both sexes, we found that the TVFL, MVFL, and CVFL all increase in a linear manner as we age. The TVFL, MVFL, and CVFL were not statistically different between males and females. Hirano et al[1] also found no evidence that there is a rapid increase in the length of any portion of the vocal folds corresponding to the age of vocal mutation (puberty), but they reported that the TVFL and MVFL were longer in males than in females at about ages 10 to 15 years. Likewise, Harries et al[19] followed males progressing through puberty with serial vocal fold ultrasounds and observed no significant increase in vocal fold length to account for their patients' sudden drop in fundamental frequency.

Our study had a few limitations. Although we measured more than 200 patients, fewer were older adolescents. Despite this fact, we had many patients at the critical ages of fundamental frequency change for both females and males. If we had had approximately 120 females rather than 87, we might have been able to assess whether the MVFL of males indeed increased more quickly compared with females. Otherwise, our sample size appeared to be adequate in showing a linear increase in the MVFL as well as the other vocal fold lengths. Next, our method of vocal fold length measurement required some estimation. We estimated our lengths based on the vocal fold measuring sticks but could not ensure that we were measuring exactly at the posterior insertion point of the cartilaginous vocal fold. Despite this estimation, our MVFLs were similar to previously published data; however, the CVFLs were roughly twice as long, which could have been the result of overestimating the CVFL. Last, our patients were under a general anesthetic, which has been shown to elongate vocal folds in adults.[20] Evaluating younger children while awake would not be possible given our current measurement devices.

In conclusion, this is the largest longitudinal pediatric study specifically examining vocal fold length as a function of age. Each length of the true vocal fold appeared to linearly increase for both females and males. The M/C ratio remained relatively constant, unlike previously reported data, possibly due to in vivo vs cadaveric measurements. These findings suggest that the critical periods of vocal development in females and males are not explainable by changes in vocal fold length alone, and other factors such as vocal fold layers need further exploration.

Authors' Note

Major Rogers is a military service member. This work was prepared as part of his official duties. Title 17 U.S.C. 105 provides

Author Contributions

Derek J. Rogers, concept and design, wrote article, acquisition/analysis/interpretation of data, critical revision for intellectual content, final approval, agree to be accountable for all aspects of work; **Jennifer Setlur**, collected data, critical revision for intellectual content, final approval, agree to be accountable for all aspects of work; **Nikhila Raol**, collected data, critical revision for intellectual content, final approval, agree to be accountable for all aspects of work; **Rie Maurer**, acquisition/analysis/interpretation of data, formal statistical analysis, critical revision for intellectual content, final approval, agree to be accountable for all aspects of work; **Christopher J. Hartnick**, concept and design, acquisition/analysis/interpretation of data, critical revision for intellectual content, final approval, agree to be accountable for all aspects of work.

Disclosures

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Supplemental Material

Additional supporting information may be found at http://otojournal.org.

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Facial Fractures in Children

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KEYWORDS

• Pediatric facial trauma • Maxillofacial trauma • Orbital fractures • Mandible fractures • Facial growth

KEY POINTS

- The stages of facial growth and development often determine the fracture patterns seen for each age group.
- Children are more likely to sustain an intracranial injury in combination with a facial fracture.
- Extraocular muscle entrapment is more common in children and may present with a fairly normal-appearing eye.
- Most mandibular fractures can be treated with either soft diet or a closed reduction.
- Long-term follow-up to assess for growth disturbances is needed.

INTRODUCTION

Pediatric facial trauma can be especially disturbing to the family and to the physician faced with the task of reconstruction. The expectation and goal of complete resolution to the premorbid facial structure and appearance can be a daunting task. Fortunately, many advances in the diagnosis and treatment of maxillofacial trauma have helped bring the achievement of this goal closer. Although much of the understanding and experience in regards to maxillofacial trauma comes from the adult population, one must recognize that there are additional concerns in the growing facial skeleton and that the solution for an adult may be entirely different than the solution for a child. Nevertheless, the principles of a comprehensive initial evaluation, a correct diagnosis of the injury, and a patient-based treatment plan remain the same.

GROWTH AND DEVELOPMENT

Many of the unique features of pediatric facial trauma are directly related to the underdevelopment and continuing growth of the facial skeleton. Most of the bone of the

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craniofacial structure is derived from membranous ossification, although there are portions of the skull base and temporomandibular joints that undergo endochondral ossification.[1] The functional matrix concept of growth posits that the growth of the facial skeleton is directed by the overlying muscles acting on the bone.[2] This translates to the theory that scarring and contraction of the soft tissue envelope is responsible for growth disturbances secondary to trauma or surgery.[1]

One of the key factors that relates to the incidence of pediatric facial injuries is the ratio between cranial and facial volume, which is approximately 8:1 starting at birth. This small proportion of the midface in comparison with the cranium is thought to be responsible for the higher incidences of cranial injuries in young children.[3,4] Brain growth continues to expand the cranium to reach approximately 85% of adult size by the age of 5 years.[5,6] During the same time period the orbit is growing rapidly and reaches about 90% of its adult size by age 5.[7] However, mid and lower facial growth lag behind considerably. Midfacial growth proceeds in a vertical and anterior direction and nasal growth typically does not reach full adult size until the late teenage years.[8] The mandible reaches its adult width early, by about age 1 year; however, its height is not complete until the teenage years.[8]

The gradual pneumatization of the paranasal sinuses is also thought to contribute to the decreased frequency of facial fractures, because the bone is more solid. The paranasal sinuses grow at different rates. In the newborn period the ethmoid sinuses are present but the remainder of the paranasal sinuses is relatively underdeveloped. The maxillary sinus may begin to develop before 1 year of age, but significant growth may not be seen until 5 years.[9,10] The frontal sinus is the slowest to pneumatize, starting around 2 years of age, and may not even be identifiable radiologically until around 8 years of age.[11] The frontal sinus continues to grow past puberty to reach full size in young adulthood.[12]

The unerupted teeth in the maxilla and mandible are also thought to contribute to form more dense and stable bone thus increasing the force required to produce a fracture in pediatric patients.[13] Additionally, the prominent buccal fat pads in children are thought to help disperse the force of a blow to the midface region. The bone in this region is also considered more elastic and therefore less likely to completely fracture, but more likely to result in greenstick fracture patterns.

The variations seen in the types of facial injuries that occur between children and adults are related to these variations in the structural anatomy. Initially, children younger than age 2 have much more of the surface anatomy of their craniofacial skeleton centered on the cranium and are therefore more likely to experience more frontoorbital injuries.[14] As children age and their facial structure begins to grow downward and outward their injury patterns begin to mirror those of adults. Therefore, by the teenage years the patterns of injury are very similar to adult patients.

EPIDEMIOLOGY

Despite advancements in child safety, trauma remains the most common cause of pediatric morbidity and mortality in this country.[15] It has been reported that facial trauma may comprise up to 11% of pediatric emergency department visits.[1] However, most of these visits are related to dentoalveolar and soft tissue injuries.[16,17] Imahara and colleagues[18] examined 277,008 pediatric trauma patients requiring admission and found facial fractures present in 4.6% of cases. In regard to the total population of maxillofacial fracture patients, children younger than age 17 comprise approximately 14.7% of patients.[19] However, a large number of these patients are teenagers, because the reported incidence of fractures in children younger than the age of 5 years

ranges from less than 1% to 5%.[16,19] It has been reported that the risk of a child with facial trauma to sustain a fracture of the facial skeleton increases by 14% with every year of age.[13]

The cause of pediatric facial fractures also changes with age, but most are related to falls or recreational sports.[13,20] However, motor vehicle accidents are the most common cause of severe facial fractures or fractures in those children with multisystem injuries.[18] It should also be noted that craniofacial injuries are commonly seen in cases of child maltreatment.[21]

Male gender also increases the likelihood of facial trauma, with boys outnumbering girls almost 2 to 1.[13,22] It is thought that increased participation in sporting activities or a tendency toward dangerous activities may be responsible for this difference. Interpersonal violence, which is a common cause of maxillofacial fractures in adults, is less common; however, its incidence increases in the teenage population.[23]

The most common site of injury varies according the study population. Because most studies are conducted based on data from trauma databases or from patients seen at trauma centers, many minor, isolated fractures are likely underreported, such as dentoalveolar and nasal bone fractures. Imahara and colleagues[18] examined the National Trauma Data Bank and found the most common pediatric fractures to be mandible (32.7%), nasal bone (30.2%), and maxilla/zygoma (28.6%). Mandible fractures were found more commonly in teenagers.[18] Grunwaldt and colleagues[14] examined the frequency of fractures seen at their emergency room based on age group. In 0 to 5 year olds and in 6 to 11 year olds, orbital fractures were the most commonly seen fractures.[14] However, in 12 to 18 year olds mandible fractures were the most common.[14]

DIAGNOSIS AND INITIAL MANAGEMENT

The initial evaluation of a child sustaining facial trauma is to confirm and maintain adequate airway, breathing, and circulation, just as in an adult patient. However, a child's airway is much smaller and therefore can be more prone to airway compromise from swelling or bleeding. Furthermore, children have lower blood volumes and can quickly lose hemodynamic stability.

As with any trauma patient, once the patient is stabilized it is necessary to give priority to diagnosing and addressing life-threatening or high morbidity injuries before focusing on their facial injuries. Because of the previously mentioned small size of the face and its increased bony density, a pediatric facial fracture often indicates high-energy trauma and concomitant injuries to other organ systems must be evaluated. In fact, concomitant injuries have been reported in up to 55% of pediatric facial trauma patients.[14]

Among pediatric trauma service admissions, those with facial fractures have been reported to have almost double the mean Injury Severity Score, and much higher rates of cerebrovascular injuries.[18] In these children, facial fractures were associated with a 63% higher mortality rate.[18] Given the cranial to facial proportions in the growing patient, infants and toddlers have a significantly higher incidence of severe intracranial injuries, and 57% of children younger than 5 years of age with a facial fracture have been found to have a concomitant intracranial injury.[14,18] In contrast to adults, who may experience cervical spine injuries in around 10% of cases, children are less likely to suffer a concomitant cervical spine injury (0.9%–2.3%).[14,24,25] However, concomitant ocular injuries are just as common in children as in adults and because orbital fractures are more frequently seen in children, a thorough ophthalmic examination is crucial. Fifty percent of orbital fractures in children result in ocular injuries and 0.5% to 3% of these may be blinding.[14,26,27]

The assessment begins with a thorough history and physical examination. Fear and pain can make this evaluation especially challenging in children. Interviewing the parents or any witnesses to the trauma is likely necessary. The physical examination is commonly compromised by poor cooperation from the child, and therefore, should be approached gently and with as little trauma as possible. Caution is advised in regards to sedated examinations during the primary evaluation. A comprehensive orbital examination is indicated in all patients and should include pupil reactivity and size, visual acuity if possible, assessment for diplopia, and evaluation of extraocular muscle function. Assessment of extraocular movement is even more important in children because of the so-called "white eye" syndrome, in which the eye looks otherwise completely normal except for extraocular movement limitation. Because greenstick fractures are more common in children, orbital floor fractures causing a trapdoor effect and muscle impingement are more likely to be seen in the pediatric population. These patients may also have pain with eye movement, nausea, vomiting, and bradycardia that can mimic the symptoms of a closed head injury. Enophthalmos or hypoglobus should also be noted. The orbital rims can be palpated for bony step-offs but these are often difficult to feel in the pediatric patient. Presence of lateral subconjunctival hemorrhage is a good indicator of an underlying periorbital fracture. A cranial nerve examination can reveal numbness of the V2 or V3 distributions suggesting a fracture. Facial nerve function should also be documented initially because intervention for peripheral or temporal segment injuries may be indicated. Assessing the contour of the zygomatic arch and the symmetry of malar emminences may be difficult because of the increased fat distribution of this region in children. A good nasal examination focusing on symmetry and support of the nasal dorsum and assessing for a septal hematoma should also be part of the initial evaluation. Examination of the oral cavity includes assessing for dental trauma, trismus, malocclusion, and visible step-offs. Remember that the history and physical examination guides the use of further diagnostic testing, not the other way around—this is especially true in the pediatric population.

After suspicion is raised for a fracture a radiologic evaluation is indicated. Although there are many plain film options, these are notoriously unreliable in children because the undeveloped sinuses, unerupted tooth buds, propensity for greenstick fractures, and incompletely ossified areas make identifying fractures difficult.[28] However, panoramic radiography (panorex) continues to be useful in the evaluation of mandibular fractures. Ultimately, computed tomography (CT) remains the gold standard for assessing facial fractures in adult and pediatric patients. Coronal and sagittal formatting of the images allows for improved evaluation of displacement and volume changes around the midface and orbits. CT offers the distinct advantage of providing the operating surgeon with a visible conceptualization of the reconstruction needing to occur in the operating room; this is further aided by three-dimensional reformatting.

Recently there have been significant concerns regarding excess radiation exposure in children. The multiplanar techniques that allow for excellent, detailed images also incur a higher radiation dose.[28] As a result, many institutions have been exploring protocols that lower the dose of radiation with a sacrifice in image quality. This requires a certain balance between the ability to identify subtle greenstick fractures and the need to decrease radiation exposure. Unfortunately, there is insufficient data regarding the diagnostic sensitivity and specificity of these low-dose CT scans in pediatric maxillofacial trauma. However, because many nondisplaced pediatric facial fractures can be treated conservatively, these low-dose CT scans should be considered as a means to diagnose large disruptions in the facial skeleton that require operative intervention. Furthermore, additional postreduction scans are discouraged if the postoperative

physical examination is normal. For postoperative evaluation of mandibular injuries, a panoramic radiograph is recommended instead of CT.

Fronto-Orbital Fractures

Because of the increased ratio of cranial vault to the facial skeleton, fractures of the frontal bone and superior orbital rim and roof are more common in children.[1,14] Thus, these fractures are more common in children younger than 5 years of age when the skull is at its largest.[14] Because the frontal sinus does not start to pneumatize substantially until age 6, these frontal bone fractures are more accurately cranial fractures, which may explain the increased frequency of intracranial injuries in the pediatric population. Without the "crumple zone" of the frontal sinus, forces to the frontal region may result more commonly in fractures of the supraorbital rim and the orbital roof. Because of this differential anatomy, orbital roof fractures are the most common orbital fractures seen in children younger than 10 years of age.[27,29] Although a fracture of the supraorbital rim can sometimes be palpated on physical examination, diagnosis of an orbital roof fracture can be difficult without CT imaging. However, a depressed fracture of the orbital roof can result in exophthalmos or muscle entrapment limiting extraocular movement. Superior orbital fissure syndrome is also possible in severe fracture patterns. These frontal and orbital roof fractures require a multidisciplinary effort with Neurosurgical and Ophthalmologic involvement. In general, orbital roof fractures rarely require surgical intervention, except for cases with muscle entrapment or when the defect is large-which may lead to orbital pulsations or a late encephalocele.[1,30] Frontal bone fractures that are displaced more than the full-thickness width of the bone are often repaired to reduce contour deformities.[1] This should be performed in concert with Neurosurgery to evacuate epidural hematomas, repair dural tears, and manage brain injuries. These patients need long-term follow-up because continued brain growth can push apart the fracture site and result in brain herniation that may require cranioplasty in the future.[31]

As children age and the frontal sinus develops, true frontal sinus fractures are more common and are similar to their adult counterparts. However, it has been reported that frontal sinus fractures in children are twice as likely to sustain posterior table injuries and to develop a cerebrospinal fluid leak.[32] The treatment of these injuries is essentially the same as their adult counterparts. Displacement of the posterior table more than the full-thickness width of the bone is a general indication of the possibility for dural injury and mucosal displacement, thus necessitating operative intervention in the form of cranialization.[1] Significant disruption of the nasofrontal duct is another indication for operative intervention. As in adults, there has been a shift away from frontal sinus obliteration and a move toward sinus preservation and delayed endoscopic sinus surgery if necessary. Therefore, follow-up clinic visits and imaging are needed at regular intervals.

Naso-Orbito-Ethmoid Fractures

Naso-orbito-ethmoid (NOE) fractures are often considered the most challenging facial fractures to repair. Fortunately, although reported incidences vary, they are considered relatively rare in children.[28,33] One of the problems with diagnosing NOE fractures in children is that children already tend to have a low nasal dorsum and an overrotated nasal tip. Therefore, it is necessary to palpate the nasal dorsum to assess whether it is impacted into the midface. This part of the examination can help distinguish between simple nasal bone fractures and NOE fractures needing CT imaging. In addition to a saddle nose deformity, NOE fractures can also result in telecanthus from bony displacement or from medial canthal tendon (MCT) disruption. Disruption at the

MCT can be assessed by pulling the eyelids laterally while palpating over the medial canthal region. Normally, the MCT creates an area of tautness (bowstring sign), which may still be present if the MCT is not completely avulsed from the bone. Therefore, bimanual palpation of the medial orbital wall using an intranasal instrument should be performed to test for mobility of the entire complex.

The management of NOE fractures is primarily surgical with open reduction and internal fixation. However, some authors advocate for closed reduction and extraction of the impacted nose if the reduced nasal pyramid feels stable.[1] Open reduction and internal fixation is commonly approached through existing brow lacerations or via a coronal approach. The primary goals are to restore nasal dorsal height and to restore medial canthal attachments and contour. However, bony fragments are often very small and not amenable to screw fixation. Transnasal wiring to stabilize the MCTs or MCT-bearing bone fragments may be necessary, along with cantilevered bone grafts for support at the nasal dorsum. The initial surgery is often the best chance to restore normal positioning, because revision NOE surgery is difficult.[34] The normal narrowing and convexity at the medial canthal region is difficult to re-establish; therefore, external bolsters are recommended to help coapt the overlying soft tissue and splint the underlying bony fragments. Typically these are made from petroleum gauze and secured with transnasal wires or sutures to be left in place for as long as possible (usually 4–6 weeks). Nguyen and colleagues[34] have shown excellent results after long-term bolsters caused ulceration that was allowed to heal secondarily. Stenting of the nasolacrimal system is generally not necessary during the immediate repair, and long-term complaints of epiphora are rare.[35] Ultimately, there are few long-term studies examining outcomes of NOE fracture repairs in children, but the need for revision surgery is common, especially in the growing child.[36]

Orbital Fractures

Orbital fractures are common in children, but treatment strategies remain controversial. It is important to again emphasize that greenstick "trapdoor" fractures with muscle entrapment are more common in children and to be aware of the "white eye" orbital fracture (**Fig. 1**). In general, after 5 years of age orbital floor fractures become more common than orbital roof fractures.[14] Ophthalmology evaluation is warranted in all cases of pediatric orbital injury. Traumatic optic neuropathy may be discovered, which

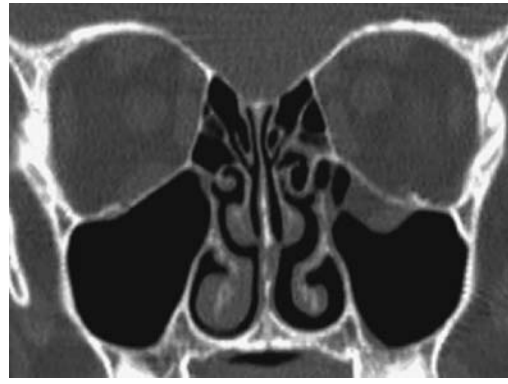

Fig. 1. Computed tomography of left orbital floor blowout fracture. Note the greenstick fracture pattern with entrapment of the inferior rectus muscle. (*From* Fraioli RE, Branstetter BF, Deleyiannis WB. Facial fractures: beyond Le Fort. Otolaryngol Clin N Am 2008;41:67; with permission.)

would warrant aggressive steroid therapy. If visual acuity does not respond or if bony fragments impinge on the optic canal, optic nerve decompression can be considered, although results have been mixed in pediatric trauma patients.[37,38]

Fractures of the orbital floor remain controversial in regard to which ones require repair. However, most surgeons agree on the criteria of large floor defects (>1 cm^2) or extraocular muscle entrapment.[1,39] Muscle entrapment is the most pressing cause for early repair, and those with an oculocardiac reflex require emergent repair. Children heal quickly; therefore, muscle entrapment in a child may result in fibrosis and shortening of the muscle within a couple days. As a result, diplopia can be present for months after the initial injury, or it may be permanent.[40] Fractures of the medial wall should also be considered. A transcaruncular approach can allow for access to place an implant to reduce the intraorbital volume; however, some surgeons prefer to compensate with augmentation of the orbital floor instead.[39]

Repair of an orbital floor fracture can be performed through a variety of approaches; however, the transconjunctival approach is favored from a cosmetic standpoint and also may reduce the incidence of postoperative ectropion.[41] A variety of implants can be used to reconstruct the orbital floor. Split calvarial bone grafts have classically been used, and some surgeons continue to advocate for their use in children younger than 7 years of age who may continue to undergo further orbital growth.[1] Otherwise, titanium and porous polyethylene are commonly used with significantly less donor site morbidity.

Nasal Fractures

Nasal bone fractures are suspected to be the most common facial bone fracture in children, because their true incidence is very likely underreported in the literature.[42] Because these fractures are often isolated and occur without concomitant injuries, they are more likely to be treated on an outpatient basis. These fractures can also remain undiagnosed if swelling obscures the assessment of nasal bone symmetry. An initial intranasal examination is key to diagnosing airway obstruction and to defining concomitant septal fracture or septal hematoma. Most nasal bone fractures can be diagnosed on physical examination alone, thus conserving radiologic examinations for those patients in whom the history or physical examination warrants further investigation. The finding of a septal hematoma should prompt urgent surgical evacuation to prevent cartilage necrosis and saddle nose deformity.

Long-term growth disturbance is a cause for concern. The septum is thought to harbor important growth zones, which if injured may result in a lack of nasal projection.[43] Because full growth of the nose is not achieved until age 16 to 18 years in girls and 18 to 20 years in boys, damage to these growth centers from either the initial trauma or from surgery can have long-lasting effects.

Early closed reduction of nasal bone fractures within a few days of the injury is usually recommended.[44,45] This can be accomplished under sedation or general anesthesia. However, the results of closed nasal reduction are often dissatisfying for the surgeon and the patient. Grymer and colleagues[46] examined the long-term results of nasal bone fractures treated in childhood, and found that by adulthood these patients tended to have a higher incidence of dorsal humps, saddle nose deformities, and deviations of the dorsum, despite most patients being satisfied with the outcomes after the initial closed reduction. Therefore, there is some indication that despite best efforts to correct these injuries, there may be deformities that develop gradually with growth. Parents should be counseled regarding this possibility.

Septal fractures can also be managed conservatively with a closed reduction technique. In those children with significant nasal airway obstruction, a limited,

cartilage-sparing septoplasty can be performed, although the risk of growth impairment is always a concern. If the nasal obstruction is without secondary consequences then delay until the teenage years is recommended.

An unusual fracture pattern that is typically only seen in children is that of the "open book."[42] Direct frontal impact to the nose can cause blood to develop and spread apart the nasal bones centrally (**Fig. 2**). This is suspected to occur in children more readily because of incomplete fusion of the nasal bones at the midline. This type of injury has been treated in young children with the conservative technique of frequent bimanual compression in the clinic.[47]

Midface and Zygomaticomaxillary Fractures

Because of the aforementioned small paranasal sinuses and unerupted tooth buds in children, midface fractures of the classical Le Fort patterns are unusual. Therefore, they are usually the result of high-impact trauma, such as motor vehicle accidents.[48] Goals of repair are similar to those in adults, such as restoration of facial contour, height, and dental occlusion. Many fractures in children are nondisplaced and can be treated conservatively. Maxillomandibular fixation can be applied to stabilize many of these fractures. Despite concerns that subperiosteal elevation can cause long-term maxillary growth restriction, fractures resulting in significant displacement of the buttresses typically require open reduction and internal fixation.[49] Screw placement can injure the unerupted tooth follicles and should be used judiciously and as far away from the dentition as possible. In cases of severely comminuted fractures at the buttresses, primary bone grafting can be considered.[3] Because of growth concerns, some authors recommend removing titanium hardware at 3 to 4 months postoperatively.[50] Resorbable plating can also be effectively used to stabilize midface fractures, especially at the zygomaticomaxillary buttress where the elevated profile of the plates is less noticeable.

Indications for zygomaticomaxillary complex fracture repair in children are similar to adult indications: mainly cheek asymmetry and functional concerns related to the orbital component. Nondisplaced fractures can be observed, but comminuted fractures should be addressed with fixation. Minimally invasive approaches, such as the transconjunctival approach to the orbital rim, are recommended. In children, one-point fixation of noncomminuted zygomaticomaxillary complex fractures has been reported as sufficient.[39] Outcome studies of one- and two-point fixation have

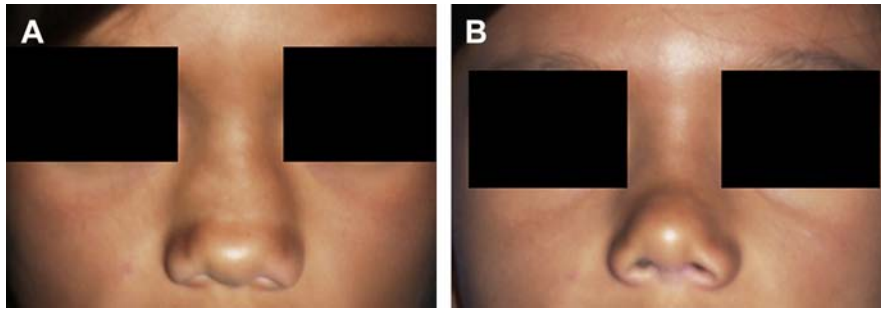

Fig. 2. "Open-book" nasal fracture pattern that can be encountered in pediatric patients. (*A*) Splayed appearance of the nasal bones on frontal view. (*B*) Treatment of splayed nasal bones with sequential manual compression in clinic and no surgical intervention. (*Courtesy* of Dr Frederick Stucker, Shreveport, LA.)

generally not included children, but given the rapid bone healing of children, the findings of these studies should translate well to the pediatric population.[51,52]

Mandibular Fractures

Mandible fractures are commonly reported as the most frequent facial fracture seen in children, and many more may go undiagnosed.[18,53,54] The management of pediatric mandibular fractures presents several challenges related to unerupted teeth, temporomandibular joint dysfunction, and facial growth disturbances. In children, not every fracture needs an open reduction and internal fixation. Instead, the surgeon must contemplate the interplay of fracture location to bony growth and dental development, and chose an intervention that lessens the potential for long-term impairment and deformity (**Fig. 3**). In contrast to adults, many pediatric mandibular fractures can be treated with conservative measures, such as soft diet alone.

The condyle is the most frequently injured portion of the mandible.[54] However, the location of the condylar fracture changes with age, because children younger than 5 years are more likely to sustain condylar head fractures, whereas older adolescents are more likely to sustain condylar neck fractures.[55,56] Symphaseal fractures are the second most commonly seen in all age groups.[57] However, as adolescents get older mandibular fracture patterns begin to resemble adult fractures and body and angle fractures can be encountered.[57]

In very young children, fractures that are nondisplaced and that do not affect dental occlusion can be treated with soft diet.[3,57] Noncompliance with diet restrictions is less of a problem in children than adults, since parents can control the child's diet. Many nondisplaced condylar fractures can therefore be treated with this conservative approach. However, displaced fractures of the condyle should undergo closed reduction.[1,22,57] Intermaxillary fixation can then be applied to further stabilize the fractured segments; however, only a brief period (7–10 days) of intermaxillary fixation is recommended because prolonged intermaxillary fixation can cause severe ankylosis in children.[1,3,57,58]

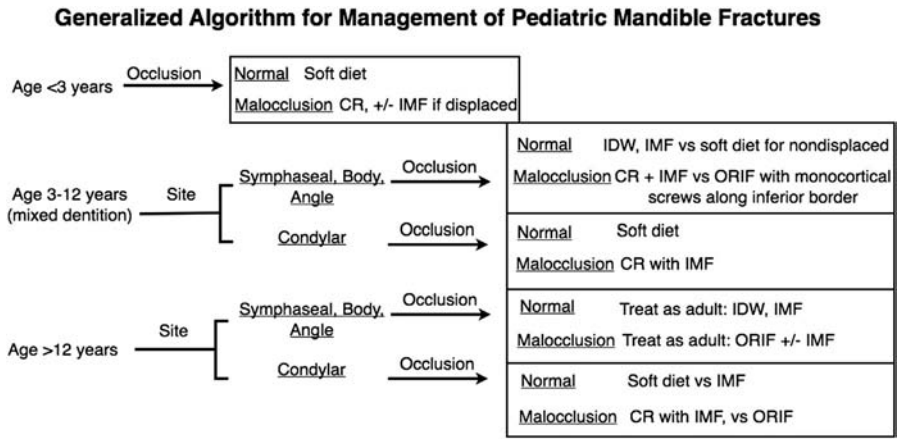

Fig. 3. Algorithm for the treatment of mandible fractures in children. These are general considerations and may not be appropriate for all patients. The degree of fracture displacement necessitates consideration of a more aggressive fixation approach. CR, closed reduction; IDW, interdental fixation; IMF, intermaxillary fixation; ORIF, open reduction internal fixation.

Displaced fractures of other regions of the mandible can be treated with closed reduction and dental stabilization or open reduction and internal fixation. In general, an attempt at a closed technique is recommended for younger children (<6 years of age), whereas teenagers can be treated with open reduction and internal fixation similar to adults. If closed reduction is successful, there are many methods to achieve stability including traditional arch bars, wire ligatures, or Risdon cables.[1] Acrylic splints fixated with circum-mandibular wires are also a good option if the deciduous dentition does not support wiring. However, the child must undergo general anesthesia up to three times because the mold must first be made, the splint wired in place, and then the splint removed. In general, these types of fixation can be removed after 3 weeks.[57]

Open reduction internal fixation is a viable and necessary option in many patients. In general, open reduction internal fixation is applied to displaced fractures of the tooth-bearing portion of the mandible that cannot be properly reduced or stabilized with closed techniques.[57] Multiple fracture sites or comminuted fractures are another indication.[59] As mentioned previously, if the patient has already reached skeletal and dental maturity, open reduction internal fixation can be applied similar to an adult patient. In a recent study, Smith and colleagues[59] report on using open reduction internal fixation on 75% of mandible fractures in children older than 12 years of age.

The use of internal fixation in younger children with developing dentition requires that screws be placed to avoid damaging the unerupted teeth (**Fig. 4**). Single miniplate fixation is typically all that is necessary for stabilization in children.[57,60] Fixation at the inferior border of the mandible with monocortical screws avoids damaging the unerupted tooth buds. Additional stabilization to prevent rotation at the superior border can be obtained with an arch bar. Avoiding placement of permanent rigid fixation across the midline of the mandible in young children is recommended, because there is a potential for growth restriction.[61,62] Although some surgeons recommend hardware removal after a few months, this practice is controversial and objective evidence is lacking.[57,62,63]

However, long-term problems with mandibular growth are a major concern. Growth disturbance following mandibular fractures is more commonly encountered with fractures of the condyle because this area is considered the primary growth center.[53,58,64] Fractures sustained during the years of active vertical growth have been demonstrated by Demianczuk and colleagues[58] to later require orthognathic surgery in up to 24% of cases. Proffit and colleagues[53] have reported that up to 10% of adult patients with dentofacial deformities have evidence of a condylar fracture in childhood.

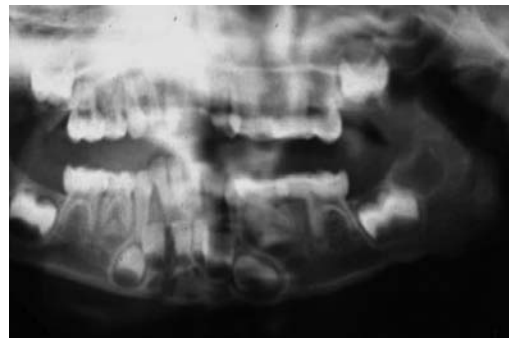

Fig. 4. Panorex radiograph demonstrating unerupted tooth buds of the pediatric mandible. Note the particularly low-lying position of the tooth buds in the parasymphaseal region.

Therefore, parents of children with condylar fractures should be counseled that growth disturbance and need for future orthognathic procedures may be needed. Additionally, there have been concerns about growth in the tooth-bearing portion of the mandible following rigid fixation, although recent animal studies have suggested no effect on growth.[65,66] Regardless, these concerns have stimulated interest in applying bioresorbable fixation to pediatric mandibular fractures.

RESORBABLE FIXATION

Perhaps the greatest area of current debate in the management of pediatric facial trauma is use of bioresorbable fixation hardware (**Fig. 5**). Its widespread use in cranial vault remodeling has spurred interest in applying it to maxillofacial fractures to address the same concerns about rigid titanium fixation causing growth disturbances. Features, such as less muscular load on the hardware and rapid bony healing, make resorbable plating ideal for the pediatric population. The downsides to resorbable hardware are that they have less inherent strength, the plates are more bulky, the screws require tapping, the plates have little memory to allow for overbending, and inflammatory reactions may occur.[57,62]

Resorbable hardware has been used successfully for maxillofacial fractures in children.[50,67] Most notably, Eppley[50] reported on its use in 44 pediatric patients younger than 10 years of age with no reported implant-related complications. However, the same advantages achieved in cranial vault surgery do not necessarily translate into the face, because titanium fixation is not typically placed in regions of such rapid growth or over bony suture lines. Pediatric facial fractures are also commonly managed with judicious use of fixation and closed techniques in very young patients. Therefore, the use of resorbable fixation in maxillofacial fractures has been questioned because there is not a significant amount of data indicating that titanium fixation results in maxillofacial growth restriction.[62,65,66] Furthermore, a recent Cochrane review questioned whether resorbable hardware was as effective as titanium hardware.[68] Therefore, although many surgeons are exploring the use of resorbable fixation hardware in pediatric facial fractures, definitive indications and recommendations for its use cannot be made at this time.

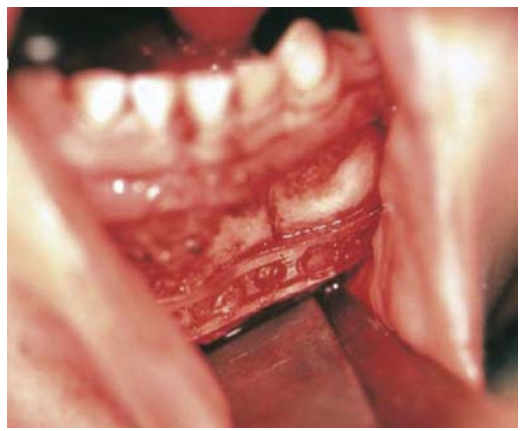

Fig. 5. Resorbable plate fixation used for a parasymphaseal mandibular fracture. (*From* Eppley BL. Use of resorbable plates and screws in pediatric facial fractures. J Oral Maxillofac Surg 2005;63(3):386; with permission.)

SUMMARY

Although maxillofacial fractures are not as common in children as in adults, the constantly growing facial skeleton adds several levels of complexity to the treatment of these injuries. Fortunately, children heal well and conservative techniques can frequently be used. Growth disturbances from the initial trauma and from the surgeon's interventions are difficult to predict, but avoiding aggressive dissection and extensive fixation is recommended. Long-term follow-up with a multidisciplinary team is often needed to manage the future changes in facial development that may occur with these injuries.

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Original Investigation

Outcomes of Mandibular Distraction Osteogenesis in the Treatment of Severe Micrognathia

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IMPORTANCE Patients with severe micrognathia are predisposed to airway obstruction. Mandibular distraction osteogenesis (MDO) is an alternative to tracheotomy that lengthens the mandible in order to improve the retrolingual airway. This study presents outcomes from one of the largest cohorts reported.

OBJECTIVE To assess the rate and predictors of surgical success and complications among (1) patients who underwent MDO prior to other airway procedures (MDO first), and (2) patients who required an initial tracheotomy and were subsequently treated with MDO (tracheotomy first).

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study at a tertiary care pediatric medical center of patients diagnosed as having micrognathia resulting in symptomatic airway obstruction (Pierre Robin sequence) and who underwent MDO from September 1995 to December 2009.

INTERVENTIONS Electronic medical records were reviewed. Multivariable regression analysis was used to assess for predictors of outcome.

MAIN OUTCOMES AND MEASURES Rates of surgical success (defined as either tracheotomy avoidance or decannulation) and complications. Potential predictors included demographics, syndrome presence, follow-up time, and surgical history.

RESULTS A total of 123 patients (61 in MDO-first subgroup, 62 in tracheotomy-first subgroup) underwent MDO during the study period. Median age at time of distraction was 21 months (range, 7 days–24 years). Surgical success and complication rates were 83.6% and 14.8% in the MDO-first subgroup and 67.7% and 38.7% in the tracheotomy-first subgroup. Tracheotomy-first patients were more likely to have a syndromic diagnosis (66.0% vs 43.0%; $P = .009$) and were older at the time of MDO (median age, 30 months vs 5.1 months; $P < .001$). Poorer odds of success were associated with the need for 2 or more other airway procedures (odds ratio [OR], 0.14 [95% CI, 0.02-0.82]) in the MDO-first subgroup and craniofacial microsomia or Goldenhar syndrome (OR, 0.07 [95% CI, 0.009-0.52]) in the tracheotomy-first subgroup.

CONCLUSIONS AND RELEVANCE Mandibular distraction osteogenesis has a high rate of success in avoiding tracheotomy. Patients who required a tracheotomy before MDO had a lower success rate in achieving decannulation and a higher rate of complications. However, these patients also had a higher rate of syndromic diagnoses and associated comorbidities. Patients with Goldenhar syndrome have a decreased likelihood of surgical success.

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Pierre Robin sequence is characterized by the triad of micrognathia, glossoptosis, and resultant airway obstruction owing to constriction of the retrolingual space.[1] Though not classically described as part of its definition, cleft palate is a commonly associated finding that occurs in up to 90% of children with Pierre Robin sequence. Symptoms of airway obstruction may range from snoring and stertor while asleep to frank obstruction and retractions when awake. Gasping or aspiration while feeding is frequently encountered, and this in combination with chronic airway obstruction can cause failure to thrive. Long-term sequelae of severe airway obstruction can lead to cor pulmonale and cardiorespiratory arrest.

Interventions aimed at relieving such symptoms vary depending on the severity of the symptoms. Conservative measures for less severe symptoms include prone positioning and use of a nasopharyngeal airway.[2] In the event that such conservative treatments are unsuccessful or for more severe symptoms, options for surgical intervention include tongue-lip adhesion, tracheotomy, and mandibular distraction osteogenesis (MDO). Tongue-lip adhesion has been shown to significantly improve obstructive sleep apnea due to micrognathia[3] but has generally been less effective than MDO at normalizing obstructive symptoms, particularly in severely symptomatic patients. In addition, tongue-lip adhesion can lead to dysphagia and feeding difficulties.[4] Tracheotomy offers a definitive treatment for upper airway obstruction but has associated risks of accidental decannulation or mucous plugging. There is also potential long-term morbidity related to peristomal scarring and tracheal erosion in addition to the need for long-term maintenance and home care.[5,6] In recent years, there have been an increasing number of reports on the results of MDO as an alternative to tracheotomy.[7-15]

The goals of this study were to assess the surgical success and complication rates of MDO for treatment of severe micrognathia and to identify potential predictors of surgical success and complications. Surgical success was defined as either (1) avoidance of tracheotomy or (2) decannulation among those patients treated initially with a tracheotomy.

Methods

Participants

This was a retrospective cohort study of all patients who underwent MDO from September 1, 1995, to December 31, 2009, at Cincinnati Children's Hospital Medical Center. Inclusion criteria included any patients who underwent initial MDO during the study period. All patients were seen through a multidisciplinary craniofacial clinic, and those with a concern for syndromic Pierre Robin sequence were routinely evaluated by clinicians from both the genetics and ophthalmology departments in addition to the craniofacial surgery and otolaryngology departments to ensure proper diagnosis and management. Electronic and paper chart medical records were reviewed for relevant data. Patients who were lost to follow-up after MDO or had incomplete medical records were excluded. Mandibular distraction osteogenesis was performed with short sagittal split osteotomies using primarily external distraction devices, although internal distraction devices were used in a minority of patients based on surgeon preference. This study was approved by the institutional review board of Cincinnati Children's Hospital.

Potential Predictors

Variables included as potential predictors of outcome included demographics (sex, age at time of distraction), follow-up time, syndrome presence (categorized as isolated Pierre Robin sequence, craniofacial microsomia [CFM] or Goldenhar syndrome, Treacher-Collins syndrome, and other syndromes), type of initial surgical intervention (tracheotomy vs MDO), length of mandible distracted, number of distractions, and number of subsequent airway procedures (eg, laryngotracheoplasty, endoscopic airway procedures, base of tongue procedures, choanal atresia repair).

Outcomes

While the primary goal of MDO was to improve the retrolingual airway and relieve airway obstruction, the definition of surgical success necessarily differed for patients who were initially treated with tracheotomy prior to MDO compared with those who underwent MDO as an initial procedure. Thus, surgical success was defined as (1) avoidance of tracheotomy among patients who were treated first with MDO and (2) successful decannulation among patients who initially underwent tracheotomy prior to MDO. Complications assessed included open bite deformity, premature bone consolidation, temporomandibular joint (TMJ) ankylosis, facial nerve injury, emergent reintubation, and prolonged intubation. For the purposes of this analysis, the need for repeated distraction more than 30 days after the initial distraction was not considered a complication because it was felt that this need reflected a lack of innate growth of the distracted mandible over time rather than a failure of the initial distraction.

Statistical Analysis

Descriptive statistics are reported as means (SDs) and medians with interquartile ranges (IQRs) or frequencies with percentages. The characteristics of the 2 subgroups defined by initial surgical treatment were compared using the Wilcoxon rank sum test for continuous variables and the χ^2 or Fisher exact test for categorical variables. Logistic regression analysis was used to assess the relationship between the potential predictors and each dichotomous outcome of interest (surgical success and occurrence of complications). The analysis of surgical success was stratified by initial surgical intervention (tracheotomy vs MDO), since the definition of outcome differed between these subgroups. For potential predictors of a complication, all complications were grouped together as a dichotomous outcome (any complication or no complication). The entire cohort was included in this regression analysis since the definition of a complication was the same regardless of the initial intervention. For each outcome (surgical success and occurrence of a complication), logistic regression models were constructed to identify potentially important associations between the predictor variables and each outcome of interest. A conservative criterion $P = .20$ was used as a cutoff for inclu-

Table 1. Characteristics and Outcomes of 123 Patients in Cohort

Characteristic	No. (%)	Tracheotomy First (n = 62 [50.4%])	MDO First (n = 61 [49.6%])	*P* Value
Male	69 (56.1)			
Isolated Pierre Robin sequence	54 (43.9)	21 (33.9)	35 (57.4)	
Syndromic	69 (56.1)	41 (66.3)	26 (42.6)	
Treacher-Collins syndrome	12 (9.8)	8 (12.9)	4 (6.6)	.009
CFM-Goldenhar syndrome	11 (8.9)	7 (11.3)	4 (6.6)	
Stickler syndrome	4 (3.3)	3 (4.8)	1 (1.6)	
Other[a]	42 (3.1)	23 (3.7)	17 (2.8)	
Age at distraction, mo				
Mean (SD)	40 (52)	46 (47)	34 (57)	.20
Median (IQR)	21 (2.2-48.2)	30 (15.2-52.8)	5.1 (0.6-42.1)	<.001
Range	6 d-20 y	25 d-20 y	6 d-19 y	
Follow-up time, mean (SD), y	3.2 (3.2)	3.8 (3.8)	2.5 (2.3)	.03
Amount distracted, mean (SD), mm	22.3 (7.9)	23.1 (7.9)	21.6 (7.7)	.28
Distractions, No.				
1	107 (87.0)	55 (88.7)	52 (85.2)	.52[c]
2	14 (11.4)	7 (11.3)	7 (11.5)	
≥3	2 (1.6)	0	2 (3.3)	
Subsequent airway procedures, No.[b]				
0	67 (55.4)	24 (38.7)	43 (72.9)	.002
1	27 (22.3)	18 (29.0)	9 (15.2)	
2	10 (8.3)	7 (11.3)	3 (5.1)	
≥3	17 (14.0)	13 (21.0)	4 (6.8)	
Outcomes by treatment group				
Surgical success	93 (75.6)	42 (67.7)	51 (83.6)	<.001
Avoidance of tracheotomy	NA	NA	51 (83.6)	
Decannulation	NA	42 (67.7)	5 (8.2)	
Complications	33 (26.8)	24 (38.7)	9 (14.8)	.03
Premature consolidation	14 (11.4)	12 (19.4)	2 (3.3)	.005
Open bite deformity	9 (7.3)	5 (8.1)	4 (6.6)	>.99[c]
Temporomandibular joint ankylosis	5 (4.1)	5 (8.1)	0	.06[c]
Other[d]	9 (7.3)	6 (9.7)	3 (5.0)	.49[c]

Abbreviations: CFM, craniofacial microsomia; IQR, interquartile range; NA, not applicable.

[a] Includes arthrogryposis; Pfeiffer, Nager, Klippel-Feil, amniotic band, orofaciodigital, Cornelia de Lange, Loeys-Dietz, Dandy-Walker, cri-du-chat, Crouzon, Moebius, and Katel-Manske syndromes; achondroplasia; and chromosomal abnormalities.

[b] Includes laryngotracheoplasty, endoscopic airway procedures, base of tongue procedures, choanal atresia repair.

[c] Fisher exact test.

[d] Need for repeated distraction within 30 days of initial distraction, transient facial nerve injury, emergent reintubation, prolonged intubation, and internal carotid artery dissection.

sion in subsequent multivariable regression models. An $\alpha = .05$ was considered for statistical significance in all final models. SAS statistical software (version 9.3; SAS Institute) was used to conduct all analyses.

Results

There were 132 patients who underwent MDO during the study period. Of these, 8 patients were lost to follow-up, and 1 died shortly after distraction owing to congenital heart disease. These patients were excluded from subsequent analysis, leaving 123 patients in the cohort. Patient characteristics for the entire cohort and stratified by initial treatment group are described in **Table 1**. A slight majority of patients were male, and 56.0% were diagnosed as having an associated syndrome. Treacher-Collins (9.8%) and CFM-Goldenhar (8.9%) syndromes were the most commonly encountered syndromes. Median age at time of distraction was 21 months (range, 6 days-24 years). Sixty-two patients (50.4%) underwent an initial tracheotomy prior to MDO while 61 (49.6%) underwent MDO first. Median follow-up time was approximately 5 years (range, 30 days-16.2 years). The median distraction amount was 22 mm (range, 7-52 mm). One hundred seven patients (87.0%) underwent a single distraction, while the remainder of the cohort required repeated distractions. Most these patients underwent repeated distractions at least 6 months after the initial distraction. Seven patients (5.7%) required repeated distractions within 30 days of the initial procedure. Of these, 4 could be attributed to either hardware malfunction or premature consolidation. Sixty-seven patients (55.0%) did not require any further airway procedures after distraction, although a substantial minority of patients required at least 1 other procedure.

Patients who underwent tracheotomy first were significantly more likely to have an associated syndromic diagnosis compared with those who underwent MDO first (66.0% vs 43.0%, respectively). Patients treated with MDO first were also significantly younger at the time of distraction than those treated with tracheotomy first (median age, 5 months vs 30 months) and required fewer subsequent airway procedures.

Table 2. Unadjusted Associations Between Potential Predictors and Surgical Success, Stratified by Initial Treatment Group

	Tracheotomy First (n = 62)		MDO First (n = 61)	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Male	0.43 (0.14-1.30)	.14	1.30 (0.34-5.10)	.69
Diagnosis[a]				
Treacher-Collins syndrome	0.50 (0.07-3.70)	.50	0.45 (0.04-4.60)	.50
CFM-Goldenhar syndrome	0.01 (0.01-0.52)	.009	1.70 (0.06-51.80)	.75
Other	0.27 (0.06-1.10)	.08	0.71 (0.17-2.90)	.63
Age at distraction, y	1.10 (0.94-1.30)	.20	0.94 (0.84-1.00)	.26
Follow-up length, y	1.00 (0.89-1.20)	.70	0.97 (0.74-1.30)	.84
Distraction length, mm	0.98 (0.92-1.00)	.54	1.00 (0.95-1.20)	.39
Distractions, No.				
2 vs 1	3.20 (0.36-28.30)	.30	3.70 (0.16-85.00)	.41
3 vs 1	NA		1.20 (0.03-54.00)	.91
Other airway procedures, ≥2 vs <2	0.83 (0.27-2.60)	.75	0.14 (0.02-0.82)	.03

Abbreviations: CFM, craniofacial microsomia; MDO, mandibular distraction osteogenesis; NA, not applicable; OR, odds ratio.

[a] Reference diagnosis was isolated Pierre Robin sequence.

Rates of surgical success and complications are described in Table 1. The overall success rate for MDO in the cohort was 75.6%. There was a significant difference in the success rate between patients who underwent tracheotomy prior to MDO (67.7% successfully decannulated) compared with those who underwent MDO first (83.6% avoided tracheotomy; $P < .001$). In the entire cohort, there were 72 patients who underwent tracheotomy, 62 who underwent tracheotomy as an initial procedure, and 10 who underwent tracheotomy after MDO. Approximately one-third of these were performed at outside institutions prior to referral. Five of the 10 patients who required a tracheotomy after MDO were eventually decannulated. The overall complication rate was 26.8%, with a significantly higher complication rate in the tracheotomy-first subgroup compared with the MDO-first subgroup (38.7% vs 14.8%, respectively; $P = .003$). In the overall cohort, premature bony consolidation (11.4%), open bite deformity (7.3%), and TMJ ankylosis (4.1%) were the most common complications. Patients who underwent a tracheotomy first had greater rates of premature consolidation (19.4% vs 3.3%; $P = .005$) and TMJ ankylosis (8.1% vs 0%; $P = .06$) compared with those who underwent MDO first. Among the 5 patients who developed TMJ ankylosis, 1 was a patient with amniotic band syndrome and bilateral Tessier 7 clefts who required 4 distraction procedures and developed ankylosis after the last distraction. One patient with Catel-Manzke syndrome had preexisting TMJ ankylosis that was thought to be related to her underlying syndrome, and another had Goldenhar syndrome (Pruzansky grade 1). Both of these patients required 3 distractions each. One patient with isolated micrognathia had premature consolidation requiring a second distraction procedure that was complicated by a pin site infection, and the last patient had isolated micrognathia requiring only 1 distraction. In this case, the cause of the TMJ ankylosis was unclear.

In the tracheotomy-first subgroup, univariable logistic regression modeling identified sex, syndrome diagnosis, and age at distraction as potentially important predictors of surgical success (**Table 2**). When adjusting for sex and age at distraction, patients with CFM-Goldenhar syndrome had the lowest probability of surgical success (OR, 0.07 [95% CI, 0.009-0.52]) compared with patients with isolated Pierre Robin sequence (**Table 3**). To better illustrate the impact of these different variables on the probability of surgical success, **Figure 1** shows the modeled probabilities of success as a function of age and syndrome diagnosis, stratified by sex. For both male and female patients, at any given age, the probability of surgical success is significantly worse for patients with CFM-Goldenhar syndrome compared with any other syndromic diagnosis. In contrast, patients with isolated Pierre Robin sequence have the greatest probability of success. For example, a 10-year-old girl with Goldenhar syndrome who went through a tracheotomy before MDO has a 60% probability of surgical success. For all patients, the probability of success seems to increase with greater age at the time of distraction.

In the MDO-first subgroup, the only variable associated with surgical success in univariable regression analysis was number of other airway surgical procedures (**Table 4**). Thus, multivariable regression analysis was not performed in this subgroup. In the univariable regression model, patients who had undergone fewer than 2 airway procedures had 7 times greater odds of success compared with those requiring more than 2 procedures. Among the 10 patients who required a tracheotomy after an initial MDO, airway pathology contributing to failure of initial MDO in these patients included persistent glossoptosis or lingual tonsil hypertrophy (8 patients), tracheal stenosis (2), and choanal atresia (1). Five of 10 were subsequently successfully decannulated, but all required additional procedures to achieve decannulation, including lingual tonsillectomy and/or base of tongue reduction (3 patients), endoscopic suprastomal granulation tissue removal (2), LeFort I bimaxillary advancement (3), or choanal atresia repair (1).

When we examined potential predictors of a complication, univariable regression analysis demonstrated an association between occurrence of a complication and patients who underwent a tracheotomy prior to MDO (OR, 2.9 [95% CI, 1.2-7.1]), increasing length of follow-up (OR, 1.2 [95% CI, 1.0-1.3]), and patients who required 2 or more airway procedures (OR,

3.4 [95% CI, 1.4-8.4]) compared with patients with 0 or 1 other procedure. In a multivariable regression model adjusting for all these variables, only length of follow-up (OR, 1.2 [95% CI, 1.0-1.3]) and number of other airway procedures (OR, 3.2 [95% CI, 1.2-8.6]) remained significantly associated with occurrence of a complication. **Figure 2** demonstrates the modeled probabilities of a complication with MDO in the 2 initial treatment subgroups as a function of these 2 independent predictors. One can see that in both the MDO-first subgroup and the tracheotomy-first subgroup, the probability of a complication increases with length of follow-up time. In addition, for any given follow-up duration, there is a greater probability of a complication when 2 or more other airway procedures are required.

Table 3. Adjusted Associations Between Potential Predictors and Surgical Success in the Tracheotomy-First Subgroup

Variable	OR (95% CI)	*P* Value
Male	0.31 (0.09-1.10)	.07
Diagnosis[a]		
Treacher-Collins syndrome	0.45 (0.06-3.60)	.45
CFM-Goldenhar syndrome	0.05 (0.005-0.43)	.007
Other	0.27 (0.06-1.20)	.09
Age at distraction, y	1.15 (0.93-1.40)	.20

Abbreviation: CFM, craniofacial microsomia.

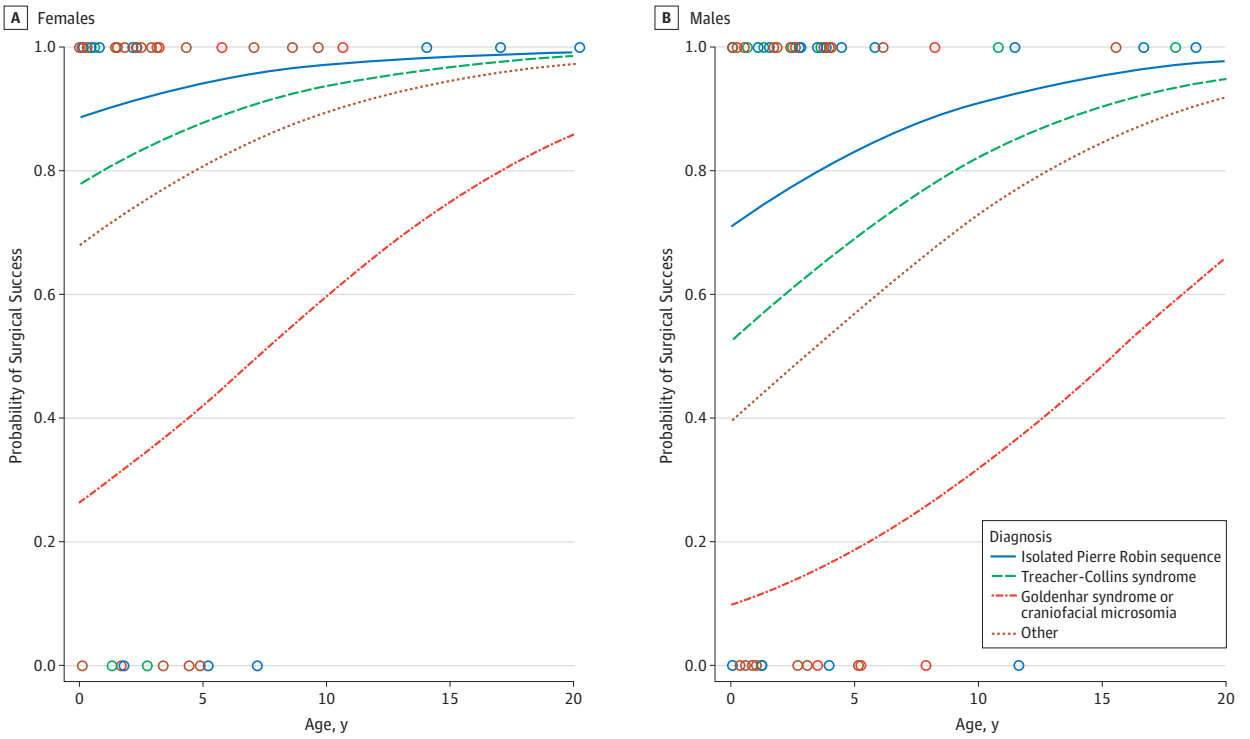
[a] Reference diagnosis was isolated Pierre Robin sequence.

Discussion

The application of distraction osteogenesis to the mandible for the treatment of symptomatic micrognathia was first described by McCarthy et al[16] in 1992, and since that time there have been increasing reports of the outcomes of this intervention in the pediatric population. Owing to the heterogeneous nature of the patient population that experiences symptomatic micrognathia severe enough to warrant surgical intervention, definitions of success have varied depending on the specific study. Given this context, success rates for MDO in improving or relieving airway obstruction due to micrognathia have been reported to range from 63% to 100% depending on the definition of success used.[8-11,17-20] In a recent meta-analysis, Ow and Cheung[19] found a 91% rate of prevention of tracheotomy among neonates undergoing MDO as an initial procedure and a 78% rate of decannulation among patients with existing tracheostomies who underwent MDO.

This study reports the outcomes of MDO in one of the largest cohorts of patients treated for symptomatic micrognathia. The relatively large cohort provided greater statistical power than most previous reports and facilitated the investigation of potential predictors of surgical success and complications. Overall, we found a high rate of surgical success among patients undergoing MDO, especially among those undergoing MDO as an initial procedure to treat symptomatic micrognathia. The

Figure 1. Predicted Probabilities for Surgical Success (Tracheotomy-First Subgroup)



Predicted probabilities of surgical success among patients who had a tracheotomy prior to mandibular distraction osteogenesis. A, Females; B, males. The colored dotted lines indicate differences in the probability of success for each diagnosis. Open circles represent the observed values.

84% rate of avoidance of tracheotomy is slightly lower than the success rates in recent reports focusing on the outcomes of neonatal MDO.[8,9,17,18] However, this may in part reflect the fact that there was a greater proportion of syndromic diagnoses (56% overall, 43% among patients treated with MDO first) than in other recent studies in which the proportion of syndromic diagnoses ranged from 24% to 35%.[8-11,20] The most frequently encountered syndromic diagnosis among all patients with micrognathia is Stickler syndrome.[2,21,22] However, in our study the 2 most frequent syndromic diagnoses were Treacher-

Table 4. Unadjusted and Adjusted Associations Between Potential Predictors and Any Complication

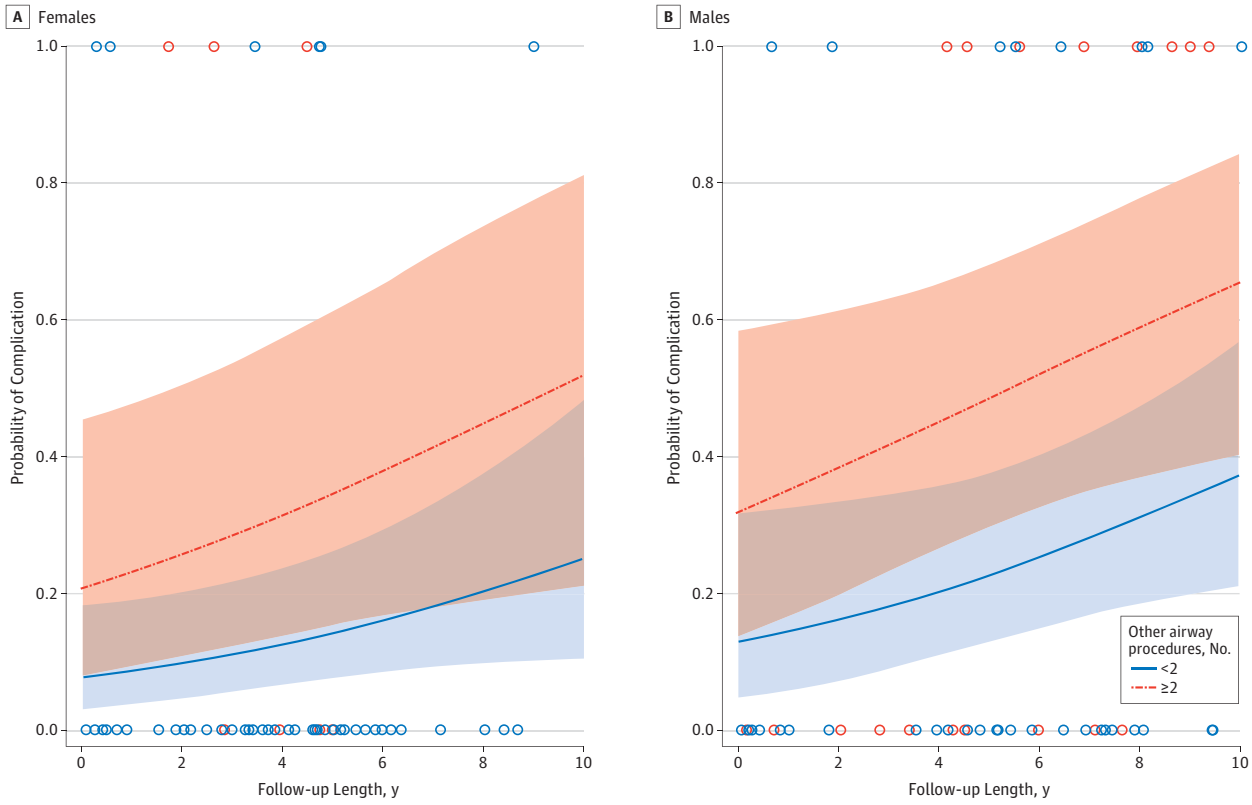
	Unadjusted		Adjusted[a]	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Tracheotomy vs MDO first	2.90 (1.20-7.10)	.02	1.80 (0.67-4.70)	.24
Male	1.50 (0.64-3.50)	.36		
Diagnosis[b]				
CFM-Goldenhar syndrome	1.10 (0.20-6.00)	.90		
Treacher-Collins syndrome	3.60 (0.90-13.80)	.07		
Other	2.20 (0.80-5.70)	.11		
Age at distraction, y	1.10 (0.98-1.10)	.14		
Follow-up, y	1.20 (1.00-1.30)	.02	1.20 (1.00-1.30)	.05
Distraction amount, mm	1.00 (0.98-1.10)	.31		
Distractions, No.				
2 vs 1	0.56 (0.13-2.40)	.44		
3 vs 1	0.56 (0.01-23.00)	.76		
Open air surgical procedures, No.	1.00 (0.44-2.30)	.99		
Other airway procedures, ≥2 vs <2	3.40 (1.40-8.40)	.009	3.20 (1.20-8.60)	.02

Abbreviations: CFM, craniofacial microsomia; MDO, mandibular distraction osteogenesis; OR, odds ratio.

[a] The final model included only significant covariates from unadjusted analysis with $P < .05$.

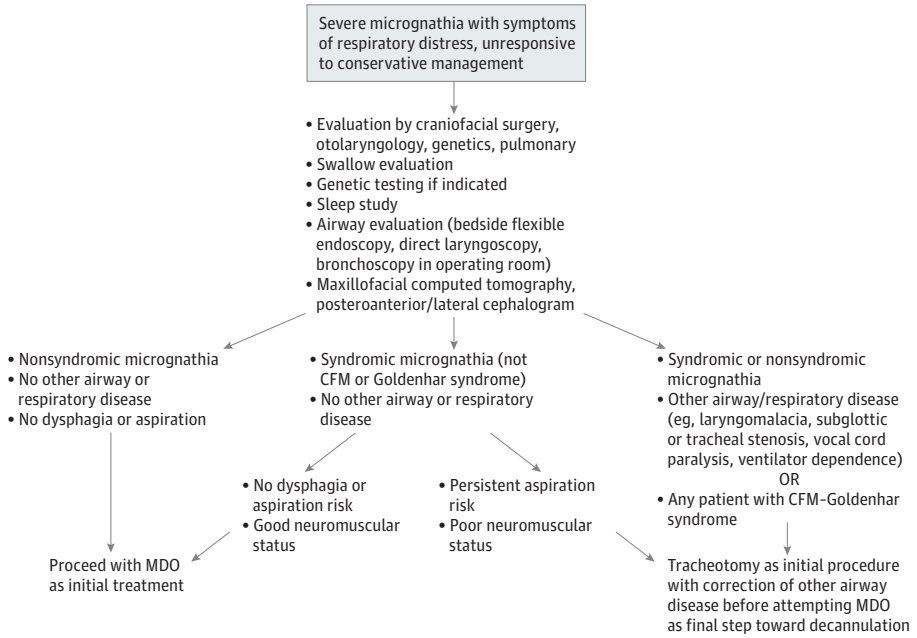
[b] Reference diagnosis was isolated Pierre Robin sequence.

Figure 2. Predicted Probabilities for Complications Stratified by Initial Treatment Subgroup



The predicted probabilities of complications stratified by the initial surgical intervention. A, Mandibular distraction osteogenesis (MDO) first; B, tracheotomy first. The colored lines indicate the differences in the probability of success for patients who had less than 2 vs 2 or more other airway procedures. The shaded areas represent the 95% CIs for these probabilities. Open circles represent the observed values.

Figure 3. Proposed Treatment Algorithm for Pediatric Patients With Symptomatic Micrognathia



The flowchart demonstrates our current algorithm for workup and decision making regarding the choice of mandibular distraction osteogenesis (MDO) vs tracheotomy for symptomatic micrognathia. CFM indicates craniofacial microsomia.

Collins and CFM-Goldenhar syndromes. It is unclear why we observed such a high prevalence of these syndromes relative to Stickler syndrome, but this may represent a relatively skewed population of patients who are referred from outside the local area for tertiary and quaternary care. These syndromes often demonstrate more severe micrognathia than in isolated Pierre Robin sequence or even other syndromic forms of micrognathia[23] and are therefore more likely to have poorer outcomes.[18] In our cohort, 4 of the 11 patients with CFM-Goldenhar syndrome and 2 of the 12 patients with Treacher-Collins syndrome had Pruzansky grade 3 classification with an absent mandibular condyle, and it is possible that this may have also limited the effectiveness of MDO in these patients. Given the greater percentage of these syndromes in our cohort, this may in part explain why the overall rate of successful MDO was slightly lower than in other published reports.

When we examined the potential predictors of surgical success, the different definitions of success for the 2 subgroups (decannulation vs avoidance of tracheotomy) necessitated separate regression analyses based on initial intervention (tracheotomy first vs MDO first). Thus, we cannot draw conclusions regarding predictors of success across both subgroups. However, we can reasonably conclude that among patients who required a tracheotomy as an initial procedure, patients with CFM-Goldenhar syndrome seem to have a far worse chance of success with subsequent MDO than patients with isolated Pierre Robin sequence. This association does not seem to hold among patients who underwent MDO first in the absence of a tracheotomy.

Compared with patients treated with MDO first, those treated with tracheotomy first had significantly more syndromic diagnoses and were older at the time of MDO. Many of these patients had additional comorbidities, such as multilevel airway obstruction, neuromuscular compromise, and other medical comorbidities that necessitated a tracheotomy as a definitive treatment for relief of their airway obstruction. Achieving decannulation in this subgroup necessitated significantly more adjunct airway procedures, such as laryngotracheoplasty or endoscopic airway procedures, compared with the subgroup that underwent MDO first. The finding in univariable regression analysis that patients who underwent tracheotomy first had greater odds of a surgical complication makes intuitive sense in this context. The fact that this association was no longer significant in a multivariable model that also adjusted for the number of adjunct airway procedures suggests that the association between initial tracheotomy and complication is perhaps mediated by the need for additional procedures in order to achieve decannulation. Taken together, these findings are consistent with our hypothesis that patients selected for tracheotomy rather than MDO as an initial procedure were more medically complex and required more airway interventions in order to achieve a stable airway. This form of selection bias may have contributed to their worse rates of success and complication and also creates an inherent confounding by indication when making comparisons between these 2 subgroups (MDO first vs tracheotomy first).

Limitations to our study include the retrospective nature of the data collection, lost or missing data, and the inherent confounding by indication that occurs in comparisons between the MDO-first subgroup vs the tracheotomy-first subgroup. In addition, prior to 2002, when neonatal MDO became part of routine practice at our institution, there may have been an even stronger selection bias toward tracheotomy as an initial procedure. To address this possibility, a secondary analysis was performed with the data set restricted to only those patients who were treated with MDO after 2002, and the

results were essentially unchanged, suggesting minimal impact of this possible bias. Regardless, the issue of confounding by indication is an important one, which is why the outcomes of surgical success were addressed in separate analyses in this study. Within the context of this broad retrospective study, we did not attempt to directly compare the 2 primary interventions of tracheotomy and MDO except with respect to overall rates of complications. However, it is clear from our analysis that patients who were syndromic or had additional airway disease abnormalities were more likely to have an initial tracheotomy to address multilevel disease. Mandibular distraction osteogenesis should be considered only as an initial procedure in a setting in which there is no other indication for tracheotomy, such as multilevel airway obstruction, ventilator dependence, or persistent dysphagia and aspiration. Because patients with CFM-Goldenhar syndrome were found to have independently lower odds of success with MDO than other syndromic conditions, we would not recommend primary MDO in these patients who have clinically significant respiratory distress due to micrognathia. A proposed treatment algorithm is presented in **Figure 3**.

Conclusions

Our study evaluated a large cohort of children that had undergone MDO. In our study we demonstrated a high rate of surgical success for MDO with a low rate of complications, particularly among patients treated with distraction as an initial procedure without an existing tracheotomy. However, it is clear that patients treated with tracheotomy initially are more likely to be syndromic and complex, requiring greater numbers of distractions and airway procedures. In addition, patients with CFM-Goldenhar syndrome have a decreased probability of surgical success compared with patients with other types of syndromes or nonsyndromic Pierre Robin sequence.

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Management of sleep apnea in the cleft population

Harlan R. Muntz

Purpose of review
Obstructive sleep apnea is prevalent in children with facial clefts. As there are increasing concerns that sleep disordered breathing and obstructive sleep apnea may lead to cognitive difficulties, it is imperative that the otolaryngologist and cleft surgeon be aware of the concerns for sleep disorders and implement appropriate interventions for the management.

Recent findings
Micrognathia associated with Robin Sequence has long been understood to have significant potential for sleep apnea. Positioning, nasopharyngeal airway, tongue–lip adhesion and mandibular distraction have been used to improve the breathing in this set of children. Screened by symptoms, a large proportion of children with clefts will have a positive sleep study. Syndromic children seem to be more prone to this, even though nonsyndromic children are also at risk. Children who have had secondary management of velopharyngeal insufficiency with pharyngeal flap and sphincter pharyngoplasty seem to be at greater risk of sleep disorder. Specific directed therapies should provide the optimum results for the correction including tonsillectomy with partial adenoidectomy, revision pharyngoplasty, maxillary advancement and continuous positive airway pressure for sleep.

Summary
Awareness of the risk of sleep disorders and the possible treatments in children with cleft deformities is very important for the otolaryngologist.

Keywords
cleft lip, cleft palate, mandibular distraction, obstructive sleep apnea, Robin Sequence, sleep disordered breathing, tongue–lip adhesion, tonsillectomy and adenoidectomy

INTRODUCTION

The awareness of sleep issues in the pediatric population has increased over the years. The snoring child is no longer just cute but a sign of obstruction that can lead to cognitive and behavioral difficulties. Many studies have been done to look at these issues. One large study by Bonuck *et al.* [1] looked at 12 447 children and found that symptoms of snoring and observed apnea were common. Habitual snoring was as high as 25% and apnea 15%, whereas 'always' snoring was seen in over 7% and apnea in 2%. In this study, the peak for symptomatic sleep disordered breathing was at about 3.5 years.

Perhaps spurred by the increasing awareness of sleep disordered breathing in the population, a number of studies have looked at this problem in the cleft population. In many cases, it seems the awareness has focused the clinician to ask the right questions. Identification of historical symptoms that define sleep apnea has not been successful in the general population, but questioning of the cleft population seems to have a higher rate of return. In Muntz *et al.* [2], over 90% of sleep studies performed on children with clefts were positive. The decision to order the sleep study was based on the presence of multiple symptoms related to obstructive sleep apnea. Unfortunately, using varied weighting schemes in both linear and cubic formulas, they could not suggest severity using multiple factors [2]. The MacLean study was similar in that 85% had positive sleep studies after referral for sleep symptoms, 28% of which suggested severe sleep apnea [3] and Robison and Otteson [4] suggested the same with 83.1% having obstructive sleep apnea.

Syndromes are common in children with clefts and more so in those with isolated cleft palate. The risk of significant obstructive sleep apnea was

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KEY POINTS

- Obstructive sleep apnea is common in all children with cleft, especially those with a syndrome, and the clinician should make certain that the right questions about sleep are asked.
- Surgical management of obstructive sleep apnea in children is not always successful, and postoperative sleep assessment should be strongly considered.
- The use of nasopharyngeal airway should be considered in those children with Robin Sequence.
- Children who have had surgical management of velopharyngeal insufficiency are at greater risk for obstructive sleep apnea.
- Clear definition of the location of the obstruction should allow improved outcomes in the surgical management of sleep apnea in the cleft population.

greater in syndromic children ($P < 0.001$) than nonsyndromic cleft, though in a multivariate analysis MacLean *et al.* [3] felt that intervention for speech with a pharyngoplasty was of a greater concern. Muntz *et al.* [2] suggested that a greater number of syndromic children had symptoms of sleep apnea ($P < 0.001$) and were more likely to have a sleep study ($P < 0.05$).

Robin Sequence is classically micrognathia causing posterior tongue placement preventing the closure of the palate. This is usually seen with a wide U-shaped cleft palate. The posterior tongue placement causes airway obstruction as a neonate. Though this can vary in severity, years ago many children had tracheotomy for this. Because of feeding issues, gastrostomy tube was common as well.

Even with a normal mandible, the child with a cleft and cleft repair is at greater risk for airway obstruction. Nasal septal deviation is a standard finding in children with any unilateral cleft lip. Scott *et al.* [5] described some of the issues that could cause obstruction in the normal repairs of the cleft palate. The use of the nasal septal mucoperichondrial flaps for closure of the nasal layer of the palate may reduce the airway at the floor of the nose. Furlow palatoplasty (the double opposing Z-plasty) has been shown to both lengthen and thicken the palate. Though this is great for speech, there should be some tendency to decrease the airway. Tonsil and adenoid hypertrophy are common in all children and the cleft population is not exempt. Midface hypoplasia is sometimes seen in children with cleft palate. This causes obstruction at the posterior nasopharynx and may be a cause of airway obstruction and sleep disordered breathing. As many as 13% of the cleft palate population are at risk of velopharyngeal insufficiency (VPI) and need surgical correction. Acute airway obstruction in pharyngeal flap and sphincter pharyngoplasty has been well documented. The chronic obstruction can cause both nasal airway compromise and sleep disordered breathing or obstructive sleep apnea. The balance between good speech and breathing is most critical in this group.

Continuous positive airway pressure (CPAP) is a standard approach for the treatment of obstructive sleep apnea in the adult and pediatric population. CPAP may be tolerated by children, but just as in the adult many children may refuse to wear the device or because of the anatomy have difficulty with fitting the mask. Though CPAP is a treatment, it seems that if the anatomical obstruction can be remedied surgically the patient would be better served. The surgical management of sleep disordered breathing and obstructive sleep apnea in the cleft population requires an intimate understanding of the anatomical reasons for the obstruction. Careful planning must be done to reduce the risk and yet open the airway. As treatments are often not successful, diligence is required to ask the right questions and to study the sleep after intervention.

MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA

The following is a review of the multiple management strategies available for the treatment of primarily obstructive sleep apnea in the cleft population.

Robin Sequence

Robin Sequence is the classic cleft palate related obstruction [6▪▪]. Many children will do very well with positioning alone (prone or side). As they grow and the neuromuscular tone improves, tongue position can come forward making further intervention unnecessary. A significant segment of the Robin population though will not be successfully treated in this way. The child managed this way may do well until the baby is more mobile and then the airway may be obstructed if on the back.

The Seattle Children's Hospital Team has promoted the use of nasopharyngeal airways in the treatment of children with Robin Sequence. Over one-third of the children in the initial study had Robin Sequence and an additional 11% had other mandibular abnormalities. The median duration of the nasopharyngeal airway was 8 weeks before the airway was secure [7▪▪]. This offers a nonsurgical approach to the airway and in selected children may be an alternative. It may also be used with high flow in the infant.

Tongue–lip adhesion has been a mainstay of treatment for airway obstruction in children with Robin Sequence. In this procedure, the undersurface of the tongue is secured to the mucosa and muscle of the lower lip, often with a retention sure to remove tension on the wound while healing. In general, it seems to be more effective in the child without a syndrome. Sedaghat *et al.* [8] reviewed a small number of children with tongue–lip adhesion and found that most were benefited, but that only 38% had complete resolution based on polysomnography. Abramowicz *et al.* [9] felt that one could more accurately predict the success of tongue–lip adhesion with using a GILLS score of less than 2. This takes into consideration gastroesophageal reflux, preoperative intubation, low birth weight, syndromic diagnosis and late surgical intervention. Certainly, not all are benefited by this particular intervention as some would promote but may be considered in the decision for treatment.

Much attention has been focused on bilateral mandibular osteotomy with distraction osteogenesis for children with micrognathia with or without Robin Sequence [6▪▪]. It makes sense that as the jaw is distracted anteriorly, the tongue will also be pulled forward, opening the posterior airway. It is usually very successful for improving the airway as well as feeding. This has been done both with internal and external distraction devices. Internal devices usually offer only linear distraction that may leave the child with an open bite. The multivector external distractors have the advantage of allowing differential distraction based on the observed relation to the maxillary alveolus. This may include the closure of the open bite with a rotational distraction as well decreasing the resistance in linear distraction with varus–valgus adjustments. Scott *et al.* [6▪▪] looked at 18 children under 3 months with early distraction and felt the procedure to be both well tolerated and effective as seen from a 3-year follow-up. Though this procedure seems effective for airway and feeding, there are significant risks including facial nerve injury (9%), tooth loss (16%) and a 5.2% need for additional distraction as the child aged.

Tonsillectomy and partial adenoidectomy

For most otolaryngologists, the understanding of the benefit of tonsillectomy and adenoidectomy in children with sleep apnea is apparent. The cleft population is a concern because of the risk of exacerbating VPI if the adenoids are removed. Some even refuse the use of adenoidectomy in children with cleft palate. Shapiro [10] initially discussed partial (superior) adenoidectomy as a way to reduce this risk. Since then, there have been a number of reports on techniques to improve the partial adenoidectomy. It has been promoted for all children with palatal abnormalities undergoing adenoidectomy. Removing the superior and leaving the inferior rim of adenoid tissue should improve airway but allow the palate to contact the residual adenoid tissue for speech. Some also promote this for children with Down syndrome.

In a study by Muntz *et al.* [2], tonsillectomy and partial adenoidectomy were the initial intervention for most of the cleft children with obstructive sleep apnea. Though there was a significant overall improvement in the sleep, many of the children continued to have sleep apnea. It is very important to follow these children to make certain there is not a significant obstructive sleep issue even after tonsillectomy and partial adenoidectomy.

Midface hypoplasia

Midface hypoplasia is often associated with craniofacial syndromes and cleft palate. Though often blamed on early hard palate repair, this is frequently seen regardless of the timing of palatal repair. The bony hypoplasia sets back the hard palate pushing the soft tissue of the soft palate posterior as well. This results in a decreased airway and as such can increase the likelihood of obstructive sleep apnea. Occasionally, we also see midface hypoplasia as a result of chronic CPAP use. Smatt and Ferri [11] and Ronchi *et al.* [12] both suggest there is a significant improvement in obstructive sleep apnea with mandibular and maxillary advancement. This has also been documented in children with craniofacial syndromes such as achondroplasia [13]. As many of the children will need the distraction or advancement for occlusion and aesthetics, the more important issue of airway may be corrected at that same time. Midface advancement may result in VPI if the upper jaw is displaced forward interfering with the closure of the child's velopharyngeal port.

Obstruction postsurgical correction of velopharyngeal insufficiency

The treatment of VPI includes surgical management either with further palatal surgery or the creation of a velopharyngeal obstruction to allow appropriate oral pressure for speech. Classically, pharyngeal flap and sphincter pharyngoplasty have been used to correct the VPI. Additionally, multiple methods of velopharyngeal augmentation have been used. If a surgery has been done to improve the speech and sleep apnea results, one must balance the issues of airway and speech production [14,15]. Many of

these children may be managed with CPAP in the acute setting and with time the sleep improves. Some may require chronic assistance with CPAP. Alteration of the obstructing flap may be an effective alternative [16].

Flexible endoscopic evaluation of the velopharynx is done during speech. This will allow the assessment of the palatal and lateral wall function to see if there is an obvious area that the obstructive flap(s) can be altered. As an example, if there was good velar motion and the sphincter pharyngoplasty had lateral velopharyngeal obstruction that was unneeded for speech, the flaps can be altered to open the lateral aspects of the velopharyngeal port increasing the airway. These alterations need to be done precisely with attention to reduce scaring by closing the mucosa. There have been many reports of the takedown of a pharyngeal flap for the improvement of the airway with no deterioration of the speech [17].

CONCLUSION

It is imperative that we screen children with clefts for sleep disordered breathing. Though often the history may be significant enough for intervention, most of the children in this category will have abnormal sleep studies. Understanding the severity may assist in defining the need for intervention. Intervention for sleep disordered breathing and obstructive sleep apnea may vary depending on the anatomical findings. Though tonsillectomy and partial adenoidectomy may be the initial approach, there is a high likelihood that this alone will not solve the problem. Midface advancement, mandibular distraction, flap alteration and CPAP must all be considered in the care of these patients. Coordination of care between cleft surgeons, otolaryngologists, sleep medicine and pediatrics is necessary to optimize the treatment and decrease the risk for cognitive disruption.

Acknowledgements

None.

Conflicts of interest

The author has no conflict of interest in this area.

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Current approaches to management of nonsyndromic craniosynostosis

Haruko Okada and Arun K. Gosain

Purpose of review
Surgical alternatives to traditional cranial vault remodeling for the treatment of craniosynostosis are being discussed in recent plastic and neurosurgical literature. This review highlights recent developments and discusses the risks as well as benefits of each.

Recent findings
Surgical treatment of craniosynostosis has evolved from simple suturectomy, to extensive cranial vault remodeling, and now back to the minimally invasive. Options today include endoscopic suturectomies, spring-mediated cranioplasties, and distraction osteogenesis as well as cranial vault remodeling. There are disagreements among centers on the most optimal timing and best operative procedure.

Summary
Clinicians should be aware that different surgical treatments are rapidly being developed for nonsyndromic craniosynostosis.

Keywords
cranial suture, cranial vault remodeling, cranioplasty, craniosynostosis, spring-mediated cranioplasty, strip craniectomy, suture

INTRODUCTION

Craniosynostosis is the premature fusion of a cranial suture, which can occur in isolation or with an associated syndrome. Its prevalence is approximately one in 2500 births [1]. The most commonly affected sutures are sagittal (40–55%) followed by coronal (20–25%), metopic (5–15%), and lambdoid (0–5%) [2]. More than one suture is affected in 5–15% of cases. In sagittal craniosynostosis, there is a four to one male to female predominance, whereas women outnumber men three to one in unilateral coronal synostosis [3]. There is no sex predominance in metopic craniosynostosis.

Although the pathology is in the cranial vault, clinically the disorder affects the cranial base and facial bones as well. Patients with craniosynostosis can have elevated intracranial pressure, learning disabilities, midface hypoplasia, and speech impairments. The operative treatment is demanding and requires teamwork between neurosurgery, plastic surgery and anesthesiology. Therefore, such complex patients are best cared for in a craniofacial center with multidisciplinary coordination.

PATHOGENESIS

The human skull develops from a neural crest and mesodermal origin, at 23–26 days of gestation [4]. The cranial base, namely the occipital, sphenoid, ethmoid, and petrous temporal bones, is formed by endochondral ossification. The cranial vault is formed by membranous ossification. Cranial growth is a passive response to the expanding brain and cerebrospinal fluid compartments. Cranial sutures allow head compression and bony overlap during birth, causing a deformation that may last weeks afterward, but quickly normalizes with rapid brain growth and subsequent cranial expansion. These patent cranial sutures are active sites of bone deposition and growth, accommodating rapid brain volume expansion in the first 3 years of life. The metopic suture is the first to close physiologically at 9 months and the sagittal suture closes last at 16 years [3].

Premature closure of sutures was first described by Sommering [5], and the concept that a single

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KEY POINTS

- The treatment of nonsyndromic craniosynostosis begins with the proper diagnosis. Computed tomography scans remain the gold standard imaging modality.
- Cranial vault remodeling achieves the desired cranial contour without relying on underlying brain expansion, thus allowing treatment for older children.
- Minimally invasive alternatives such as strip craniectomy with helmet therapy are limited to patients under 6 months of age, as they rely on rapid brain expansion to achieve the desired cranial shape.

premature suture closure causes predictable restriction and compensatory growth was developed by Virchow [6]. According to Virchow's law, premature suture fusion results in decreased growth perpendicular to the suture and increased compensatory growth parallel to it. The predictable clinical phenotypes of single suture synostoses are as follows. Metopic craniosynostosis results in trigonocephaly, a keel-shaped deformity with midline forehead ridging, and narrowed bitemporal distance (Fig. 1). Sagittal craniosynostosis causes scaphocephaly, a long 'boat-shaped' head with narrowed interparietal distance and compensatory lengthening in the anterior posterior dimension (Fig. 2). Unilateral coronal synostosis results in anterior plagiocephaly characterized by recession in the ipsilateral forehead; there is accompanying displacement of the ipsilateral superior orbital rim towards the synostotic suture, known as the 'harlequin deformity' (Fig. 3). There is compensatory contralateral forehead bossing and a subsequent inferior displacement of the contralateral superior orbital rim. Predictable facial deformities also accompany unilateral coronal synostosis: the nasion is deviated ipsilaterally, the ipsilateral zygoma is displaced anteriorly and the chin point is displaced to the contralateral side. Bilateral coronal synostosis is more often associated with craniosynostosis syndromes (Fig. 4). The resulting deformity is brachycephaly, or short head. There is shortening in the anterior–posterior dimension, bilateral recession of the superior orbital rims and excessive height of the anterior forehead.

Lambdoid synostosis is the rarest form of synostosis, and can be mistaken for deformational plagiocephaly. In true synostosis, there is ipsilateral occipital flattening, compensatory bulging of the contralateral occiput, and a deviation of the petrous temporal bone toward the offending suture, causing the external ear to be malpositioned posteriorly (Fig. 5). The head assumes a trapezoidal shape viewed from above. In deformational plagiocephaly, there is ipsilateral occipital flattening, but ipsilateral frontal bossing and contralateral frontal flattening, creating a parallelogram shaped head without deformation of the cranial base.

In the last 15 years, we have expanded our knowledge of the genetics of craniosynostosis.

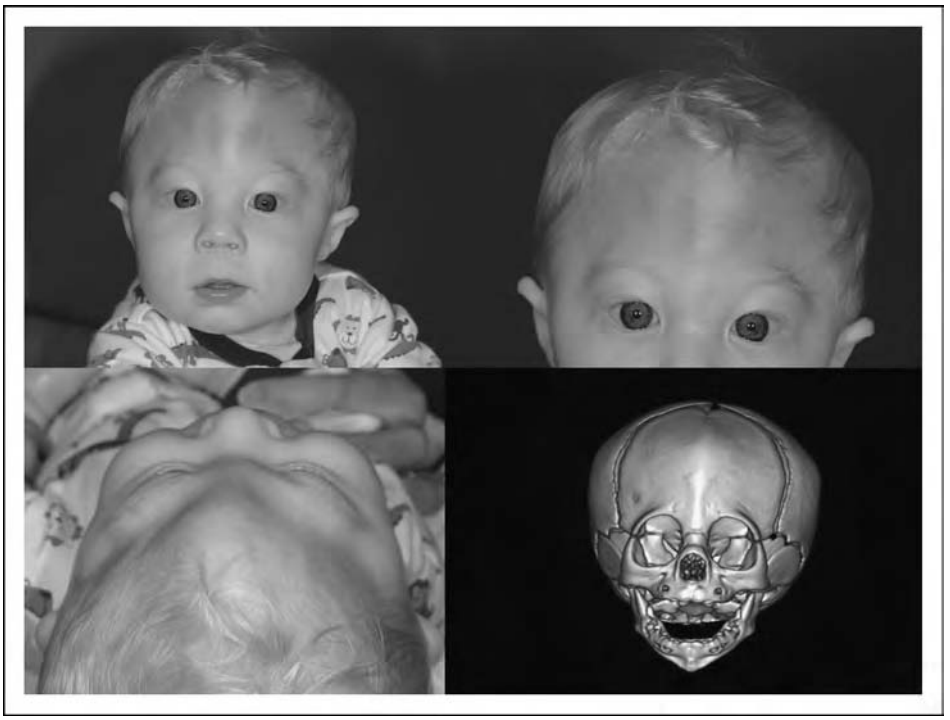

FIGURE 1. 6-month-old male with metopic synostosis.

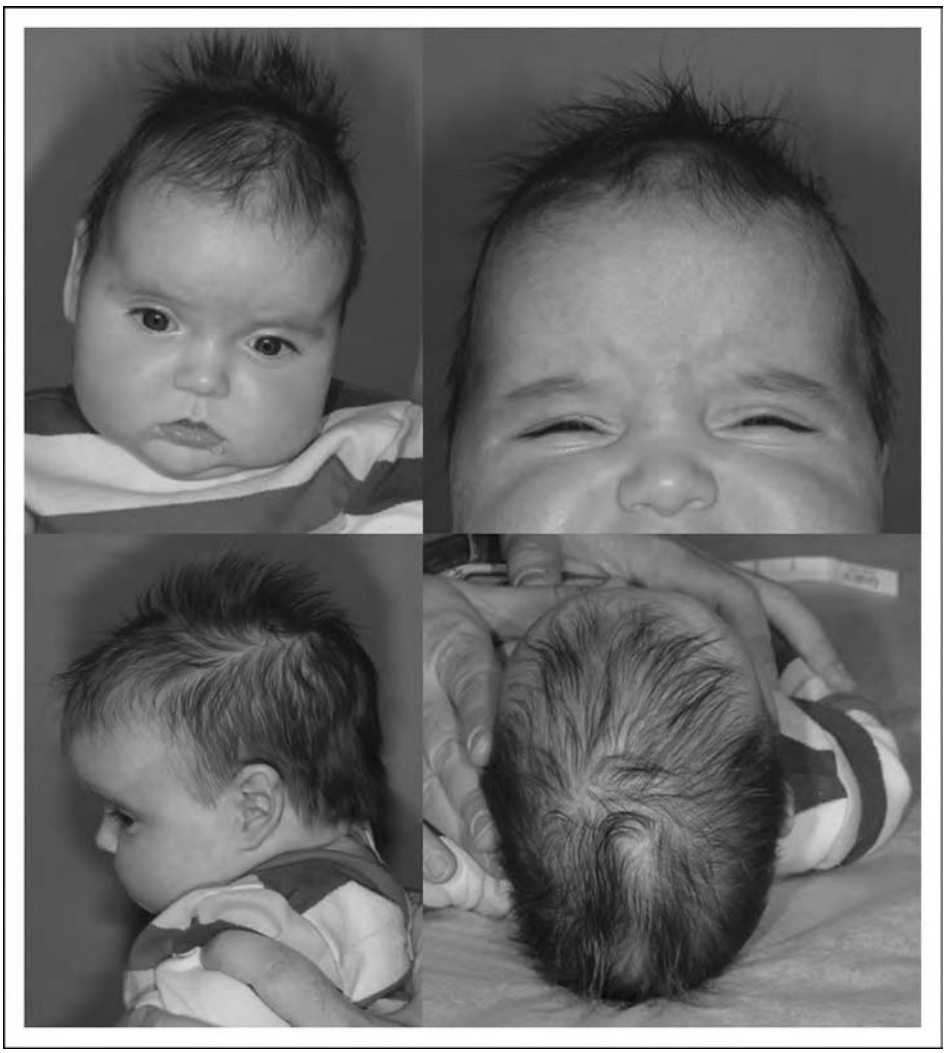

FIGURE 2. 3-month-old female with sagittal synostosis.

Mutations in fibroblast growth factor receptors 1, 2, and 3, TWIST and MSX2 have been implicated in certain syndromic craniosynostoses [7]. The exact pathways of how these mutations cause premature sutural fusion are still unknown.

INTRACRANIAL PRESSURE, HYDROCEPHALUS AND COGNITIVE DEFICITS

Intracranial hypertension results from a mismatch between a constricted cranial vault and the growth of the underlying brain. This condition is an indication for early operative treatment for craniosynostosis, as delayed treatment has irreversible consequences for vision and cognitive development.

Marchac and Renier [8] found a 42% incidence of intracranial hypertension in multisuture synostosis and 13% in single suture synostosis. Although changes associated with elevated intracranial pressure (ICP) are more common in syndromic craniosynostosis, one must be cognizant of these findings in any patient with craniosynostosis. The standard for measuring ICP is direct intradural or intraventricular monitoring for a 24-h period to record fluctuations during activity, sleep, and the elevations caused by airway obstruction. Measuring ICP via lumbar puncture is less invasive; however, the results vary by positioning and provide measurement at only a single point in time, making it less reliable. Bulging fontanelles only offer a qualitative assessment of intracranial hypertension. Papilledema has a sensitivity of only 22% in detecting elevated ICP in children under 8 years old [9]. Copper beating seen on either computed tomography (CT) or plain radiographic studies is a late finding of intracranial hypertension, caused by remodeling of the inner table due to adjacent gyri. Hydrocephalus is a rare finding in nonsyndromic craniosynostosis. In a large series of 1727 cases of craniosynostosis, hydrocephalus was found in only 0.3% of nonsyndromic patients and 12.1% in

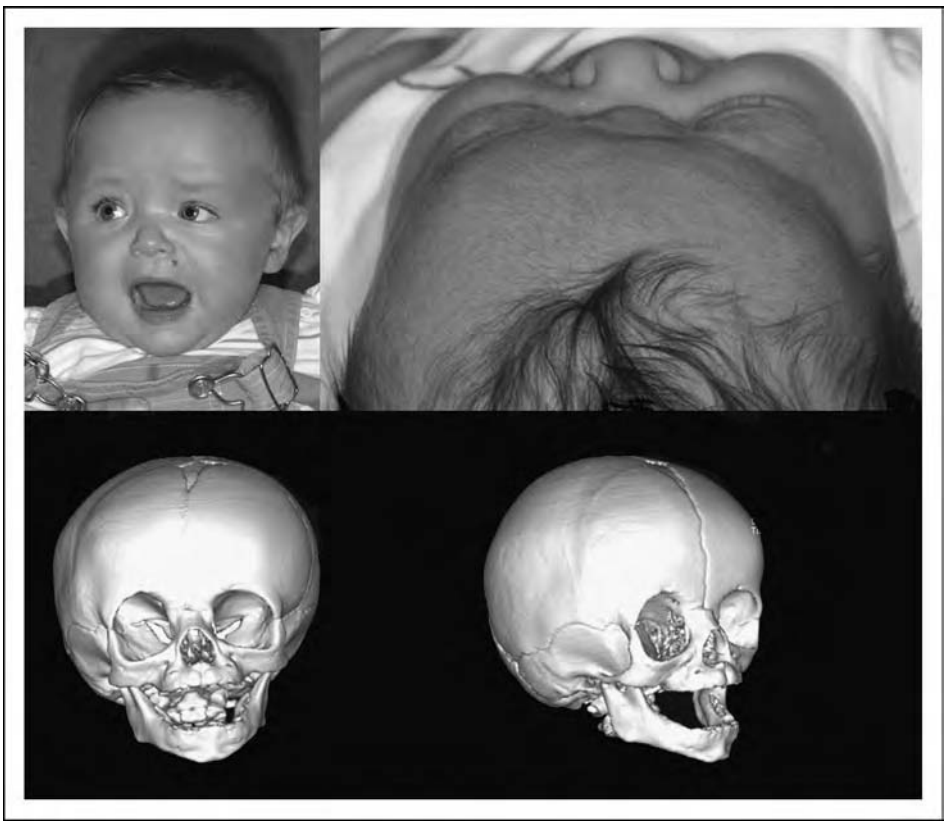

FIGURE 3. 6-month-old female with unicoronal synostosis.

syndromic cases, most commonly in Crouzon syndrome [10].

There is disagreement on whether operative intervention for craniosynostosis prevents mental disability. Renier [11] contended that surgical correction allows maintenance of normal mental development. On the contrary, Kapp-Simon *et al.* compared the developmental quotient in children with nonsyndromic single suture disease who underwent surgery and those whose parents declined and found that developmental quotient did not correlate with operative intervention [12]. Developmental studies are unfortunately limited as children who have developmental delay often normalize later, and such studies fail to assess subtle differences. Although developmental studies on infants who undergo surgery show little difference in scores, a study on 16 children with nonsyndromic sagittal craniosynostosis showed that half of them had a reading and/or spelling disability [13]. Whether surgery for nonsyndromic craniosynostosis has a positive effect on subtle mental ability needs further study.

PREOPERATIVE CONSIDERATIONS AND THE USE OF IMAGING

With the proper understanding of Virchow's law and physical examination, clinicians can diagnose a single suture craniosynostosis based on cranial shape. Whereas CT has been used to confirm the diagnosis of craniosynostosis, its use for preoperative assessment of single suture synostosis is controversial. Proponents of preoperative CT scanning cite cases of misdiagnosis of craniosynostosis as deformational plagiocephaly and the utility of these studies in preoperative planning [14].

The unnecessary use of ionizing radiation and the risk of cancer and developmental delay, and its associated sedation, is always a concern. Proponents of CT scanning argue that, despite repeated scans, the cumulative radiation is far less than the levels shown to increase carcinogenesis or cognitive delay. In a study of 77 patients by Jaffurs and Denny [15], newly diagnosed patients underwent an average of 1.74 scans per year at 1.39 mSv per scan, and 4.11 total scans throughout treatment. Syndromic patients underwent an average of 9.73 total scans throughout treatment. The authors felt that these radiation doses are 100-fold less than published levels shown to cause carcinogenesis, and 40-fold less than levels for cognitive delay. However, harmful doses of radiation in infants have not yet been established.

Other authors feel that clinical diagnosis alone is sufficient for the diagnosis and treatment of patients

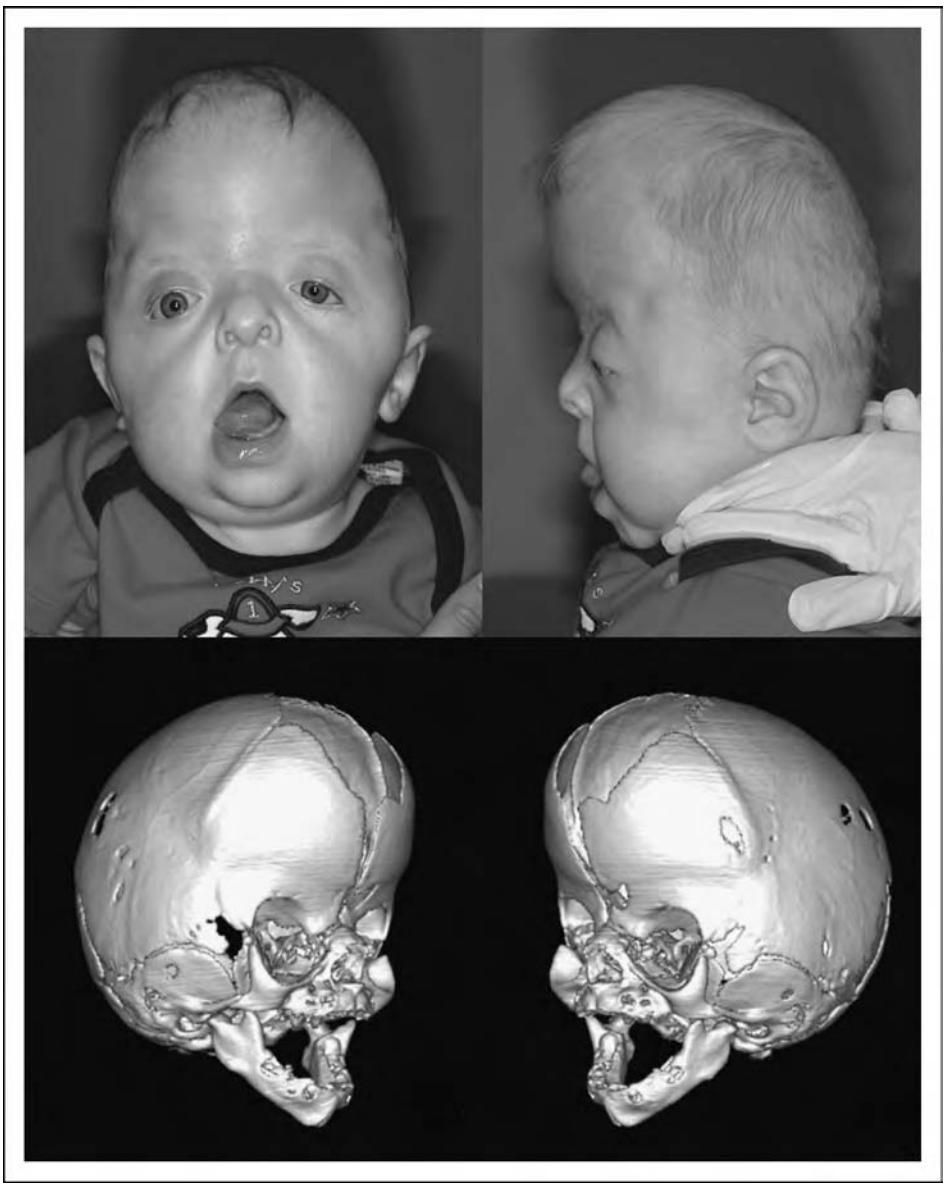

FIGURE 4. 6-month-old male with Apert syndrome and bicoronal synostosis.

with single suture synostosis [16]. Fearon *et al.* [17] showed that 66 out of 67 such patients at four different centers were accurately diagnosed by clinical exam prior to confirmation with a CT. Ultrasonography has also been used as a nonionizing technique for the diagnosis of craniosynostosis in patients up to 12 months of age, after which time narrowing of the sutures and increased bony thickness makes ultrasonography less reliable [16]. A study by Regelsberger *et al.* [18] showed no missed diagnoses of sutural synostosis with ultrasonography in 26 patients.

OPERATIVE TREATMENT

There are disagreements among centers on the optimal timing and best operative procedure. Historically, craniosynostosis surgery began as a simple suturectomy. Interestingly, it seems that surgical treatment has come full circle from strip craniectomies, to extensive cranial vault remodeling, and back to the minimally invasive in the form of endoscopic suturectomies and spring-mediated cranioplasties. Lane and Lannelogue independently described strip craniectomies for craniosynostosis in the 1890s. Their techniques were quickly adopted by others. The technique was fraught with reossification of sutures and an unacceptably high mortality rate of 15 out of 33 patients, as shown in one review by Jacobi [19]. Surgery evolved decades later to the extensive cranial vault remodeling after Tessier's work in the 1960s [20]. His work involved direct removal of the bone and contouring and offered

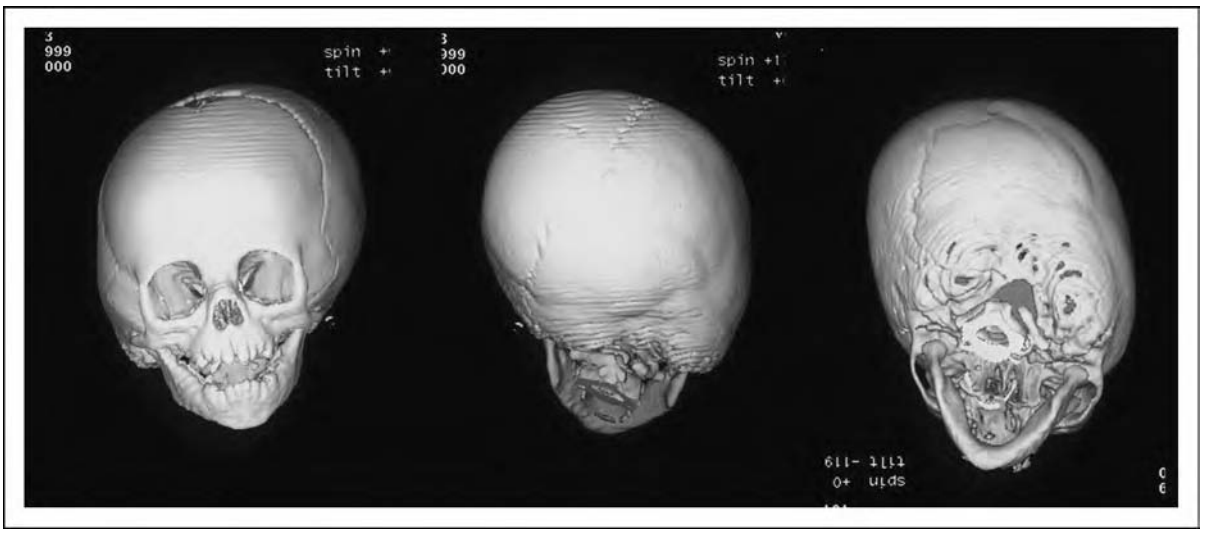

FIGURE 5. Computed tomography scan of a 6-month-old male with right lambdoid synostosis.

predictable desired head shape not possible with simple suturectomy.

Cranial vault remodeling and frontoorbital advancement remains the standard operative treatment for craniosynostosis, today. The benefit of cranial vault remodeling is that the desired contour is achieved without relying on expansion from the growing brain. Thus, it can be employed successfully on older children who have matured past the age of rapid brain expansion. The pi procedure, one method for treating sagittal craniosynostosis, is named after the shape of the bone removed. Sagittal, coronal and lambdoid sutures are removed and parietal bones are outfractured. The frontal bone is then secured more posteriorly, thus restoring a shorter anterior–posterior cranial dimension [21].

There are many described variations of cranial vault remodeling for each fused suture, but the mainstays of treatment are frontoorbital advancement for metopic and coronal synostosis and the judicious use of osteotomies such as barrel-stave techniques to normalize the cranial index and vault height. Surgeons perform remodeling procedures between 4 and 13 months of age and stable results have been demonstrated at 1 year postoperatively [16].

Cranial vault remodeling, while efficacious, is limited by its significant morbidity, including blood loss and prolonged time under anesthesia. In the 1990s Jimenez and Barone [22,23] introduced endoscopic suturectomy for the treatment of sagittal synostosis, an alternative with minimal blood loss and shorter hospital stay. Their approach was early intervention to capitalize on brain growth and expansion of the skull. They combined suturectomy with orthotic helmet therapy, a passive splinting of the growing calvarium introduced by Persing *et al.* in the 1980s [24]. Properly designed helmets limit growth in one dimension while allowing room for compensatory expansion in another.

In a study comparing extended strip craniectomies without orthotic helmets versus traditional cranial vault remodeling for sagittal craniosynostosis, Panchal *et al.* [25] showed no improvement in cranial index for the strip craniectomy group, whether or not they were operated on before 4 months of age. The cranial vault remodeling group demonstrated age-appropriate cranial index values at 1 year postoperatively. These results imply that simple suture release procedures alone are ineffective and must be coupled with helmet therapy [22,25].

Spring-assisted distraction is a more recent development introduced by Lauritzen *et al.* [26]. In his follow-up study of 100 consecutive cases, omega-shaped springs designed to either expand or compress were applied across suture osteotomies for sagittal, metopic, bicoronal, and multiple suture synostoses [27]. Average time until spring removal was 7 months for the sagittal synostosis group. Complications included spring dislodgement (5%) in his earlier cases and one case of overcorrection for metopic synostosis. Cranial index in the first 20 patients with sagittal synostosis was normalized from a mean of 67 preoperatively to 74 at 6 months postoperatively, with stable results 3 years later. Hypotelorism was also corrected during the spring-mediated expansion for metopic synostosis. The authors felt that this method had comparable results to other methods of correction, justifying the inherent need for repeat surgery to remove the springs.

Distraction osteogenesis has an established role in treating secondary midface hypoplasia in patients

with syndromic craniosynostoses, but its role in cranial vault surgery is still limited. Steinbacher *et al.* [28] published a case series of eight syndromic patients who underwent posterior cranial vault distraction osteogenesis using mandibular distractors. They were successful in expanding the posterior cranial vault (mean advancement of 23 mm) and state that the technique allows greater advancement due to the expansion of the constricting scalp. However, there are several limitations of distraction osteogenesis for the cranial vault, including the absence of devices specific to the cranial vault, the need for a second surgery to remove the devices, and the inability to mould gross calvarial deformities.

Rare cases of treating the adult patient with craniosynostosis have been reported. Marchac *et al.* [29] reported on a series of 13 patients (mean age 24 years); 11 underwent cranial vault remodeling and two had camouflage surgery with polymethylmethacrylate implant and correction of nasal deformities. Cranial vault remodeling for patients presenting later in life is primarily a cosmetic procedure involving significant operative risk, as well as the risk of irregular contour deformities from their less malleable bone. The authors indicated the exception in one patient with intractable headaches and copper beating of the skull indicative of increased intracranial pressure. The patient's headaches resolved after surgery. The authors advocate avoiding radical cranial vault remodeling in the adult patient presenting with limited frontal asymmetry, reserving cranial vault remodeling for patients with neurological signs or symptoms or those with orbital dystopia.

There is no consensus on the best operative procedure. Proponents of endoscopic suturectomy claim shorter operative time, less blood loss and transfusion requirements, and shorter hospital stay. Advocates of cranial vault remodeling argue that contemporary surgery is much safer and new benchmarks are necessary to compare the morbidity of each procedure [30▪]. In 1979, Whitaker *et al.* [31] reported 2.2% mortality and 25.7% complication rate in a combined trial of 793 craniofacial operations. In 2010, Seruya *et al.* [30▪] found a complication rate of 3.3% in 212 patients who underwent craniofacial operations (two cerebral contusions, two hematomas, one cerebrospinal fluid leak, one infection, and one wound breakdown). Improved outcomes can be attributed to specialized anesthesiology and the use of controlled intraoperative hypotension and improved critical care. The senior author feels that sagittal synostosis in patients under 6 months of age can be treated with craniectomy and barrel stave osteotomies followed by helmet therapy with predictable outcomes. Other presentations of nonsyndromic craniosynostosis are most predictably managed with cranial vault remodeling between ages 6 and 9 months, and rarely is helmet therapy of benefit following surgery.

Timing of surgery is determined primarily by the choice of surgical procedure, as described above. Suture release procedures such as endoscopic suturectomy, spring-mediated distraction and the pi procedure are usually done earlier than 6 months of age. Cranial vault remodeling is performed between 4 and 13 months of age. We prefer to delay cranial vault remodeling until greater than 6 months of age as before this time the bones are too malleable to retain their shape following surgical correction. In addition, delaying major cranial vault surgery until after 6 months provides a larger infant who can tolerate extended surgery better than the neonate.

CONCLUSION

The management of nonsyndromic craniosynostosis is rapidly evolving with the introduction of alternatives to cranial vault remodeling. Cranial vault remodeling remains the gold standard treatment and allows contouring without relying on the underlying expanding brain, but the technique is limited by significant morbidity. Newer minimally invasive techniques include strip craniectomy with helmet therapy, spring-assisted cranioplasty and distraction osteogenesis for posterior vault remodeling.

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None.

Conflicts of interest

There are no conflicts of interest.

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Cost Analysis of Mandibular Distraction versus Tracheostomy in Neonates with Pierre Robin Sequence

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Abstract

Objective. To evaluate costs associated with surgical treatment for neonates with Pierre Robin sequence (PRS).

Study Design. Retrospective cohort study.

Setting. Cincinnati Children's Hospital Medical Center.

Subjects and Methods. With Institutional Review Board approval, we retrospectively studied neonates with PRS treated from 2001 to 2009 with either tracheostomy (Trach), mandibular distraction (MD), or Trach with subsequent MD (Trach+MD). Actual charges over a 3-year period associated with operative costs, hospital stay, imaging and sleep studies, clinic visits, and related emergency room visits were collected. Home tracheostomy care charges were estimated individually for each patient. Charges were compared using regression and appropriate statistical analyses.

Results. Forty-seven neonates were included in the study (MD, n = 26; Trach, n = 12; Trach+MD, n = 9). Trach group patients had 2.6-fold higher charges than the MD group despite no difference in length of hospital stay. This difference increased to 7.3-fold when including home trach care-related costs. Trach+MD group patients had longer hospital lengths of stay and higher operation room (OR) fees, but no increased total charges compared with the Trach only group.

Conclusions. For patients with severe PRS, mandibular distraction provides significant cost savings over tracheostomy ($300,000 per patient over 3 years). Increased costs with tracheostomy come from greater hospital-related charges, more frequent airway procedures, a higher incidence of gastrostomy tube feeds, and home trach care costs. A careful examination of long-term outcomes will be critical as mandibular distraction continues to gain acceptance for treatment of PRS.

Keywords

Pierre Robin sequence, tracheostomy, mandibular distraction osteogenesis

Introduction

Defined by the triad of micrognathia, glossoptosis, and airway obstruction,[1] Pierre Robin sequence (PRS) is a morbid and potentially lethal condition among neonates. In PRS, mandibular hypoplasia leads to abnormal cephalad and posterior positioning of the tongue, which frequently results in failure of fusion of the secondary palate, and a U-shaped cleft palate.[2] PRS occurs in 1:8500 live births and may occur in isolate or with a genetic syndrome, most commonly Stickler and Velocardiofacial syndromes, and hemifacial microsomia.[3,4] Clinically, PRS is marked by oxygen desaturations, apnea, gastroesophageal reflux, feeding difficulties, and failure to thrive. Mortality rates associated with PRS range from 0% to 21% (median 4.5%).[5] Mild cases may be managed conservatively, using prone positioning, nasopharyngeal or laryngeal mask airways, or palatal obturators. Moderate to severe cases require surgical intervention to relieve or bypass the airway obstruction.

Surgery for PRS consists of tongue-lip adhesion (TLA), tracheostomy, or mandibular distraction. Given the

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controversy in the suitability of TLA for more severely affected infants[6,7] along with the interference of tongue mobility and the possibility of tongue dehiscence,[8] this procedure is not used at our institution. Tracheostomy is effective at bypassing the obstruction but doesn't address the cause of the airway obstruction and requires extensive maintenance. Until recently, this has been the standard treatment of moderate to severe PRS.[9] Mandibular distraction (MD) consists of performing an osteotomy on the ramus of the mandible and gradually pulling it forward, correcting the micrognathia and tongue-based airway obstruction by providing more space for the tongue and oropharyngeal airway.

An important consideration with these surgical interventions is the associated cost for patients' families and the health care system. In our institution, patients with PRS receiving MD seemed to have shorter hospital stays and fewer subsequent interventions than those receiving tracheostomy. We therefore hypothesized that MD would be associated with significantly lower costs than tracheostomy. To test this we performed a retrospective cohort study comparing the costs associated with MD and tracheostomy for infants with PRS, both isolated and syndromic. Additionally, costs for neonates with PRS who underwent tracheostomy and secondarily underwent MD within the first year of life were compared.

Methods

Data Collection

A retrospective chart review was performed on neonates with PRS whose treatment at Cincinnati Children's Hospital Medical Center (CCHMC) began between 2001 and 2009. This study was approved by the Institutional Review Board (IRB) at CCHMC (#2009-0162). A multidisciplinary airway team including neonatologists, geneticists, otolaryngologists, pulmonologists, speech therapists, and plastic surgeons evaluated patients identified with PRS in the neonatal ICU. Workup typically included bedside nasopharyngoscopy, cephalogram, pulse oximetry monitoring, feeding assessment, and a sleep study. Mildly abnormal sleep studies despite repositioning lead to discharge with supplemental oxygen as appropriate and close follow-up. Moderately/severely abnormal sleep studies are followed by further imaging including microlaryngoscopy, bronchoscopy, and/or CINE MRI to evaluate for multilevel obstruction. Patients with moderate-severe sleep studies and additional risk factors (eg, multilevel obstruction, neurologic delay) or those requiring early intervention (eg, ex utero intrapartum [EXIT] to airway) are often referred for tracheostomy. Others receive tracheostomy or MD based on team recommendations. Seventy neonates (defined as infants less than 1 year old) were identified with PRS who underwent MD or tracheostomy. These included a subset of patients for whom our group recently published separate outcomes data.[10] Patients with incomplete billing records or incomplete follow-up charges (<3 years) were excluded (n = 23). One syndromic patient who received both tracheostomy and subsequent MD was excluded due to lengthy cardiac ICU stay unrelated to PRS.

The CCHMC billing department provided records of all charges to patients over a 3-year period. These included daily inpatient fees (for all admissions over 3 years including patient-specific nursing care, mechanical ventilation, enteral feeding, radiologic studies, medications, and laboratory tests), surgical fees (gastrostomy, microlaryngoscopy and bronchoscopy [ML&B], tracheostomy, mandibular osteotomies and distractor placement/adjustment/removal including distractor hardware costs), anesthesia fees, inpatient consultation fees, outpatient clinic fees, emergency room visits, and radiologic and sleep studies. Operations, imaging studies, and emergency room and clinic visits unrelated to the PRS diagnosis were excluded. Charges prior to 2009 were adjusted for inflation using an annual rate of 3%.

All patients discharged with a tracheostomy received home tracheostomy care. The monthly cost for home tracheostomy care was estimated based on a patient's level of respiratory support (CPAP vs ventilator), the number of months with tracheostomy before decannulation, estimated equipment rental and tracheostomy supply costs, and individualized home nursing care recommendations. A common recommendation provided 8 hours of home nursing care per night for 8 weeks. A list of the home nursing care and tracheostomy rental and supply rates used may be found in Supplemental Table S1 at www.otojournal.org.

Data Analysis

Data distributions for continuous data were assessed using means with standard deviations and medians with ranges (minimum and maximum) and interquartile ranges. Categorical data were reported as frequencies and percentages. Comparisons of median costs (adjusted for inflation) across the 3 groups (mandibular distraction only, tracheostomy only [Trach], and tracheostomy with subsequent mandibular distraction [Trach+MD]) were made using the Kruskal-Wallis test. Post hoc pairwise comparisons between groups were conducted using a Wilcoxon rank sum test with a Bonferonni adjustment. Total costs for year 1 were also adjusted for the number of days in the ICU using a general linear model (with least square means reported as the adjusted means). The data did not follow a Gaussian distribution, and therefore a log transformation was conducted on total costs for year 1 in order to control for number of days in the ICU, and the results were back transformed into whole dollar amounts for the purpose of interpretation. Adjusted mean total costs were reported with 95% confidence intervals.

Results

Forty-seven patients with PRS were identified who were treated with mandibular distraction (MD, n = 26), tracheostomy (Trach, n = 12), or tracheostomy with subsequent MD (Trach+MD, n = 9) and who met inclusion criteria (**Table 1**). The MD group had a higher percentage of patients with nonsyndromic PRS (82%) compared to the Trach (58%) and

Table 1. Demographics of Patients with Pierre Robin Sequence Included in the Study.

Treatment	MD	Trach	Trach+MD
Number of patients	26 (55%)	12 (26%)	9 (19%)
Gender distribution	Female = 12	Female = 6	Female = 4
	Male = 14	Male = 6	Male = 5
Isolated PRS	22 (85%)	7 (58%)	5 (56%)
Syndromic PRS*	4 (15%)	5 (42%)	4 (44%)
	Treacher-Collins	Treacher-Collins	Nager
	Hemifacial microsomia	Moebius	Mansky-Catel
	Stickler	Miller	Cornelia de Lange
	Unknown	Popliteal Pterigium	Unknown
		Velocardio-facial	

Abbreviations: MD, mandibular distraction only; Trach, tracheostomy only; Trach+MD, tracheostomy with subsequent mandibular distraction; PRS, Pierre Robin sequence.
*P = .10 (Fisher exact test).

Table 2. Year 1 Cost-Related Aspects of Mandibular Distraction versus Tracheostomy.[a]

Treatment	MD n = 26	Trach n = 12	Trach+MD n = 9	P Value
Age (days) at first surgery: median (range)	19 (6-233)	16 (0-32)	3 (0-105)	
Age (days) at second surgery: median (range)			105 (17-210)	
Total days of hospital stay: median (range)	28 (5-72)	33 (12-67)	50 (6-154)	.10
Mean (SD)	31.5 (18.4)	33.7 (18.5)	55.4 (41.5)	.04
Operation room–related charges year 1: median	$18,151	$24,045	$30,028	.001[b]
Mean (SD)	$17,552 ($5102)	$23,705 ($9007)	$30,680 ($8983)	<.001
Hospital-related charges year 1: median	$25,230	$73,845	$32,559	.15
Mean (SD)	$30,318 ($22,567)	$87,904 ($85,990)	$46,310 ($40,156)	.007
Total charges year 1: median	$47,858	$107,139	$84,333	.017
Mean (SD)	$53,890 ($25,394)	$126,516 ($96,286)	$87,829 ($43,481)	.002[c]
Adjusted for days in hospital: mean (95% confidence intervals)	$53,489 ($44,549-$64,223)	$96,674 ($74,076-$126,166)	$59,761 ($43,177-$82,716)	

Abbreviations: MD, mandibular distraction only; Trach, tracheostomy only; Trach+MD, tracheostomy with subsequent mandibular distraction.
[a]Medians and ranges and means (SD) reported for all continuous values. Costs do not include tracheostomy supplies or private nursing care. All costs adjusted for inflation. Comparisons across groups regarding continuous variables conducted using Kruskal-Wallis test (nonparametric).
[b]Post hoc group comparison P values adjusted for multiple comparisons with Bonferonni correction. Groups MD versus Trach, P = .09; MD versus Trach+MD, P = .0002; Trach versus Trach+MD, P = .44.
[c]Because the data were not normally distributed (significantly skewed), cost values were log transformed to conduct general linear models to obtain an adjusted mean with 95% confidence intervals and then back-transformed to provide an estimated cost in dollar figures for each group. Group comparison P values using Tukey-Kramer adjustment for multiple comparisons. MD versus Trach, P = .002; MD versus Trach+MD, P = .83; Trach versus Trach+MD, P = .07.

Trach+MD (56%) groups, although this was not statistically significant (P = .10).

Table 2 shows that the MD group had significantly lower charges ($47,858) during the first year compared to the tracheostomy ($107,139) and Trach+MD ($84,333) groups (P = .017). This difference was due in part to different surgical charges between the groups, with MD ($18,151) the lowest, Trach ($24,045) in between, and Trach+MD ($30,028) the highest (multiple comparisons of means, $P < .001$), which directly correlated with increased operation frequency for those receiving tracheostomy due to serial gastrostomy tube and airway maintenance procedures (eg, ML&B, removal of subglottic granulations, **Table 3**). Patients receiving MD (28 days) and Trach (33 days) had similar lengths of stay, however those with both operations (50 days) had longer stays (multiple comparisons of means, P = .04). However, this difference did not correlate with ICU-related charges. Surprisingly, the Trach group had higher ICU charges ($73,845) than the Trach+MD ($32,559) and MD ($25,230) groups (multiple comparisons of means, P = .007). When adjusted for the different lengths of stay between the 3 groups, the total average charges for

Table 3. Three Year Cost-Related Aspects of Mandibular Distraction versus Tracheostomy.

Treatment	MD n = 26	Trach n = 12	Trach+MD n = 9	*P* Value[a]
Median number operations year 1 (range)	3.5 (2-6)	5 (2-6)	6 (4-8)	.0006
(Mean)	(3.6)	(4.4)	(6.0)	
Median number operations years 1-3 (range)	4 (2-11)	10 (6-12)	8 (4-15)	<.0001
(Mean)	(3.9)[b]	(9.2)	(9.8)	
Median number ER visits years 1-3 (range)	0 (0-14)	1.5 (0-11)	1 (0-10)	.016
(Mean)	(1.0)	(3.2)	(3.1)	
Tracheostomy tube (n decannulated)	n/a	4	5	.40
Nasogastric tube (n treated, n home with, n weaned from)	22, 14, 22	4, 3, 4[c]	0, 0, 0	<.0001
Gastrostomy tube (n treated, n home with, n weaned from)	4, 3, 3	6, 3, 3[c]	9, 9, 2	<.0001

Abbreviations: MD, mandibular distraction only; Trach, tracheostomy only; Trach+MD, tracheostomy with subsequent mandibular distraction.
[a]Kruskal-Wallis test for continuous variables or Fisher's exact test for categorical variables.
[b]Two of 26 patients in the MD group had persistent airway obstruction requiring subsequent tracheostomy.
[c]For nasogastric and gastrostomy tube data, only the *proportion* of patients treated was analyzed.

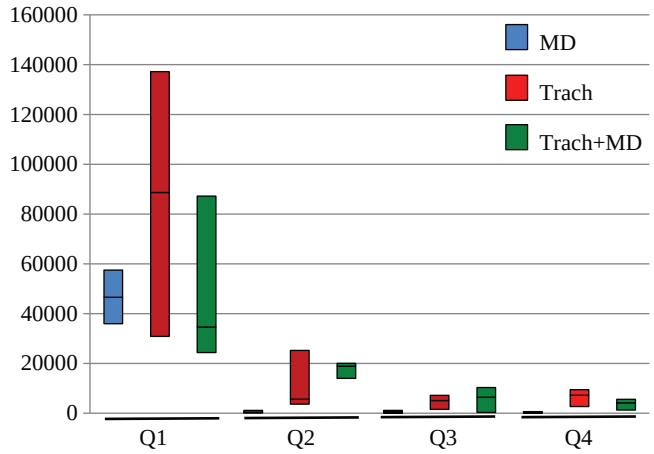

Figure 1. Charges ($USD) of groups over first year by quartile. Total charges over the first year following initial surgical intervention for patients with Pierre Robin sequence receiving mandibular distraction (MD), tracheostomy (Trach), or tracheostomy with subsequent MD (Trach+MD). Median values (horizontal line) are presented with twenty-fifth through seventy-fifth percentile ranges. Statistical analyses by quartile: first: $P = .28$; second through fourth: $P < .0001$ (Kruskal-Wallis comparison for nonparametric data).

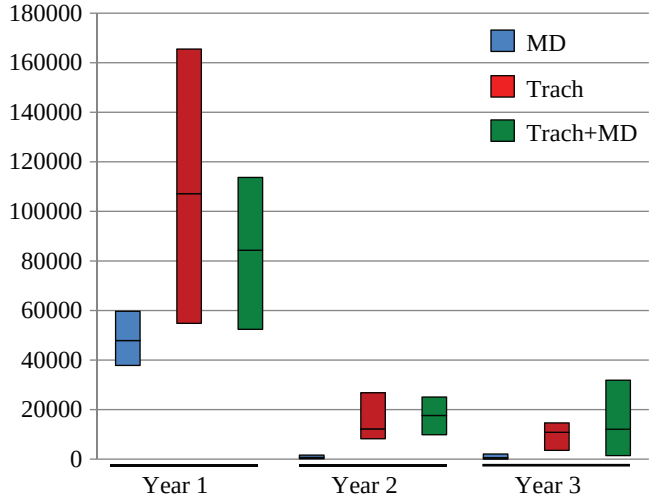

Figure 2. Annual charges ($USD) of groups over a 3-year period. Cost analysis of patients with Pierre Robin sequence receiving mandibular distraction (MD), tracheostomy (Trach), or tracheostomy with subsequent MD (Trach+MD), over a 3-year period following initial treatment. Median values (horizontal line) are presented with twenty-fifth through seventy-fifth percentile ranges. Statistical analyses by year: year 1: $P = .017$; year 2: $P < .0001$; year 3: $P = .0003$ (Kruskal-Wallis comparison for nonparametric data).

the first year were no different ($P = .83$) between the MD group ($53,489) and the Trach+MD group ($59,761), whereas the Trach group ($96,674) continued to be significantly higher than the MD group ($P = .002$).

The first year was divided into quartiles for a further analysis of associated charges (**Figure 1**). As expected, all groups had the greatest charges during the first quartile, corresponding with the initial admission and operations, with no differences between groups ($P = .28$). The low median charges of the Trach+MD group during the first quartile were influenced by a delay in receiving MD until after the initial tracheostomy. Over the last 3 quartiles, charges for the MD group were significantly less than those of the other 2 groups ($P < .0001$).

A 3-year follow-up period was examined for all patients (**Figure 2**). As with the first year ($P = .017$), charges from the Trach and Trach+MD groups continued to be significantly greater than the MD group in years 2 ($P < .0001$) and 3 ($P = .0003$). These increased costs correlate positively with increased numbers of operations ($P < .0001$) and ER visits ($P = .016$) for patients receiving tracheostomy (**Table 3**).

To incorporate home tracheostomy care-related costs, a personalized estimate was made for each patient based on individual requirement for respiratory support, length of time prior to decannulation, and charges related to equipment rental, tracheostomy supplies, and home nursing care. These home care charges were combined with actual

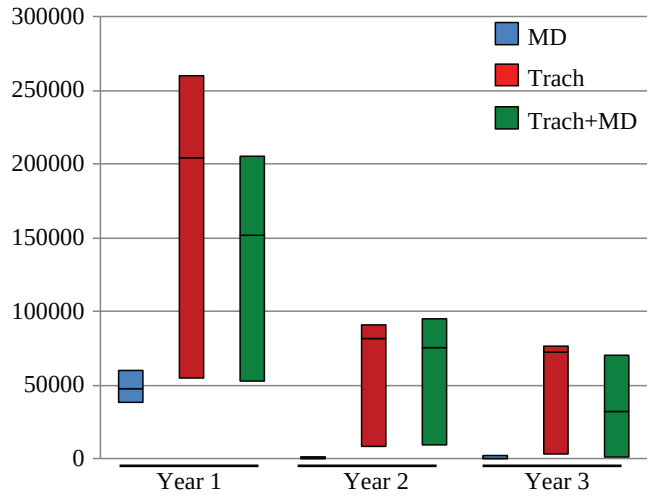

Figure 3. Estimated total charges ($USD) of groups inclusive of home health care costs. Total charges over 3 years following initial surgical intervention for patients with Pierre Robin sequence receiving mandibular distraction (MD), tracheostomy (Trach), or tracheostomy with subsequent MD (Trach+MD), including home tracheostomy-care costs (eg, supplies, equipment rental, and home nursing fees). Median values (horizontal line) are presented with twenty-fifth through seventy-fifth percentile ranges. Statistical analyses by year: years 1-3: $P < .01$ (Kruskal-Wallis comparison for nonparametric data). A Wilcoxon rank sum test was used to compare Trach vs Trach+MD groups at each time point: year 1: $P = .27$; year 2: $P = .30$; year 3: $P = .29$.

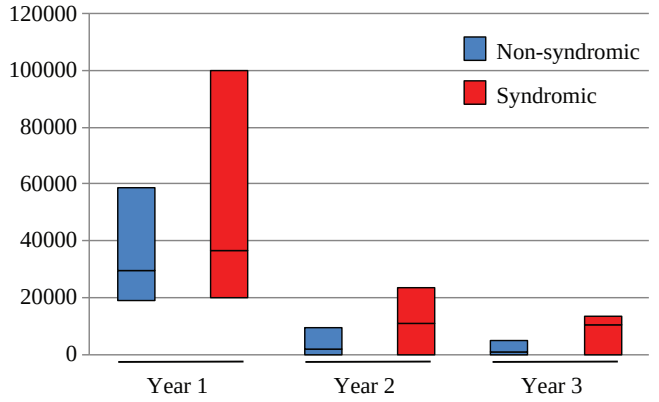

Figure 4. Annual charges ($USD) of syndromic versus non-syndromic patients. Cost comparison (not including home care charges) of patients with non-syndromic versus syndromic Pierre Robin sequence over 3-year period. Median values (horizontal line) presented with twenty-fifth through seventy-fifth percentile ranges. Wilcoxon rank sum tests used to compare the 2 groups at each time point: Year 1: $P = .26$; Year 2: $P = .03$; Year 3: $P = .13$.

hospital charges to identify total charges for the groups (**Figure 3**). As expected, the addition of home health care resulted in a greater disparity between patients receiving a tracheostomy versus those receiving MD only. We observed that the Trach+MD group incurred fewer charges than the Trach group in all 3 years, although this difference was not statistically significant (Year 1 $P = .27$, Year 2 $P = .30$, Year 3 $P = .29$). This trend may be attributed to a higher rate of decannulation among Trach+MD (5 of 9, 56%) versus Trach (2 of 12, 17%) over the 3-year period.

To examine the contribution of syndromic status, all patients were grouped based on diagnosis of isolated PRS (34 patients, 72%) or syndromic (including unknown syndromes) PRS (13 patients, 28%). As shown in **Table 1**, although the MD group had a higher percentage of nonsyndromic patients, this difference was not significant ($P = .10$). **Figure 4** compares the charges between these 2 groups. Syndromic patients had higher associated charged for all 3 years; however, this was only significant during year 2 ($P = .03$).

Discussion

Tracheostomy effectively bypasses tongue-based obstruction and remains the gold standard for severe obstruction that may occur with PRS. However, tracheostomy has greater associated morbidity including negative long-term speech effects, difficulties with feeding, psychosocial delays, frequent hospital admissions for tracheitis and pneumonia, buildup of airway granulation tissue, and occasional need for complicated revision surgery, including laryngotracheoplasty and cricotracheal resection.[11-14] Further, patients with a tracheostomy typically require multiple ML&B procedures to investigate these morbidities and to prepare for decannulation. Of greatest significance, tracheostomy is associated with a small but real chance of mortality (1%-5%).[15]

Mandibular distraction differs in that it directly addresses the primary problem, micrognathia. Using MD to lengthen the mandible provides greater room for the tongue and oral soft tissues and indirectly pulls them forward by their attachments to the mandible, correcting glossoptosis and improving airway obstruction. A growing body of studies indicate MD helps PRS patients treated with tracheostomy achieve decannulation sooner or avoid tracheostomy altogether.[9,11,14,16-24] Complications associated with MD include hardware malfunction, infection, damage to tooth buds, and nerve injury and pain, although the actual incidence varies depending on surgeon experience and technique.[25,26]

Two groups have performed cost analyses to compare tracheostomy to MD for PRS. Kohan et al[27] examined 149 neonates with PRS treated with either internal MD (n = 43) or tracheostomy (n = 73). They reported a 2-fold higher cost for the Trach group ($382,246) compared to MD group ($193,128) over a 4-year follow-up period. The cost difference was due to an increased length of ICU stay in patients receiving tracheostomy. Hong et al[28] examined 52 patients with PRS: 21 received MD, and 31 had a tracheostomy. With 1 year of follow-up data, the Trach group had a 1.6-fold increase in cost compared to the MD group ($92,164 vs $57,649, Canadian dollars). This cost difference was attributed to increased hospital stay for tracheostomy patients, as their health system mandates 90 days in house for home tracheostomy care arrangement. Both studies used averaged operative and ICU per diem fees rather than individual patients' billed charges, as done in our study. Also, neither

study examined the contribution of syndromic status or home care charges.

Consistent with these reports, our study found a 2.6-fold higher cost for patients receiving tracheostomy compared to MD over a 3-year period. These figures are based on actual patients' charges and thus factor in individuals' variations in ER and clinic visits, imaging studies, and level of hospital acuity. In contrast to the other cost analyses, we found no significantly different lengths of hospital stay between the MD and Trach groups. However, the Trach group had nearly 3-fold higher hospital-related charges compared to the MD group. In our institution, patients receiving MD are extubated within a few days, typically fed by NG-tube without requiring gastrostomy, and require no or minimal oxygen support, often allowing for discharge home during active distraction. Those receiving tracheostomy more frequently require gastrostomy feeding and ventilatory support. Once stable, they are transferred to a (stepdown) complex airway unit with decreased acuity of care under management of the ENT or pulmonary services with appropriate consultants (eg, speech therapy, genetics, plastics) but without ICU team involvement. Patients receiving tracheostomy also had increased OR-related charges. MD group patients typically received 3 operations: distractor application and removal, with simultaneous microlaryngscopy/bronchoscopy, with a few requiring a distractor adjustment operation. Trach and Trach+MD group patients required their initial tracheostomy, often a gastrostomy with Nissen fundoplication, and serial ML&B procedures for airway maintenance and evaluation in preparation for decannulation, with a net greater cost to the patient over the MD group. We also observed increased clinic and ER visits for respiratory disease in Trach patients, as reported.[27] In years 2 and 3 following intervention, patients in the MD group averaged only $1000 per year in charges, which largely came from 2 patients who had persistent airway obstruction despite MD, necessitating tracheostomy.

Our study is the first cost analysis to examine patients treated with tracheostomy and subsequent MD. Early in our study, MD was performed for some patients with severe PRS initially treated with tracheostomy, anticipating difficulty in decannulation due to severity of their micrognathia. As reported,[29] we observed a higher decannulation rate in patients receiving subsequent MD. Given this, our airway team now often recommends MD for neonates with PRS treated initially with tracheostomy, including those transferred from other hospitals or those receiving ex utero intrapartum (EXIT to airway) treatment. When considering a Trach+MD approach, it is important to consider possible additional costs. Not surprisingly, we found that Trach+MD patients had greater lengths of hospital stay and OR charges. However, these patients had lower costs compared to the Trach only group within the first year largely because of lower hospital-related charges. As shown in **Table 2**, the median age at first surgery in the tracheostomy only patients is 16 days, whereas those in the Trach+MD group had a median age of 3 days at time of tracheostomy. This translates into a nearly 2-week longer stay in the ICU for the Trach only group. Over a 3-year period, patients in the Trach+MD group also had a lower median number of operations, fewer ER visits, and higher decannulation rates, resulting in lesser total costs compared to those in the Trach group. These differences weren't statistically significant, so we cannot conclude that the addition of MD to tracheostomy provides a cost savings; however, we posit that there are no increased costs when both operations are performed versus tracheostomy alone.

Costs associated with home tracheostomy care can be substantial and should be considered in any rigorous cost analysis for treatment of PRS. Although actual billed charges weren't available for each patient, we generated an informed estimate based on an individual's requirement for ventilatory support, local equipment rental rates, recommended level of home nursing care and rates, and age at decannulation. Inclusion of home care to the Trach group over the first 3 years increased the total cost to $358,395, a 7.3-fold increase over the MD group. The Trach+MD group also had increased charges due to home care, however remained lower than the Trach group each year, albeit not significantly. We did not consider the added costs of home tube feeding due to inability to obtain precise data on timing of cessation of enteral feeds. Were home feeds included, this would likely further increase charges to patients treated with tracheostomy, the majority of whom had gastrostomies, whereas most receiving MD weaned off of nasogastric tube feeds within a short time of discharge.

Our study has a number of limitations. First, our patient population may not reflect that of patients with PRS nationally. As an airway referral center we are biased toward those with severe airway obstruction. We do successfully manage patients with mild to moderate PRS conservatively, however those patients were not included in this study as our purpose was to compare *surgical* interventions for moderate to severe PRS. Next, with a 3-year follow-up period we are not evaluating the contribution of long-term sequelae to patient costs, which may change the disparity between MD and tracheostomy. These may include possible need for dental work or orthognathic surgery in patients receiving distraction and additional airway procedures in patients not decannulated within 3 years. Lastly, we cannot rule out the possibility that our data are skewed by a lower percentage of syndromic patients in the MD group (15% vs 42% for Trach group). Patients with syndromic PRS have been reported to have a greater severity of respiratory problems compared to nonsyndromic PRS, and they frequently require treatment for other congenital anomalies. We addressed this by excluding surgical fees, studies, and clinic visits associated with non-airway diagnoses. However, the length of their ICU stay or acuity may have some influence on the financial charges. However, statistical analysis of the 3 groups did not demonstrate significance in their different percentages of syndromic patients. Additionally, a direct comparison of nonsyndromic with syndromic patients showed higher charges for the latter, but which were significant only during year 2 (see **Figure 4**).

We believe these findings may have important implications for the treatment of neonatal PRS. With an incidence of

around 1:8,500,[3,4] there are approximately 500 new cases of PRS in the US annually, 30% of which may have airway obstruction severe enough to warrant operative intervention.[11] Our data suggest a $300,000 cost savings for each patient treated with mandibular distraction rather than tracheostomy, over 3 years. Hypothetically, performing MD on all patients with severe PRS would generate health care savings of $450,000,000 over a 10-year period, assuming those patients would otherwise receive a tracheostomy. This estimate does not include long-term and indirect costs, which include costs associated with scars, radiation exposure, and quality of life.

Cost savings is one important consideration for selection of treatment of PRS and is the focus of this study. Of equal or greater importance though are the long-term airway, speech, nutrition, and developmental outcomes of patients treated with mandibular distraction compared to tracheostomy. However, as described in a recent systematic review, outcomes of neonates with PRS are poorly understood due to wide variability of study inclusion criteria, lack of standardized indications for interventions, and a general paucity of data.[5] Based on the present study and our clinical experience,[10] we support the use of mandibular distraction for treatment of severe PRS but acknowledge that further study is necessary to standardize diagnostic and treatment criteria and to identify appropriate outcome measures.

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Author Contributions

Christopher M. Runyan, data collection, data analysis, majority of the writing; **Armando Uribe-Rivera**, data collection, data analysis, writing; **Audrey Karlea**, data collection, data analysis, early manuscript writing; **Jareen Meinzen-Derr**, statistical and data analyses; **Dawn Rothchild**, data collection, data analysis, early manuscript revisions; **Howard Saal**, study conception and design, data collection, data analysis, early manuscript revisions; **Robert J. Hopkin**, study conception and design, data collection, data analysis, Institutional Review Board protocol, early manuscript draft and revisions; **Christopher B. Gordon**, study conception and design, data collection, data analysis.

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Supplemental Material

Additional supporting information may be found at http://otojournal.org/supplemental.

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Ibuprofen with Acetaminophen for Postoperative Pain Control following Tonsillectomy Does Not Increase Emergency Department Utilization

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Abstract

Objective. To compare the performance of ibuprofen vs codeine for postoperative pain management after tonsillectomy as measured by need for emergency department (ED) treatment for pain and/or dehydration.

Study Design. Retrospective case series with chart review.

Setting. Tertiary children's hospital.

Subjects and Methods. Consecutive series of patients who underwent tonsillectomy with or without adenoidectomy at a tertiary children's hospital. Patients were categorized based on the type of postoperative pain management (acetaminophen with codeine vs acetaminophen and ibuprofen). The main outcome measure was the proportion of patients requiring ED visits or inpatient admissions for inadequate pain control or dehydration. Secondary measures included antibiotic use, postoperative hemorrhage, need for return to the operating room, vomiting, and oral diet tolerance.

Results. Patients in the ibuprofen/acetaminophen group were younger than those in the codeine/acetaminophen group (6.2 vs 8.1 years, $P < .05$). Patients in the codeine/acetaminophen group were more likely to use antibiotics in the postoperative period (50.3% vs 5.9%, $P < .05$). The proportion of patients requiring ED visits or inpatient admission for dehydration was not significantly different between the groups (5.1% for codeine, 2.7% for ibuprofen, $P = .12$). Multivariable analysis controlling for age and antibiotic use showed no difference in ED visits or admission for dehydration ($P = .09$). There was no difference between the groups for any of the secondary measures.

Conclusions. Ibuprofen with acetaminophen represents a safe and acceptable analgesic alternative to codeine and acetaminophen in patients undergoing pediatric tonsillectomy.

Keywords

tonsillectomy, adenoidectomy, pain management, ibuprofen, codeine

As a result of reported fatalities and serious adverse events in pediatric tonsillectomy patients, there has been significant attention focused on the optimal medication for postoperative pain control in such patients.[1-7] There exists a cohort of patients who are ultra-rapid metabolizers of codeine, which results in higher than expected serum levels of morphine.[8] As such, the US Food and Drug Administration (FDA) recently placed a boxed warning against the use of codeine in children following tonsillectomy and/or adenoidectomy.[7]

Furthermore, in January 2011, the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) published clinical practice guidelines regarding tonsillectomy in children.[9] These guidelines assist referring physicians and otolaryngologists in remaining up to date on the optimal management of patients undergoing tonsillectomy. A change from prior recommendations was the inclusion of nonsteroidal anti-inflammatory drugs such as ibuprofen in the medications deemed safe for use postoperatively.

While multiple authors have investigated the safety of using ibuprofen after tonsillectomy with regard to the primary outcome measure of postoperative hemorrhage, there exist only studies with small sample sizes that compare the efficacy of ibuprofen with codeine with regard to adequate postoperative pain control.[1-6] We initiated the current study to test the null hypothesis that there was no difference in emergency department (ED) visits for pain or dehydration

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Table 1. Summary of Results.[a]

Characteristic	Codeine and Acetaminophen	Ibuprofen and Acetaminophen	*P* Value
Sample size, n	177	489	
Mean age, y	8.1	6.2	<.05
Postoperative antibiotics	89 (50.3)	29 (5.9)	<.05
Emergency room visit	9 (5.1)	13 (2.6)	.12
Hemorrhage	3 (1.7)	17 (3.5)	.23
Return to operating room	3 (1.7)	7 (1.4)	.8
Vomiting	10 (9.2)	19 (7.1)	.5
Oral diet intolerance	13 (11.9)	30 (11.2)	.85

[a]Values are presented as number (%) unless otherwise indicated.

between ibuprofen and acetaminophen vs acetaminophen with codeine for posttonsillectomy patients.

Methods

Approval for the study was obtained from the Children's National Medical Center Institutional Review Board. Charts were retrospectively reviewed of consecutive patients who underwent tonsillectomy with or without adenoidectomy using monopolar electrocautery supervised by one of the 2 senior authors (J.R.B. and R.K.S.) from January 2011 through June 2013. Patients were categorized based on the type of postoperative pain management. One group consisted of patients receiving acetaminophen with codeine. A second group of patients received acetaminophen and ibuprofen. Acetaminophen with codeine was dosed at 0.5 to 1 mg/kg of codeine every 6 hours. Acetaminophen was dosed at 10 to 15 mg/kg every 6 hours. Ibuprofen was dosed at 5 mg/kg every 6 hours. Acetaminophen and ibuprofen were given in an alternating (every 3-hour) fashion. All medications were prescribed as standing doses for the first 3 days and as needed thereafter. Patients were further stratified based on the use of postoperative antibiotic use. In patients who received antibiotics, amoxicillin was used for nonallergic patients, and clindamycin was used for those with penicillin allergies. Early in the study period, patients were routinely prescribed postoperative antibiotics. This practice ended during the study period as a response to the strong recommendation against routine perioperative antibiotic use in tonsillectomy in the AAO-HNS guidelines.[9]

The main outcome measure was the proportion of patients requiring ED visits or inpatient admission for inadequate pain control and/or dehydration. While not a perfect substitute measure for pain control, return to the ED due to uncontrolled pain or dehydration due to pain does give insight into the efficacy of the postoperative analgesic regimen and is an acceptable surrogate for such in retrospective series of post-adenotonsillectomy pain control. Return to the ED demonstrates that the pain threshold was exceeded, resulting in the caregiver seeking higher acuity evaluation for the pain control.

Secondary outcome measures included postoperative hemorrhage, need for return to the operating room, and oral feeding tolerance on postoperative day 1 (as determined by a postoperative routine check-in phone call by recovery room nurses).

Bivariable analysis of continuous variables (ie, age) was performed using a 2-tailed Student *t* test. The χ^2 test was used for bivariable analysis of nominal data. Multivariable analysis using logistic regression was performed to examine the effect of the postoperative pain medicine on the primary outcome when controlling for patient age and antibiotic use. Statistical analysis was performed using Microsoft Excel (Microsoft, Redmond, Washington) and SPSS for Mac OS X (SPSS, Inc, an IBM Company, Chicago, Illinois).

Results

Of the 666 patients included in the study, 177 were treated with acetaminophen and codeine, and 489 received acetaminophen and ibuprofen. **Table 1** summarizes the results of this study. Specifically, patients in the ibuprofen/acetaminophen group were younger than those in the group that received codeine/acetaminophen (6.2 vs 8.1 years, $P < .05$). Patients in the codeine/acetaminophen group were more likely to use antibiotics in the postoperative period (50.3% vs 5.9%, $P < .05$).

With regard to the main outcome measure, 9 patients (5.1%) from the codeine/acetaminophen group returned to the ED due to inadequate pain control or dehydration, compared with 13 patients (2.6%) from the ibuprofen/acetaminophen group. This difference was not statistically significant, with $P = .12$. The effect of antibiotic use on the main outcome measure was not significant: 5.1% of patients in the antibiotic group returned to the ED vs 3% for patients who did not use antibiotics ($P = .2$). Multivariable analysis using logistic regression showed no significant difference between the codeine/acetaminophen and ibuprofen/acetaminophen groups for the main outcome measure when controlling for patient age and postoperative antibiotic use ($P = .09$). Age was found to be a significant factor in the multivariable model, with an odds ratio of 0.98 ($P < .05$), indicating that when controlling for antibiotic and analgesic use, older children were slightly less likely to return to the ED. **Table 2** summarizes the findings of the logistic regression analysis.

Table 2. Logistic Regression Analysis of Emergency Department Visits.

Characteristic	Odds Ratio	95% CI for Odds Ratio	*P* Value
Age	0.980	0.965-0.994	.007
Antibiotic use	0.968	0.309-3.037	.956
Analgesic medication	0.400	0.136-1.170	.094

Abbreviation: CI, confidence interval.

There were no significant differences between the groups for any of the secondary outcome measures. Three patients (1.7%) from the codeine/acetaminophen group had postoperative bleeding, compared with 17 (3.5%) in the ibuprofen/acetaminophen group ($P = .23$). Need for return to the operating room for control of posttonsillectomy hemorrhage was similar, with 3 patients (1.7%) from the codeine/acetaminophen group vs 7 (1.4%) for the ibuprofen/acetaminophen group ($P = .8$).

Data for vomiting and oral diet tolerance in the first 24 hours postsurgery were available for 376 patients (109 treated with codeine/acetaminophen and 267 treated with ibuprofen/acetaminophen). Among these patients, 10 (9.2%) children treated with codeine/acetaminophen and 19 (7.1%) treated with ibuprofen/acetaminophen reported vomiting ($P = .5$). Of these 376 patients, only 13 (11.9%) among the codeine/acetaminophen group and 30 (11.2%) in the ibuprofen/acetaminophen group were not tolerating an oral diet 24 hours after surgery ($P = .85$).

Discussion

The current study tests the null hypothesis that ibuprofen and acetaminophen do not increase ED utilization for pain or dehydration compared with codeine and acetaminophen. Our data demonstrate that a regimen of ibuprofen and acetaminophen performs the same as codeine and acetaminophen for the primary and secondary outcome measures, and the null hypothesis is accepted. However, this conclusion should be met with some caution. The span of the confidence interval for the odds ratio for ED visits suggests that our sample size may be too small to detect significant differences between the groups.

There has long been interest in the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for postoperative pain relief; this is the largest series to date addressing this question. Following reports of deaths and serious adverse events in children using codeine following tonsillectomy, as well as a subsequent boxed warning by the FDA, it has become even more important to find pain control regimens that are both safe and effective.

Codeine is a prodrug, metabolized via the CYP2D6 pathway to the active drug morphine. Genetic polymorphisms can lead to variation in an individual's ability to metabolize the drug, with some patients being ''extensive'' or ''ultra-rapid'' metabolizers of the medication.[8] Such patients will convert much more codeine to morphine and are more susceptible to adverse reactions such as respiratory depression, even at theoretically weight-appropriate doses. Kelly et al[7] reported on the deaths of 3 children who were administered codeine following adenotonsillectomy and subsequently found to be ultra-rapid metabolizers.

Ibuprofen has the theoretical concern of increasing posttonsillectomy hemorrhage; this assertion is not supported by the literature and was not a primary end point in the present study.[4-6] This study showed a rate of postoperative hemorrhage of 3.5% in the ibuprofen group, a number near the higher end of reported rates.[10] We attribute this to increased vigilance and parental counseling as we began to use ibuprofen as we had heightened sensitivity to the anecdotes and assertions. Patients were counted as having a hemorrhage even with a parental report of blood-tinged sputum but no evidence of active bleeding or clots on physical examination. Other studies have shown elevated postoperative hemorrhage rates when similar definitions of hemorrhage were used.[11,12] Notably, in the present study, the operating room return rates for hemorrhages were nearly identical between the codeine and ibuprofen groups (1.7% and 1.4%, respectively).

As a result of the data in the literature regarding ibuprofen and codeine, the guidelines from the AAO-HNS, and the recent FDA boxed warning, there has been a move toward using ibuprofen in pediatric tonsillectomy patients.[9] The senior authors in this study made the switch away from codeine in May 2011 (author R.K.S.) and November 2011 (author J.R.B.). Given the FDA warning, a prospective study comparing these 2 regimens would be ethically dubious.

There is extensive literature investigating and ultimately establishing the safety of ibuprofen use after tonsillectomy.[1,2,4-6] Ibuprofen has been shown to work with at least the same, if not greater, efficacy as codeine in children with musculoskeletal trauma.[13,14] Evidence for its efficacy after tonsillectomy has not been as robust. Studies by St Charles et al[1] in 1997 and Harley et al[2] in 1998 addressed these questions of safety and efficacy but were limited by the low power of the studies (n = 110 and n = 27, respectively). St Charles et al[1] found no difference in bleeding, pain, or temperature control but did show less nausea in patients receiving ibuprofen. Harley et al[2] found slight differences in favor of codeine in the early postoperative period, but overall, there was no significant difference in pain control or time until return to normal diet.

There was a significant difference in perioperative antibiotic use in our 2 groups. This disparity is due to shifts in

the senior authors' practice following the strong recommendation in the AAO-HNS guidelines against the routine use of perioperative antibiotics.[9] The use of antibiotics has not been definitively shown to affect postoperative morbidity, specifically pain and hemorrhage.[15] Multivariable analysis in the present study did not find antibiotic use to be a significant predictor of ED return.

The limitations of the present study include the retrospective nature of the study. It is possible that patients may have visited an outside ED, and such events would not have been included in our chart review. This potential is minimized, however, because such information is routinely obtained during the first postoperative visit. Due to the severity of the warning from the FDA, it is unethical to design a prospective study using codeine without screening in some manner for rapid metabolizers. The value of the present study is that it bridges both time periods—prior to the FDA warning and after the FDA warning. Unfortunately, the retrospective nature of the study precludes the use of direct or objective measures of pain control. The rate of return to the ED due to pain and/or dehydration is a suitable surrogate metric and provides useful clinical information on the efficacy of a given postoperative analgesic regimen.

Conclusion

There is no difference in the primary and secondary outcome measures in posttonsillectomy patients based on the use of codeine and acetaminophen or ibuprofen and acetaminophen. Codeine and ibuprofen perform similarly for postoperative analgesia in children after tonsillectomy with or without adenoidectomy with respect to ED utilization. Given the major concerns regarding codeine use in this population, ibuprofen represents an acceptable and safe alternative for pain control.

Author Contributions

Joshua R. Bedwell, conceived of and designed the study, analyzed the data, drafted the initial manuscript, and approved the final manuscript as submitted; **Matthew Pierce**, collected the data, performed initial data analysis, assisted in drafting the initial manuscript, and approved the final manuscript as submitted; **Michelle Levy**, collected the data, performed initial data analysis, and approved the final manuscript as submitted; **Rahul K. Shah**, designed the study, critically reviewed the manuscript, and approved the final manuscript as submitted.

Disclosures

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ORIGINAL CONTRIBUTION

Perioperative Dexamethasone Administration and Risk of Bleeding Following Tonsillectomy in Children

A Randomized Controlled Trial

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Context Corticosteroids are commonly given to children undergoing tonsillectomy to reduce postoperative nausea and vomiting; however, they might increase the risk of perioperative and postoperative hemorrhage.

Objective To determine the effect of dexamethasone on bleeding following tonsillectomy in children.

Design, Setting, and Patients A multicenter, prospective, randomized, double-blind, placebo-controlled study at 2 tertiary medical centers of 314 children aged 3 to 18 years undergoing tonsillectomy without a history of bleeding disorder or recent corticosteroid medication use and conducted between July 15, 2010, and December 20, 2011, with 14-day follow-up. We tested the hypothesis that dexamethasone would not result in 5% more bleeding events than placebo using a noninferiority statistical design.

Intervention A single perioperative dose of dexamethasone (0.5 mg/kg; maximum dose, 20 mg), with an equivalent volume of 0.9% saline administered to the placebo group.

Main Outcome Measures Rate and severity of posttonsillectomy hemorrhage in the 14-day postoperative period using a bleeding severity scale (level I, self-reported or parent-reported postoperative bleeding; level II, required inpatient admission for postoperative bleeding; or level III, required reoperation to control postoperative bleeding).

Results One hundred fifty-seven children (median [interquartile range] age, 6 [4-8] years) were randomized into each study group, with 17 patients (10.8%) in the dexamethasone group and 13 patients (8.2%) in the placebo group reporting bleeding events. In an intention-to-treat analysis, the rates of level I bleeding were 7.0% (n=11) in the dexamethasone group and 4.5% (n=7) in the placebo group (difference, 2.6%; upper limit 97.5% CI, 7.7%; *P* for noninferiority=.17); rates of level II bleeding were 1.9% (n=3) and 3.2% (n=5), respectively (difference, –1.3%; upper limit 97.5% CI, 2.2%; *P* for noninferiority < .001); and rates of level III bleeding were 1.9% (n=3) and 0.6% (n=1), respectively (difference, 1.3%; upper limit 97.5% CI, 3.8%; *P* for noninferiority=.002).

Conclusions Perioperative dexamethasone administered during pediatric tonsillectomy was not associated with excessive, clinically significant level II or III bleeding events based on not having crossed the noninferior threshold of 5%. Increased subjective (level I) bleeding events caused by dexamethasone could not be excluded because the noninferiority threshold was crossed.

Trial Registration clinicaltrials.gov Identifier: NCT01415583

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Adenotonsillectomy is exceedingly common, with a reported increase in tonsillectomy rates in children younger than 15 years from 287 000 to 530 000 per year over the past decade.[1,2] Although safe, adenotonsillectomy can result in significant complications, such as aspiration, pulmonary edema, postoperative dehydration, and hemorrhage.[3] Although complications are infrequent because tonsillectomy is so common, the absolute number of children experiencing tonsillectomy complications is formidable.

Postoperative nausea and vomiting (PONV) is a major source of morbidity following tonsillectomy. Perioperative administration of corticosteroids effectively manages PONV and also results in more rapid resumption of a diet, improved pain control, and decreased airway swelling.[4] The benefits

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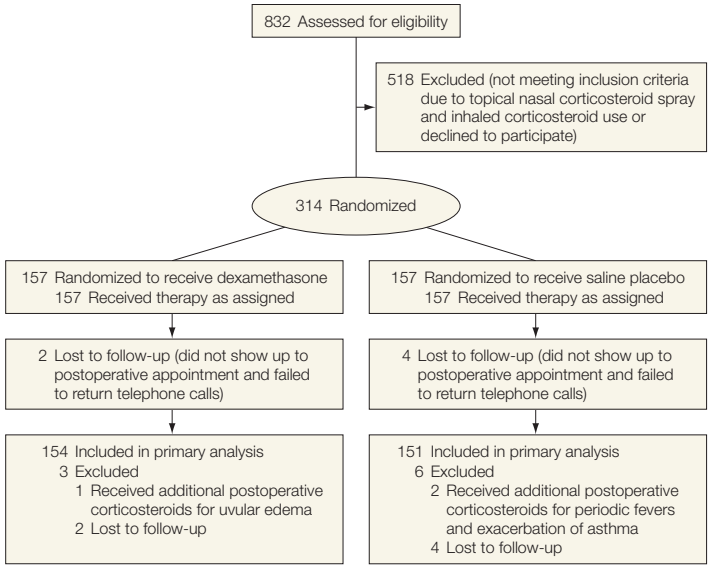
Figure 1. Participant Flow of Patients



of corticosteroid administration have been known for many years.[5] Two meta-analyses demonstrated the benefits of a single dose of dexamethasone in controlling PONV following tonsillectomy.[6,7] Consequently, the American Academy of Otolaryngology–Head and Neck Surgery Clinical Practice Guideline on pediatric tonsillectomy provided a strong recommendation for the use of perioperative corticosteroid therapy.[8]

A recent randomized trial studying the dose response of perioperative dexamethasone to PONV in children undergoing tonsillectomy was prematurely terminated due to an increased risk of postoperative hemorrhage.[9] The outcomes of the trial suggested that a single dose of intraoperative dexamethasone significantly increased posttonsillectomy hemorrhage events. In light of these findings, there is a need to reassess the safety profile for dexamethasone when used during tonsillectomy.

Given the long history of dexamethasone use during tonsillectomy and the single report questioning its safety, we performed a clinical trial to address concerns about bleeding events in children associated with dexamethasone use during tonsillectomy.

METHOD

Study Design and Conduct

Our study was reviewed and approved by the institutional review boards of both institutions (Massachusetts Eye and Ear Infirmary, Boston, and Naval Medical Center San Diego, San Diego, California). All patients, their guardians, or both provided written informed consent and assent. Our study was designed as a prospective, randomized, double-blind, placebo-controlled, noninferiority trial. Randomization was performed by the hospital pharmacist and occurred via a 1:1 scheme using a random number generator. On the day of surgery, a syringe containing either dexamethasone (0.5 mg/kg; maximum dose, 20 mg) or volume-equivalent 0.9% normal saline was then delivered to the anesthesiologist. Both the study drug and placebo were in identical packaging. The study drug was administered parenterally at the start of the operation. All nurses, anesthesiologists, surgeons, patients, patient guardians, and data collectors were blinded as to whether the patient received the dexamethasone or 0.9% normal saline.

The operation and postoperative care were standardized. All patients received a single dose of parenteral perioperative antibiotics. All tonsillectomies were performed in an extracapsular fashion using monopolar electrocautery (12 W fulgurate) and a spatula-tip. Bleeding was controlled with suction cautery (12-15 W fulgurate). Postoperatively, study patients did not receive any dexamethasone. Analgesic strategies consisted of acetaminophen with or without codeine or hydrocodone, depending on age, severity of pain, and surgical indication. Ibuprofen and any other nonsteroidal anti-inflammatory drugs were not prescribed during the postoperative period. Ondansetron was administered intraoperatively for nausea as a single parenteral dose. Promethazine was administered parenterally every 6 hours as needed for breakthrough nausea. Patients were prescribed oral antibiotics postoperatively for 5 days.

All patients had strict discharge instructions to return to the emergency department of the medical center for any signs of postoperative bleeding. On or shortly after postoperative day 14, the patient and their guardian completed a bleeding questionnaire (eMethods, available at http://www.jama.com) that was reviewed and recorded into a secure database.

The data safety and monitoring board performed an interim analysis after approximately 50% of the patients had been enrolled and their postoperative data collected, and concluded the data did not meet criteria for stopping the trial.

Study Patients

Eligible patients aged between 3 and 18 years underwent tonsillectomy by electrocautery for the indication of sleep disordered breathing or infectious tonsillitis at 2 academic medical centers (Massachusetts Eye and Ear Infirmary and Naval Medical Center San Diego). Exclusion criteria included a known personal or family history of any bleeding disorder; use of corticosteroid medications within 2 weeks of surgery, including topical nasal corticosteroids; and use of an alternative surgical technique (FIGURE 1).

Outcome Measures

The primary outcome measure for the trial was postoperative bleeding stratified by severity and is defined in the BOX. Secondary outcomes included postoperative bleeding rate stratified by age, indication for surgery, type of surgery, and surgeon.

Power Calculation

The EAST statistical software program (Cytel Inc) was used to calculate the sample size assuming a power of 90%, $\alpha = .25$, and an interim analysis at 50% of patient accrual, with early stopping for increased bleeding rates in the dexamethasone group. The primary noninferiority hypothesis required that the dexamethasone group had no more than a 5% absolute increase in the rate of bleeding compared with the placebo group. Our calculated necessary sample size was 298 patients (149 in the dexamethasone group and 149 in the placebo group). The sample size was increased to 305 after factoring in the stopping criteria for the interval analysis.

The noninferiority margin of 5% was determined by several methods. The first method was to query the authors about what they thought an acceptable difference in bleeding rates would be between the corticosteroid and saline groups. At the institution of the senior author (C.J.H.) where a majority of the cases were performed, the pediatric posttonsillectomy bleeding rate was 2.5% from their 2010 quality and outcome report. The US national benchmark is 2.2% to 7.8%. The authors believed we should not exceed the upper limit of the US benchmark, a difference of approximately 5%. A recent commentary[10] on posttonsillectomy hemorrhage discussed "normal" bleeding rates (defined as mean plus 2 SDs) of 4.5% (mean) plus 9.4% (2 SDs), suggesting a maximum bleeding rate of 13.9%. Our 5% margin is within this parameter. In addition, we reviewed the literature for studies in which posttonsillectomy bleeding was an objective (primary or secondary) and the methods section discussed use (or not use) of perioperative corticosteroids.[9,11-20] We found that studies using perioperative corticosteroids had a 2.8% higher mean bleeding rate than those studies that did not use corticosteroids. The authors believe anything more than double that margin, approximately 5%, would be unsafe.

Statistical Analysis

A noninferiority study was chosen to demonstrate that dexamethasone was not associated with a clinically significant increase in postoperative bleeding rate compared with placebo in children undergoing tonsillectomy. Consistent with the noninferiority design, the null hypothesis states that the bleeding rate in patients receiving perioperative dexamethasone differed from the bleeding rate in patients receiving perioperative placebo; the alternative hypothesis states that the bleeding rate with dexamethasone is not greater than placebo by more than the noninferiority margin. This noninferiority margin was set at 5%, meaning a difference in bleeding rates that did not exceed 5% would be taken as evidence that the bleeding with dexamethasone is not greater than that with placebo by more than 5%.

The overall significance level was .025 for a 1-sided test; sample size was such that the power to detect the difference of 5% was 0.90. This study was designed as a group sequential trial, with an interim look at 50% information (which in this setting is 50% accrual). Sample size calculations assuming an O'Brien-Fleming spending function specified the need to recruit a total of 305 patients to this study. Sample size was inflated by 5% to accommodate the expected dropout rate, thus increasing the total number of patients to 320.

The interim analysis was performed by testing the difference in level III bleeding rates between the groups and by constructing confidence intervals around the difference in the proportions of children experiencing bleeding. Using the EAST software, it was determined that at the interim analysis, one would test the alternative hypothesis of equivalent rates of bleeding if P value for testing for a difference in bleeding rates was .0015 or smaller. Using the confidence interval approach, we concluded that dexamethasone increases the rate of bleeding over placebo if the confidence interval for the difference in rates had an upper bound greater than 5%.

Baseline characteristics were compared using the χ^2, Fisher exact, or Wilcoxon rank sum tests. A 1-sided confidence interval approach was used to compare the bleeding rate between the 2 groups. The primary analysis was performed on an intention-to-treat basis, where participants lost to follow-up were included and presumed to be not having bleeding episodes. The per-protocol analysis was also performed. Adjusted analysis was also performed obtaining a difference in predicted probabilities of bleeding between the 2 groups by use of logistic regression. Analyses were performed on an intention-to-treat and per-protocol basis. SAS version 9.2 (SAS Institute) was used and $P < .05$ was considered statistically significant.

Box. Severity Levels of Bleeding

I. All children who reported to have any history of postoperative hemorrhage, whether or not there was clinical evidence.

II. All children who required inpatient admission for postoperative hemorrhage regardless of the need for operative intervention. This level excludes children undergoing evaluation in the emergency department for reported postoperative hemorrhage who had no evidence of clot formation or hemorrhage and were deemed safe for discharge.

III. All children who required return to the operating department for control of postoperative bleeding.

RESULTS

A total of 314 patients were enrolled between July 15, 2010, and December 20, 2011 (Figure 1). The trial ended once data from at least 305 patients had been recorded. One hundred fifty-seven pa-

Table 1. Characteristics of Study Patients[a]

Characteristics	Dexamethasone (n = 157)	Saline (n = 157)	*P* Value
Age, median (IQR), y	6 (4-9)	6 (4-8)	.19
Male sex	88 (56.1)	82 (52.2)	.50
Reason for surgery			
Obstructive sleep apnea	127 (80.9)	125 (79.6)	.87
Tonsillitis	16 (10.2)	14 (8.9)	
Obstructive sleep apnea and tonsillitis	13 (8.3)	17 (10.8)	
Other[b]	1 (0.6)	1 (0.6)	
Surgery type			
Tonsillectomy	16 (10.2)	15 (9.6)	>.99
Tonsillectomy and adenoidectomy	141 (89.8)	141 (89.8)	
Revision tonsillectomy	0 (0)	1 (0.6)	
Operating surgeon			
Surgeon 1	8 (5.1)	9 (5.7)	.79
Surgeon 2	2 (1.3)	2 (1.3)	
Surgeon 3	72 (45.9)	82 (52.2)	
Surgeon 4	60 (38.2)	50 (31.9)	
Surgeon 5	15 (9.5)	14 (8.9)	

Abbreviation: IQR, interquartile range.
[a]Data are shown as No. (%) unless otherwise specifed. Obstructive sleep apnea included obstructive sleep apnea, adenotonsillar hypertrophy, hypertrophy, sleep disordered breathing, and snoring. Tonsillitis included tonsillitis, recurrent tonsillitis, chronic tonsillitis, recurrent pharyngitis, and peritonsillar abscess.
[b]Included symptomatic uvular edema or a diagnosis of periodic fevers, aphthous stomatitis, pharyngitis, and adenitis.

tients were randomly assigned to receive placebo and 157 patients were randomly assigned to receive dexamethasone. TABLE 1 shows patient demographics, surgical indications, surgeries performed, and operating surgeon. Six patients (1.9%) were lost to follow-up (2 patients from the dexamethasone group and 4 patients from the placebo group).

Three patients (1.0%) received postoperative corticosteroids in addition to the study medication (1 patient from the dexamethasone group and 2 from the placebo group). Two of the 3 patients received a single dose either for symptomatic uvular edema or periodic fevers (1 patient carried a diagnosis of periodic fevers, aphthous stomatitis, pharyngitis, and adenitis). One patient in the saline group received postoperative corticosteroids on the day of surgery for 5 days due to exacerbation of asthma.

Seventeen patients in the dexamethasone group reported bleeding events (11 patients with level I, 3 with level II, and 3 with level III bleeding events were reported). Thirteen patients in the placebo group reported bleeding events (7 patients with level I, 5 with level II, and 1 with level III bleeding events were reported). One patient in the placebo group had multiple bleeding events (a level II bleed on postoperative day 12 and a level III bleed on postoperative day 16) and was counted as level II bleeding. The overall rate of bleeding events for all levels was 30 out of 314 (9.6%; 95% CI, 6.5%-13.4%).

Four patients had primary bleeding events, which are defined as occurring within 24 hours of surgery. Two patients were from the dexamethasone group (1 patient with level II bleeding and 1 with level III bleeding) and 2 patients were from the placebo group (both were level II bleeding).

Our intention-to-treat analysis and per-protocol analysis demonstrated similar results (TABLE 2). The dexamethasone treatment failed to show noninferiority for the level I bleeding, but did demonstrate that the bleeding rate with dexamethasone is not more than 5% greater than that with placebo (noninferiority) for both level II and III bleeding events. The data was stratified for primary vs secondary bleeding events and a decrease in level II and level III bleeding events in both groups was noted. TABLE 3 shows the per-protocol analysis excluding the 6 patients who were lost to follow-up and the 3 patients who received postoperative corticosteroids (including the 4 patients who experienced primary bleeding events).

Secondary analysis was performed to evaluate bleeding rates by age, indication, surgery type, and surgeon. When stratified for the above criteria, there was no significant association found with the more clinically important level II and III bleeding events. Age was found to be unevenly distributed for level I bleeding; therefore, age-adjusted analysis was conducted for level I bleeding. Predicted probability of level I bleeding was estimated for both treatments by setting for a mean age of 6.7 years. The dexamethasone treatment failed to show noninferiority for the level I bleeding after adjusting for age difference (FIGURE 2).

There were no deaths or adverse event outcomes involving any of the study patients.

COMMENT

Perioperative dexamethasone use in pediatric tonsillectomy is a common practice with strong support in the literature. A Cochrane review deemed dexamethasone "effective and relatively safe" and strongly recommended its use as a single perioperative dose. Clinical practice guidelines from the American Academy of Otolaryngology–Head and Neck Surgery also recommend this practice.[8,21] However, there are concerns about bleeding complications associated with dexamethasone use in tonsillectomy. Posttonsillectomy bleeding rates of 6.1% were reported in patients "injected with topical vasoconstrictors and corticosteroids" compared with 1.8% in the patients not injected with either drugs.[11] An audit of posttonsillectomy hemorrhage showed increased bleeding rates following initiation of corticosteroids, nonsteroidal anti-inflammatory drugs, and bipolar diathermy.[22] Both of these studies were retrospective and could not control confounding factors that might also be responsible for postoperative bleeding. A prospective trial of perioperative corti-

costeroids reported deleterious effects of corticosteroids on children undergoing tonsillectomy.[9] It appeared that dexamethasone was associated with an increased risk of postoperative bleeding. However, because posttonsillectomy bleeding was not the primary outcome variable, the study did not have sufficient statistical power to convincingly demonstrate that the corticosteroids caused postoperative hemorrhage. Additionally, surgical techniques were not standardized and there was an unexpectedly large number of primary bleeding events.[12,23]

We designed our trial to definitively resolve the question of dexamethasone causing postoperative bleeding following tonsillectomy in children. We selected a dose of 0.5 mg/kg up to a maximum of 20 mg because it was the preferred dose used clinically by the study authors. This dose was associated with significant bleeding in the study by Czarnetzki et al.[9] A recent meta-analysis[24] of prospective studies of dexamethasone use in pediatric tonsillectomy found a significantly increased odds of bleeding when stratifying for dose ranges of 0.4 mg/kg to 0.6 mg/kg.

A noninferiority study design was chosen to demonstrate that dexamethasone does not increase bleeding rates more than placebo by the prespecified noninferiority margin of 5%. To review, a noninferiority trial (1-sided test) rejects the null hypothesis that there is a difference between the 2 groups. This method is different from an equivalence study (2-sided test) and the opposite of a traditional superiority study where the null hypothesis assumes no difference between the 2 groups. Our outcome of interest was postoperative bleeding in the dexamethasone group. We hypothesized that there would not be more bleeding events in the dexamethasone group compared with the saline placebo group. It was not necessary to perform a 2-sided equivalence trial showing a dexamethasone association with either more or fewer bleeding events than saline placebo because we did not hypothesize any protective effect of dexamethasone against bleeding.

Posttonsillectomy hemorrhage must be evaluated in the context of primary (bleeding in the first 24 hours after tonsillectomy due to inadequate hemostatic technique) vs secondary (bleeding occurring more than 24 hours following tonsillectomy) bleeding.[25] In our study, there were 4 primary bleeding events, 2 in each group. When reporting postoperative hemorrhage, stratification of postoperative bleeding into primary and secondary events and the severity of bleeding should be characterized. Reporting of bleeding severity has not been standardized, complicating the interpretation of many studies of posttonsillectomy bleeding. By stratifying bleeding severity (Box), we could place more emphasis on level II and III bleeding events because they

Table 2. Bleeding Event Rate of the Intention-to-Treat and Per-Protocol Analyses[a]

Bleeding Event	No./Total No. (%) of Patients		% Difference (Upper Limit 97.5% CI)	Noninferiority *P* Value
	Dexamethasone	Saline		
Intention-to-treat analysis				
Level I	11/157 (7.0)	7/157 (4.5)	2.6 (7.7)	.17
Level II	3/157 (1.9)	5/157 (3.2)	–1.3 (2.2)	<.001
Level III	3/157 (1.9)	1/157 (0.6)	1.3 (3.8)	.002
Per-protocol analysis				
Level I	11/154 (7.1)	7/151 (4.6)	2.5 (7.8)	.18
Level II	3/154 (2.0)	5/151 (3.3)	–1.4 (2.2)	<.001
Level III	3/154 (2.0)	1/151 (0.7)	1.3 (3.8)	.002

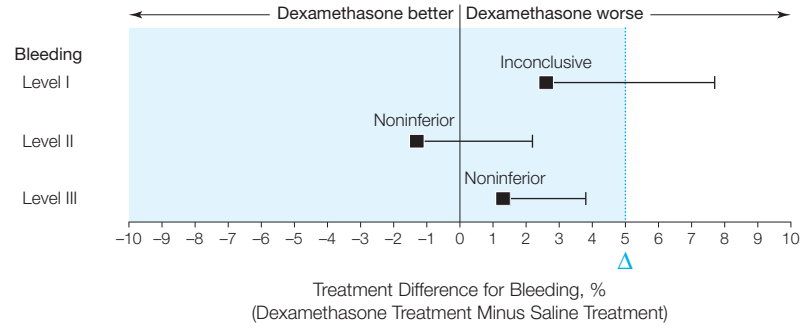
[a]Six patients who were lost to follow-up and 3 patients who received postoperative corticosteroids were excluded from the per-protocol analysis. Level I bleeding event indicates self-reported or parent-reported postoperative bleeding; level II bleeding event, required inpatient admission for postoperative bleeding; and level III bleeding event, required reoperation to control postoperative bleeding.

Table 3. Bleeding Event Rate of Per-Protocol Analysis Excluding Primary Bleeding Events[a]

Bleeding Event	No. (%) of Patients		% Difference (1-Sided 97.5% CI)	Noninferiority *P* Value
	Dexamethasone (n = 154)	Saline (n = 151)		
Level I	11 (7.1)	7 (4.6)	2.5 (0-7.8)	.18
Level II	2 (1.3)	3 (2.0)	–0.7 (0-2.2)	<.001
Level III	2 (1.3)	1 (0.7)	0.6 (0-2.8)	<.001

[a]Level I bleeding event indicates self-reported or parent-reported postoperative bleeding; level II bleeding event, required inpatient admission for postoperative bleeding; and level III bleeding event, required reoperation to control postoperative bleeding.

Figure 2. Bleeding Event Rate by Noninferiority Intention-to-Treat Analysis



Error bars indicate 1-sided 97.5% CIs. Tinted area indicates zone of inferiority. The noninferiority margin was set at 5%, meaning a difference in bleeding rates that did not exceed 5% would be taken as evidence that the bleeding with dexamethasone is not greater than that with placebo by more than 5%. Level I bleeding event indicates self-reported or parent-reported postoperative bleeding; level II bleeding event, required inpatient admission for postoperative bleeding; and level III bleeding event, required reoperation to control postoperative bleeding.

were more objective than level I (self-reported) bleeding and are associated with greater risk to patients. Although we counseled all of our parents to report any bleeding event, many patients with level I bleeding events were nondescript and self-limited. In the majority of these cases, parents did not report bleeding events until the follow-up appointment, and then only when prompted by the questionnaire. This was explained by the minor or questionable nature of these bleeding events. Some examples included a "warm sensation in the mouth" or a "bloodstain on a pillow case." The level II and III postoperative bleeding events are a more reliable indicator for complications because they are documented by treating physicians. These events are also associated with substantial morbidity and cost that occurs with prolonged hospitalization and the need for reoperations.

An inappropriately selected, noninferiority margin can result in an improperly powered study. We used level II and III bleeding events to establish our study size because these events are more objective and clinically important than level I bleeding events. We used our institutions' outcomes data for level II and II bleeding events coupled with published literature reports to determine the noninferiority margin of 5% for our study. We were limited in this approach because most published studies did not report bleeding severity. Other potential limitations include the use of multiple surgeons and institutions. Standardization of procedures should have minimized the effect of this potential limitation. We did not stratify dosing of dexamethasone. We only used a single, routinely used dose that was commonly cited in the literature. Graded dexamethasone doses would have required a much larger sample size, diminishing the feasibility of completing this study.

In conclusion, in this prospective, randomized study of 314 children undergoing tonsillectomy, perioperative dexamethasone administration was not associated with more level II or III bleeding events than placebo as shown by noninferiority. Increased subjective (level I) bleeding events caused by dexamethasone could not be excluded because the noninferiority threshold of 5% was crossed.

Author Contributions: Drs Gallagher and Hartnick had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Gallagher, Ference, Keamy, Hartnick.
Acquisition of data: Gallagher, Hill, Ojha, Keamy, Williams, Hansen, Collins, Setlur, Capra, Brigger, Hartnick.
Analysis and interpretation of data: Gallagher, Hill, Ojha, Maurer, Brigger.
Drafting of the manuscript: Gallagher, Ference, Collins, Setlur, Hartnick.
Critical revision of the manuscript for important intellectual content: Gallagher, Hill, Ojha, Ference, Keamy, Williams, Hansen, Maurer, Setlur, Capra, Brigger, Hartnick.
Statistical analysis: Ference, Maurer, Brigger, Hartnick.
Administrative, technical, or material support: Gallagher, Hill, Ference, Collins, Setlur, Capra.
Study supervision: Gallagher, Keamy, Brigger, Hartnick.
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Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the US Department of the Navy, US Department of Defense, or the US government.
Online-Only Material: eMethods is available at http://www.jama.com.
Additional Contributions: Michael Cunningham, MD (Boston Children's Hospital, Boston, Massachusetts), and Donna Neuberg, PhD (Harvard School of Public Health, Boston, Massachusetts), provided comments on the analysis of the manuscript; James Ware, PhD (Harvard School of Public Health, Boston, Massachusetts), provided comments on the design of the manuscript; and Christine Finn, PhD (Massachusetts Eye and Ear Infirmary, Boston, Massachusetts), Cheryl McNeal (Naval Medical Center, San Diego, California), Vanessa DeGuzman (Massachusetts Eye and Ear Infirmary, Boston, Massachusetts), and David Baxter (Harvard Vanguard Associates, Boston, Massachusetts) helped with the acquisition of data. Drs Cunningham, Ware, and Neuberg received no compensation and Dr Finn, Ms McNeal, Ms DeGuzman, and Mr Baxter were all compensated for their contributions.

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Growth After Adenotonsillectomy for Obstructive Sleep Apnea: An RCT

WHAT'S KNOWN ON THIS SUBJECT: Growth failure has been frequently reported in children who have obstructive sleep apnea syndrome (OSAS) owing to adenotonsillar hypertrophy. Adenotonsillectomy (AT) has been reported to accelerate weight gain in children who have OSAS in nonrandomized uncontrolled studies.

WHAT THIS STUDY ADDS: This randomized controlled trial of AT for pediatric OSAS demonstrated significantly greater weight increases 7 months after AT in all weight categories. AT normalizes weight in children who have failure to thrive, but increases risk for obesity in overweight children.

abstract

NIH FREE

BACKGROUND AND OBJECTIVES: Adenotonsillectomy for obstructive sleep apnea syndrome (OSAS) may lead to weight gain, which can have deleterious health effects when leading to obesity. However, previous data have been from nonrandomized uncontrolled studies, limiting inferences. This study examined the anthropometric changes over a 7-month interval in a randomized controlled trial of adenotonsillectomy for OSAS, the Childhood Adenotonsillectomy Trial.

METHODS: A total of 464 children who had OSAS (average apnea/hypopnea index [AHI] 5.1/hour), aged 5 to 9.9 years, were randomized to Early Adenotonsillectomy (eAT) or Watchful Waiting and Supportive Care (WWSC). Polysomnography and anthropometry were performed at baseline and 7-month follow-up. Multivariable regression modeling was used to predict the change in weight and growth indices.

RESULTS: Interval increases in the BMI *z* score (0.13 vs 0.31) was observed in both the WWSC and eAT intervention arms, respectively, but were greater with eAT ($P < .0001$). Statistical modeling showed that BMI *z* score increased significantly more in association with eAT after considering the influences of baseline weight and AHI. A greater proportion of overweight children randomized to eAT compared with WWSC developed obesity over the 7-month interval (52% vs 21%; $P < .05$). Race, gender, and follow-up AHI were not significantly associated with BMI *z* score change.

CONCLUSIONS: eAT for OSAS in children results in clinically significant greater than expected weight gain, even in children overweight at baseline. The increase in adiposity in overweight children places them at further risk for OSAS and the adverse consequences of obesity. Monitoring weight, nutritional counseling, and encouragement of physical activity should be considered after eAT for OSAS. *Pediatrics* 2014;134:282–289

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KEY WORDS
BMI, height, weight

ABBREVIATIONS
AHI—apnea/hypopnea index
AT—adenotonsillectomy
eAT—early adenotonsillectomy
FTT—failure to thrive
ODI—oxygen desaturation index
OSAS—obstructive sleep apnea syndrome
PSG—polysomnography
WWSC—Watchful Waiting and Supportive Care

Dr Katz participated in the collection and interpretation of the data and drafted and edited the manuscript; Dr Moore was primarily responsible for analyzing and interpreting the data and editing the manuscript; Drs Rosen, Mitchell, Amin, Arens, Muzumdar, Marcus, Paruthi, and Willging participated in the collection and interpretation of the data and edited the manuscript; Dr Chervin participated in the study design, oversight of data collection, interpretation of the data, and editing of the manuscript; Dr Redline designed the study, participated in the interpretation of the data, and edited the manuscript; and all authors approved the final manuscript as submitted.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00560859), Childhood Adenotonsillectomy Study for Children With OSAS (CHAT).

(Continued on last page)

Adequate growth trajectory is an important measure of wellness in children. Growth failure has been frequently reported (27%–56%) in children who have obstructive sleep apnea syndrome (OSAS).[1–5] Adenotonsillar hypertrophy is the primary cause of OSAS in children, and is usually treated with adenotonsillectomy (AT). AT has been reported to accelerate weight[6–14] in children with baseline failure to thrive (FTT),[1,3,4,15] normal weight patients,[9,11,14,16–20] obese individuals,[9,13,16,21,22] and infants.[10] The majority of studies also have demonstrated an increase in the height growth rate after AT for OSAS,[3,6,11,17,23,24] but other studies reported no significant differences.[9,12] Whereas accelerated weight gain post-AT is likely beneficial in the setting of baseline FTT, an exaggerated increase in adiposity in overweight children could increase their risk for OSAS recurrence and obesity-related morbidity.

The current study uses longitudinal anthropometric data from a large-scale, randomized controlled trial of AT for polysomnographically verified OSAS in a diverse sample of prepubertal children. The primary aim of the study is to determine if AT for OSAS leads to weight gain in children across a wide range of BMI. The secondary goal is to assess the influence of race, baseline weight, OSAS severity, and residual OSAS on growth after AT. Identifying children at risk for obesity after AT has considerable importance owing to the adverse consequences of childhood obesity.[25]

METHODS

Study Sample and Recruitment

A detailed description of this multicenter, single-blind, randomized controlled trial of AT for OSAS in children has been published[26] and the primary cognitive and behavioral outcomes have been reported.[27] The influence of AT on growth was an a priori secondary outcome for this study. Briefly, children referred for evaluation of OSAS, tonsillar hypertrophy, or frequent snoring were recruited primarily from general pediatric, sleep, and otolaryngology clinics, as well as other community sources from January 2008 to September 2011 (Fig 1). Children were eligible for study entry if they were 5 to 9.9 years of age, had a history of snoring, tonsillar hypertrophy, and were considered to be surgical candidates for AT by an otolaryngologist. Exclusion criteria included a history of recurrent tonsillitis, extreme obesity (BMI *z* score ≥3), therapy for failure to thrive, medications for psychiatric or behavioral disorders (including attention deficit hyperactivity disorder), developmental delays requiring school accommodations, and known genetic, craniofacial, neurologic, or psychiatric conditions likely to affect the airway, cognition, or behavior. Children were screened further by standardized polysomnography (PSG). Children who had OSAS, defined as an obstructive apnea-hypopnea index (AHI) between 2 and 30/hour or an obstructive apnea index between 1 and 20/hour, and without prolonged oxygen desaturation time (arterial oxygen saturation [SpO_2] <90% that was <2% of total sleep time) were eligible for study participation.

Children were randomized to either early adenotonsillectomy (eAT; surgery within 4 weeks of randomization) or to Watchful Waiting with Supportive Care (WWSC). Repeat PSG and anthropometry were performed at approximately 7 months after randomization. The study was approved by the Institutional Review Board of each institution. Informed consent was obtained from caregivers, and assent from children ≥7 years of age.

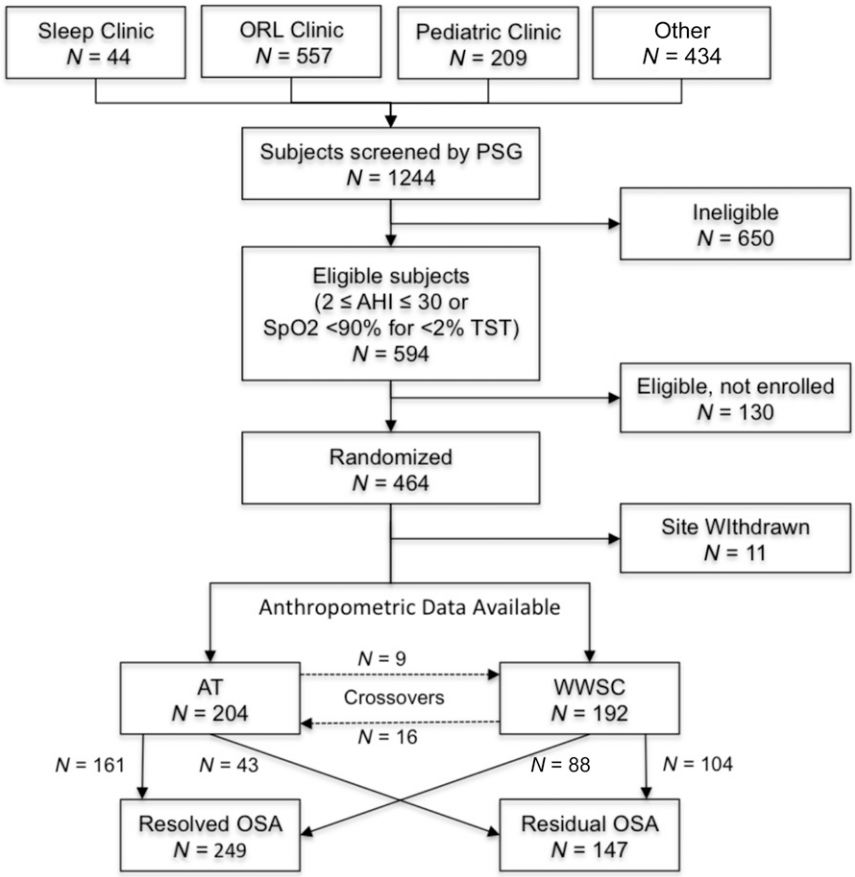

FIGURE 1
Flow diagram of subject enrollment for whom anthropometric data were available.

Protocol

Anthropometric measurements were obtained at baseline and at 7-month follow-up using a standardized protocol by centrally trained and certified personnel. Measurements were made by a 2-member team that included a "measurer" and a "recorder." All children underwent full, in-laboratory PSG by study-certified technicians according to a standardized protocol, using similar sensors, and following American Academy of Sleep Medicine guidelines.[28] The AHI was defined as the numbers of obstructive apnea and hypopneas per hour of sleep. The arousal index was defined as the number of electrocortical arousals per hour of sleep. The oxygen desaturation index (ODI) was defined as the number of 3% oxygen desaturation per hour of sleep. The sleep duration and physical activity levels of each child were determined by parental questionnaire at the baseline visit. Weight classification definitions were based on percentiles for age and gender as follows: FTT, <5th percentile; normal, ≥5th and <85th; overweight, ≥85th and <95th; and obese, ≥95th.[29]

Statistical Considerations

Comparisons of demographic, sleep, activity, and polysomnographic data within and between groups were conducted by using unpaired *t* tests or χ^2 and Fisher's exact tests. The primary outcome was change in BMI *z* score, with secondary analyses examining change in absolute BMI, weight, weight *z* score, height, height *z* score, and BMI and Weight velocities (change in variable per time in years). The primary analysis was an intention to treat analysis comparing anthropometric outcomes in children randomized to eAT versus WWSC (noted as interval change between groups). Analyses were adjusted for factors that included site, age (5 to 7 vs 8 to 9 years), race (African American versus other), baseline weight status (overweight versus non-overweight), gender, season, and baseline AHI. A series of multivariable regression models were used to also consider the possible influences of physical activity, sleep duration, and various polysomnographic indices. Secondary analyses also examined groups defined according to therapy received (eAT versus WWSC) and according to resolution of OSAS at follow-up (AHI <2/hours and obstructive apnea index <1/hour) and tested for the presence of effect modification of treatment group with race, age, weight status, and gender. Analyses were conducted for the raw and *z* scores for weight, height, and BMI. Group differences were analyzed 3 ways; as an intention to treat analysis, as an analysis based on actual treatment received, and according to resolution of OSAS. Variables with highly skewed distributions were log transformed for analysis. Exploratory analyses were performed by using the reported sleep duration, daily running duration, and polysomnographic variables. Owing to the large number of 0 values, the percentage of time with an oxygen saturation <90% was included in the models as a binary variable (0 vs >0). Analyses were performed by using SAS 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Figure 1 demonstrates the flow of participants. Baseline anthropometric, sleep, and activity characteristics were not significantly different between intervention groups (Table 1). Approximately half of the subjects were overweight or obese. Follow-up anthropometric data were available for 98% of participants. Only 14 children were considered FTT at baseline (7 eAT, 7 WWSC). Initial analyses indicated that patterns of growth change were similar for FFT and normal weight children, and for overweight and obese children. Therefore, the weight classification data are reported as a binary variable, not overweight (<85th percentile) and overweight or obese (≥85th percentile).

Baseline polysomnographic data were not significantly different between intervention groups (Table 2). At follow-up, the eAT group had greater reductions compared with the WWSC group in the AHI, arousal index, rapid eye movement (REM) ODI, and the percentage of sleep time <95% oxygen saturation (Table 2).

Weight/BMI

The weight, weight *z* scores, BMI, and BMI *z* scores all increased during the study interval in both the eAT and WWSC groups (Table 3). After adjusting for baseline weight status and other covariates, regression modeling demonstrated that eAT was associated with a significantly larger increase in the weight, weight velocity, weight *z* scores, BMI, BMI velocity, and BMI *z* scores, compared with the WWSC group. Multivariable regression modeling furthermore showed that BMI *z* score change was independently and positively associated with eAT, baseline BMI <85% percentile, and baseline but not follow-up AHI. After considering these variables, BMI *z* score change was not associated with age, gender, or race (Table 4). Exploratory models did not identify BMI *z* score change to be associated with reported duration of sleep or daily running activity. Of the polysomnographic measures, only the baseline REM ODI and decrease in REM ODI had a significant positive relationship to the interval change in the BMI *z* score (after adjusting for baseline AHI). There was no evidence of interactions between intervention arm and baseline weight status, race, age, or gender. The findings for the weight *z* score were generally similar to the BMI *z* score in all regression models.

TABLE 1 Demographic, Sleep, and Activity Data

	eAT (n = 204)	WWSC (n = 192)	P value
Age (y)	7.03 (1.41)	6.99 (1.39)	.73
Gender (% female)	54	49	.12
Race (% African American)	55	54	.74
Failure to thrive (%)			
Baseline	3.4	3.6	.58
Follow-up	0.9	2.2	.25
Interval change P value	.055	.766	.38
Overweight and obese (%)			
Baseline	47.4	46.7	.89
Follow-up	51.8	48.7	.51
Interval change P value	.34	.67	.15
Obese (%)			
Baseline	32.7	33.5	.87
Follow-up	36.7	35.0	.69
Interval change P value	.37	.74	.57
Sleep duration (h)			
Baseline	9.46 (1.54)	9.59 (1.39)	.40
Follow-up	9.38 (1.28)	9.56 (1.30)	.17
Interval change P value	.48	.98	.64
Running (min/d)			
Baseline	5.22 (11.33)	7.38 (12.40)	.05
Follow-up	6.76 (11.94)	7.62 (12.82)	.49
Interval change P value	.07	.63	.44

Mean (SD).

There were 14 children who were defined as FTT at baseline (7 eAT and 7 WWSC). In the eAT group, all 7 of these children increased their weight z scores at follow-up ($P < .05$), and entered the normal range. In the WWSC group, 5/7 of the FTT children increased their weight z score, 3 of whom entered the normal range ($P = .13$). Considering children who had a normal BMI, 16 children (15%) in the eAT group became overweight at follow-up, compared with 17 (17%) in the WWSC group ($P = .72$). Considering only children who were overweight at baseline, 14 (52%) in the eAT group became obese at follow-up, compared with only 5 (21%) in the WWSC group ($P < .05$). Both children <10th percentile and between the 10th and 85th percentile had a significant increase in the BMI z score in the eAT group compared with the WWSC group (Fig 2A). Children who were overweight at baseline and randomized to eAT had a larger absolute BMI change compared with comparable children randomized to WWSC (Fig 2B). Table 5 further shows the absolute weight change as a function of age, treatment group, and baseline weight.

TABLE 2 Polysomnographic Data

	eAT (n = 204)	WWSC (n = 192)	P value
Apnea/hypopnea index (events/h)			
Baseline	5.22 (2.05)	5.00 (2.12)	.46
Follow-up	0.71 (4.22)	2.12 (5.47)	<.0001
Interval change P value	<.0001	<.0001	<.0001
Arousal index (events/h)			
Baseline	8.08 (1.43)	7.85 (1.45)	.30
Follow-up	6.69 (1.42)	7.69 (1.57)	.0007
Interval change P value	<.0001	.64	<.0001
Slow wave sleep (% TST)			
Baseline	31.5 (7.2)	31.6 (7.6)	.84
Follow-up	29.9 (7.0)	30.9 (6.8)	.14
Interval change P value	.01	.08	.48
REM sleep (% TST)			
Baseline	18.6 (4.2)	18.2 (4.3)	.24
Follow-up	18.7 (4.0)	17.8 (4.2)	.04
Interval change P value	.85	.36	.61
ODI in REM ≤3% (events/h)			
Baseline	10.6 (3.3)	9.1 (3.6)	.21
Follow-up	3.9 (6.0)	6.5 (3.9)	<.0001
Interval change P value	<.0001	.0008	<.0001
Oxygen saturation ≤95% (% of total sleep time)			
Baseline	1.8 (5.8)	1.7 (5.8)	.73
Follow-up	0.8 (6.0)	1.4 (5.5)	.004
Interval change P value	<.0001	.023	.012

Mean (SD).

Height

An increase in height over the 7-month follow-up period was observed in both the eAT and WWSC groups. The follow-up height z score was slightly but significantly higher in the eAT group (Table 3). However, the interval changes in height and height z score, as well as the height velocity measures (data not shown) were not significantly different between the eAT and WWSC groups. Height change was not associated with age, race, gender, treatment arm, site, weight status, baseline AHI, or follow-up AHI.

Other Secondary Analyses

Approximately 5% of children did not receive the assigned intervention do to parental preferences or treatment failure. There were no significant differences between the intention-to-treat analysis and that based on actual intervention received. Analyzing the changes in height, weight, and BMI as a "velocity" (expressed as changes over the individual time intervals between measurements) was comparable to the primary analyses. In an alternative analysis, children whose OSAS resolved did not differ in regard to change

TABLE 3 Anthropometric Measures in the Early Adenotonsillectomy Compared With the Watchful Waiting Group at Baseline and Follow-up

	eAT (n = 204)	WWSC (n = 192)	Unadjusted P	P value 1	P value 2
Wt (kg)					
Baseline	31.21 (12.96)	30.45 (12.37)	.524		
Follow-up	34.58 (14.11)	32.76 (12.60)	.175		
P value	<.0001	<.0001			
Interval change between groups			.005	.004	.013
Wt (z score)					
Baseline	1.02 (1.32)	0.99 (1.23)	.748		
Follow-up	1.20 (1.22)	1.03 (1.16)	.152		
P value	<.0001	<.0001			
Interval change between groups			.003	.001	.001
BMI (kg/m^2)					
Baseline	19.10 (5.02)	18.92 (4.80)	.682		
Follow-up	19.98 (5.27)	19.27 (4.72)	.157		
P value	<.0001	<.0001			
Interval change between groups			.015	.014	.026
BMI (z score)					
Baseline	0.87 (1.35)	0.87 (1.25)	.998		
Follow-up	1.18 (1.21)	1.00 (1.27)	.163		
P value	<.0001	<.0001			
Interval change between groups			.004	.003	.003
Height (cm)					
Baseline	125.5 (11.30)	124.8 (10.76)	.503		
Follow-up	129.2 (11.17)	128.5 (10.57)	.479		
P value	<.0001	<.0001			
Interval change between groups			.113	.068	.070
Height (z score)					
Baseline	0.69 (1.02)	0.62 (0.99)	.445		
Follow-up	0.74 (1.02)	0.62 (0.96)	.235		
P value	.0022	.2612			
Interval change between groups			.412	.371	.295

P value 1 adjusts for site, race (African American vs non-African American), age (5–7 vs 8–10 y), and weight (<85th vs ≥85th percentile).

P value 2 adjusts for site, race (African American vs non-African American), age (5–7 vs 8–10 y), and weight (<85th vs ≥85th percentile), gender, season (August to November vs other), baseline Log (AHI), and baseline value of outcome variable.

Mean (SD)

in anthropometric variables compared with children who did not have resolution of OSAS.

DISCUSSION

This randomized controlled trial of eAT for polysomnographically confirmed pediatric OSAS revealed significantly greater increases in weight and BMI z score 7 months after AT as compared with WWSC. After adjusting for demographic variables and overweight status at baseline, eAT was associated with an average increase in BMI z score of 0.12 U compared with WWSC. Furthermore, we observed no evidence of a significant interaction between intervention group and baseline overweight status on change in BMI, indicating that BMI increases associated with eAT occurred in both overweight and non-overweight children. However, overweight but not normal weight children randomized to eAT were more likely to become obese at follow-up compared with children randomized to WWSC. Overweight and obese children also had an increase in the absolute BMI in the eAT compared with the WWSC group. Although not statistically significant, children who were initially classified as FFT tended to be more likely to develop a normal weight when treated with eAT as compared with WWSC. There was no evidence that the influence of eAT varied by gender, race, age, or baseline OSAS severity. Thus, these findings are consistent in demonstrating greater increases in weight in the 7 months after eAT compared with WWSC, and suggest that eAT results in a small overall increase in weight in children regardless of their baseline weight. Thus, in children who are initially FFT, eAT may have a positive effect on reaching targeted weight goals. In contrast, in children who are overweight at baseline, eAT may increase the short-term likelihood of developing obesity.

TABLE 4 Regression Modeling to Predict the Change in BMI z score

Variable	Model 1			Model 2			Model 3		
	β	SE	p	β	SE	p	β	SE	p
eAT	0.121	0.04	.0031	0.116	0.04	.0039	0.136	0.04	.0019
Race (African American)	0.26	0.04	.545	0.005	0.04	.9141	0.021	0.04	.629
Weight <85%	0.206	0.04	<.0001	0.211	0.04	<.0001	0.206	0.04	<.0001
Age (5 to 7 y)	0.054	0.05	.281	0.05	0.05	.308	0.055	0.05	.272
Gender	−0.024	0.04	.563						
Baseline AHI				0.081	0.03	.004			
Follow-up AHI							0.012	0.01	.397

Recruitment site was not a significant variable (not shown). Age variable was 5 to 7 vs 8 to 10 years.

Several previous studies have also reported excessive weight gain post-AT in obese and non-obese children.[16,21,22] Weight gain measured using population z scores has been reported to increase after AT in some uncontrolled studies,[12] but not others.[30–32] However, the observation that untreated children in the WWSC group also significantly increased their weight and BMI z scores during the 7-month follow-up interval underscores the importance of the randomized controlled design of the study in quantifying treatment effects. Previous longitudinal population-based anthropometric studies have observed that school-aged children are increasing their BMI z score over time.[33] The explanation for the increasing

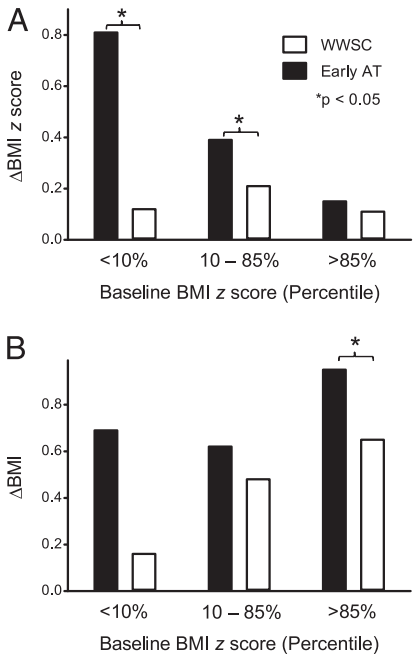

FIGURE 2

Change in the A, BMI *z* score, and B, absolute BMI for both treatment groups as a function of baseline BMI *z* score percentile. The change in BMI *z* score for children who had a baseline BMI *z* score either <10% or between the 10th and 85th percentile was significantly increased in the eAT group compared with the WWSC group. The absolute change in BMI for children who had a baseline BMI *z* score >85th percentile was significantly greater in the eAT group compared with the WWSC group.

incidence of obesity has been attributed to a shift toward sedentary lifestyles and high caloric food choices. Nevertheless, children in the eAT group had greater increases in weight and BMI *z* scores compared with WWSC controls over the study interval, suggesting that AT has an independent effect on weight gain in this population. Analyses showed that non-obese children had the greatest increases in BMI *z* score after AT, consistent with previous studies.[34] Nevertheless, increases in the absolute BMI were also observed in the overweight and obese children, and overweight children treated with eAT were the ones most likely to develop obesity. Thus, the risk for worsening overweight and obesity after AT should be incorporated into the preoperative counseling for at-risk children.

Significant increases in height *z* scores after adenotonsillectomy for pediatric OSAS have been reported in many studies,[3,11,14,16,18] but not others.[9,12] Our results demonstrated no significant differences between the eAT and WWSC groups with regard to postoperative height, although in the eAT group there was a significant increase in the height *z* score after 7 months. Linear height is generally more resistant to changes in nutrition and growth hormone dysregulation than body weight. Also, 1 study reported that an increase in height post-AT was observed in the second 6-month postoperative period, but not the first.[14] Furthermore, a study with a 5-year follow-up demonstrated a significantly increased height post-AT.[35] Nevertheless, the observation that only the eAT group had a statistically significant increase in the height *z* scores over the study interval suggests that perhaps an association would be observed in a larger population of children, with more severe OSAS, or over a longer postoperative interval.

The baseline AHI was positively correlated with increases in weight and BMI *z* scores during the study interval regardless of treatment group or baseline BMI. There are 2 broad mechanisms by which OSAS could mediate alterations in growth. First, the intermittent hypoxemia associated with OSAS may result in metabolic compensation that aims to maintain adequate growth. With improvement of OSAS severity (which was seen in both treatment arms), this metabolic adaption may predispose toward excessive weight gain. We indeed observed a relationship between the baseline REM ODI and change in the REM ODI with growth. Second, children who have OSAS may consume excessive calories in the setting of disrupted metabolism or insufficient sleep.[36] Once the OSAS has been treated, the hormonal dysregulation resolves in the setting of continued high caloric intake. The mechanisms by which AT results in increased weight gain in children who have OSAS include increased caloric intake,[3] unhealthy food choices,[7] decreased caloric expenditure owing to lower work of breathing, resolution of intermittent hypoxemia, and increased growth hormone secretion. Hyperactivity and total daily activity are also reported to decrease after AT, thus potentially contributing to a higher BMI *z* score. Differences in the work of breathing resulting in changes in energy expenditure over the course of the study may also explain the greater weight gain in children who had a higher baseline AHI. Finally, several studies have reported increases in growth velocity after AT in children who had recurrent adenotonsillitis.[8,35] The decreased number of tonsillitis episodes post-AT may reduce inflammation, thereby improving growth.[12] However, it is possible that some of the children in these studies with recurrent infection also had unrecognized OSAS. Alternatively, chronic inflammation per se may mediate the growth-inhibiting effects of adenotonsillar enlargement.

Amin et al reported that 1 year after AT for OSAS, the BMI increased more in the children who had recurrence of OSA after resolution of their apnea measured 6 weeks after AT.[25] In our study, children

TABLE 5 Average Weight (kg) Gain Over 7-Month Study Interval

Age (y)	eAT (*n* = 204)					WWSC (*n* = 192)				
	5	6	7	8	9	5	6	7	8	9
FTT	2.4	2.8	NA	0	NA	1.1	1.4	NA	NA	NA
<10th	2.2	2.3	2.2	2.6	NA	1.2	1.6	1.7	1	3.1
Normal	2.5	2.4	2.9	2.4	3	2	2.2	2.5	1.7	3
Overweight	3.6	2.5	3.9	2.7	6.8	1.6	1.7	4.1	3.9	3.9
Obese	4	5.1	4.5	4	4.7	2.6	3.4	4.7	4.3	4

FTT, <5th percentile; <10th, weight less than the 10th percentile; NA, not available.

who had a higher AHI at baseline, and in particular those who had an elevated REM ODI, had greater postoperative increases in their ponderal indices 7 months after AT. However, there was no significant association between changes in any anthropometric measure and follow-up AHI, or between children with or without OSAS resolution. This paradox may be explained by several mechanisms. First, the AHI may not fully define the severity of OSAS. More precise measures of respiratory effort, such as esophageal manometry, were not made during this study and therefore airflow limitation unassociated with obstruction may have been missed. Secondly, changes in AHI and BMI are correlated, which may limit the ability to discern longitudinal associations between changes in those measures.[37] Third, Amin et al observed a significant increase in the AHI from the 6-month to the 12-month time point, whereas our study followed children only 6 months postoperatively.

There are several limitations of the study that may have influenced our interpretation of the results. First, the follow-up study interval was limited to only 7 months and therefore it is possible that greater changes in anthropometric measures, especially height, would have been seen with a longer follow-up period. Conversely, it is unknown whether the observed increases in weight *z* scores will be sustained long-term. Second, we primarily used BMI *z* scores, which may lead to a "ceiling effect" for children who have high baseline BMI in longitudinal studies.[38] That is, for children who have a high BMI *z* score at baseline, large increases in BMI result in small additional increases in the BMI *z* score. We thus performed an additional analysis using absolute BMI changes along with age in the regression model to establish that excessive weight gain was also observed in obese children.

CONCLUSIONS

This is the first study to evaluate the effect of eAT for OSAS on anthropometric variables using a randomized controlled design including laboratory-based PSG. eAT resulted in greater increases in weight and BMI *z* scores in generally healthy 5- to 9.9-year-old children who had OSAS than did WWSC. Particularly, increases in the BMI *z* score were observed after AT in children who had FTT, normal weight, and overweight. Notably, 51% of overweight children randomized to eAT became obese after eAT over the study interval. OSAS has been shown to have important adverse effects on energy balance and metabolism, and this study suggests that these changes are at least partially reversible after treatment. However, the observation that increases in the BMI *z* score were observed even in overweight children after AT suggests that monitoring weight, nutritional counseling, and encouragement of physical activity are important considerations after surgical intervention for OSAS in children.

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Antiinflammatory Therapy Outcomes for Mild OSA in Children

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BACKGROUND: OSA is highly prevalent in children and usually initially treated by adenotonsillectomy. Nonsurgical alternatives for mild OSA primarily consisting of antiinflammatory approaches have emerged, but their efficacy has not been extensively assessed.

METHODS: A retrospective review of clinically and polysomnographically diagnosed patients with OSA treated between 2007 and 2012 was performed to identify otherwise healthy children ages 2 to 14 years who fulfilled the criteria for mild OSA and who were treated with a combination of intranasal corticosteroid and oral montelukast (OM) for 12 weeks (ICS + OM). A subset of children continued OM treatment for 6 to 12 months.

RESULTS: A total of 3,071 children were diagnosed with OSA, of whom 836 fulfilled mild OSA criteria and 752 received ICS + OM. Overall, beneficial effects occurred in > 80% of the children, with nonadherence being documented in 61 children and adenotonsillectomy being ultimately performed in 12.3%. Follow-up polysomnography in a subset of 445 patients showed normalization of sleep findings in 62%, while 17.1% showed either no improvement or worsening of their OSA. Among the latter, older children (aged > 7 years; OR, 2.3; 95% CI, 1.43-4.13; $P < .001$) and obese children (BMI z-score > 1.65; OR: 6.3; 95% CI, 4.23-11.18; $P < .000001$) were significantly more likely to be nonresponders.

CONCLUSIONS: A combination of ICS + OM as initial treatment of mild OSA appears to provide an effective alternative to adenotonsillectomy, particularly in younger and nonobese children. These results support implementation of multicenter randomized trials to more definitively establish the role of ICS + OM treatment in pediatric OSA.

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ABBREVIATIONS: AHI = apnea-hypopnea index; ICS = intranasal corticosteroid; NPSG = nocturnal polysomnography; OM = oral montelukast; RCT = randomized controlled trial; Spo_2 = arterial oxygen saturation; T&A = adenotonsillectomy; TST = total sleep time

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Since the initial description of OSA, this condition has emerged as being highly prevalent in children and as imposing potentially reversible neurocognitive, behavioral, cardiovascular, and metabolic morbidities.[1] Adenotonsillar hypertrophy has been recognized as the major pathophysiologic contributor to OSA in children and has been customarily managed by surgical removal of enlarged adenoids and tonsils with overall favorable results reported for moderate to severe OSA.[1-3] More recently, however, surgical adenotonsillectomy (T&A) for mild OSA has come under scrutiny,[1-3] particularly regarding the possibility that a significant proportion of the polysomnographic abnormalities associated with milder forms of OSA may not normalize after surgery, thereby prompting the need for development of nonsurgical therapeutic alternatives.[4] Based on such initial reports, preliminary evidence on the potential beneficial effects of oral montelukast (OM) and intranasal corticosteroids (ICSs) on improving breathing patterns during sleep in pediatric cases of mild OSA has emerged.[5-15] Furthermore, the biologic plausibility of the potential efficacy of these approaches has been substantiated,[16,17] raising the possibility that randomized controlled trials (RCTs) using antiinflammatory approaches would be justified for pediatric OSA. However, the effects of combined topical steroid and montelukast in mild OSA have not yet been explored.

Here we report on the retrospective assessment of our clinical experience in a large cohort of patients diagnosed with mild OSA with polysomnography who were treated with a combination of ICS + OM for $\geq$ 12 weeks, followed by either no further treatment or by continued OM therapy for an additional 6 to 12 months.

Materials and Methods

Patients

This retrospective review study of our clinical experience was approved by the institutional human study review committees of the University of Louisville (protocol number 474.99) and the University of Chicago (protocol numbers 09-008-A and 10-615-A). The population for the study was identified by screening charts from the Sleep Center medical records at Kosair Children's Hospital in Louisville, Kentucky, for the time period from January 2007 until December 2008; St. Mary Women and Children's Hospital, Evansville, Indiana, from January 2007 until December 2012; and Comer Children's Hospital at the University of Chicago, Chicago, Illinois, from January 2011 until December 2012. The charts of children aged 2 to 14 years who were referred by their primary care pediatricians or pediatric otolaryngologists and underwent overnight sleep studies for suspected OSA were identified. Exclusion criteria were as follows: past T&A, genetic disorders, neuromuscular diseases, craniofacial abnormalities, or current treatment with medications such as corticosteroids (either oral, inhaled, or intranasal) or OM.

The period covered by this retrospective review corresponded to the implementation of a standard clinical management protocol whereby children with OSA and obstructive apnea-hypopnea index (AHI) $>$ 5.0/h of total sleep time (TST) were referred for surgical T&A or occasionally for CPAP therapy, while those with obstructive AHI $>$ 1.0/h TST but $<$ 5.0/h TST were initially recommended treatment with ICS + OM, following which a second overnight sleep study was performed to assess clinical response to therapy. Children with an obstructive AHI $<$ 1.0/h TST were considered to have primary snoring and did not receive treatment.

For children receiving ICS + OM, nonadherence was considered to be present if they received $<$ 3 weeks of any of the two medications as indicated by the parents or based on the absence of prescription refills. Otherwise, if the second nocturnal polysomnography (NPSG) documented improvement, OM was usually continued for up to 12 months. If no changes or worsening of the NPSG results occurred, then T&A was recommended. A third NPSG was conducted after 6 to 12 months of OM, and based on the findings (ie, worsening OSA, persistent mild OSA, or normal NPSG results), T&A, OM, or no treatment were recommended, respectively (Fig 1).

In addition to demographic information including age, sex, and ethnicity, height and weight were extracted from all the charts. Tonsil size derived from a score of 0 (no tonsils present) to 4 (kissing tonsils),[18] Mallampati score (Likert scale range, 1-4),[19] and adenoid size as estimated from lateral neck radiographs based on the degree of choanal obstruction on a Likert scale range, 1 to 4 (4: 75% to 100%; 3: 50% to 75%; 2: 25% to 50%; and 1: 0% to 25%) were tabulated when available, as previously described.[20,21]

BMI z-Score Calculation

Height and weight were recorded when each child arrived for NPSG. BMI *z*-score was calculated using an online BMI *z*-score calculator provided by the US Centers for Disease Control and Prevention.[22] Children with BMI *z*-score values $>$ 1.67 were considered obese.[23]

Overnight Sleep Study

An NPSG was performed in the laboratory in the presence of a trained polysomnographic technologist at each sleep center using the computerized clinical-data-acquisition system in use at that site. Briefly, the bilateral electrooculogram, eight channels of EEG, chin and anterior tibial electromyograms, tracheal sounds, and analog output from a body position sensor were monitored, along with chest and abdominal wall movement, ECG, and airflow using nasal pressure catheter, end-tidal capnography, and an oronasal thermistor. Arterial oxygen saturation (Spo_2) was assessed by pulse oximetry with simultaneous recording of the pulse waveform. In addition, a digital time-synchronized video recording was performed.

After removal of movement and technical artifacts, the studies were scored according to standard criteria as defined by the American Academy of Sleep Medicine in 2007, with all scoring technologists being supervised by one of the authors to ensure consistency across centers.[24] The proportion of time spent in each sleep stage was expressed as percentage of TST (%TST). Central, obstructive, and mixed apneic events were counted, and hypopneas were assessed. Obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for duration of at least two breaths. Hypopneas were defined

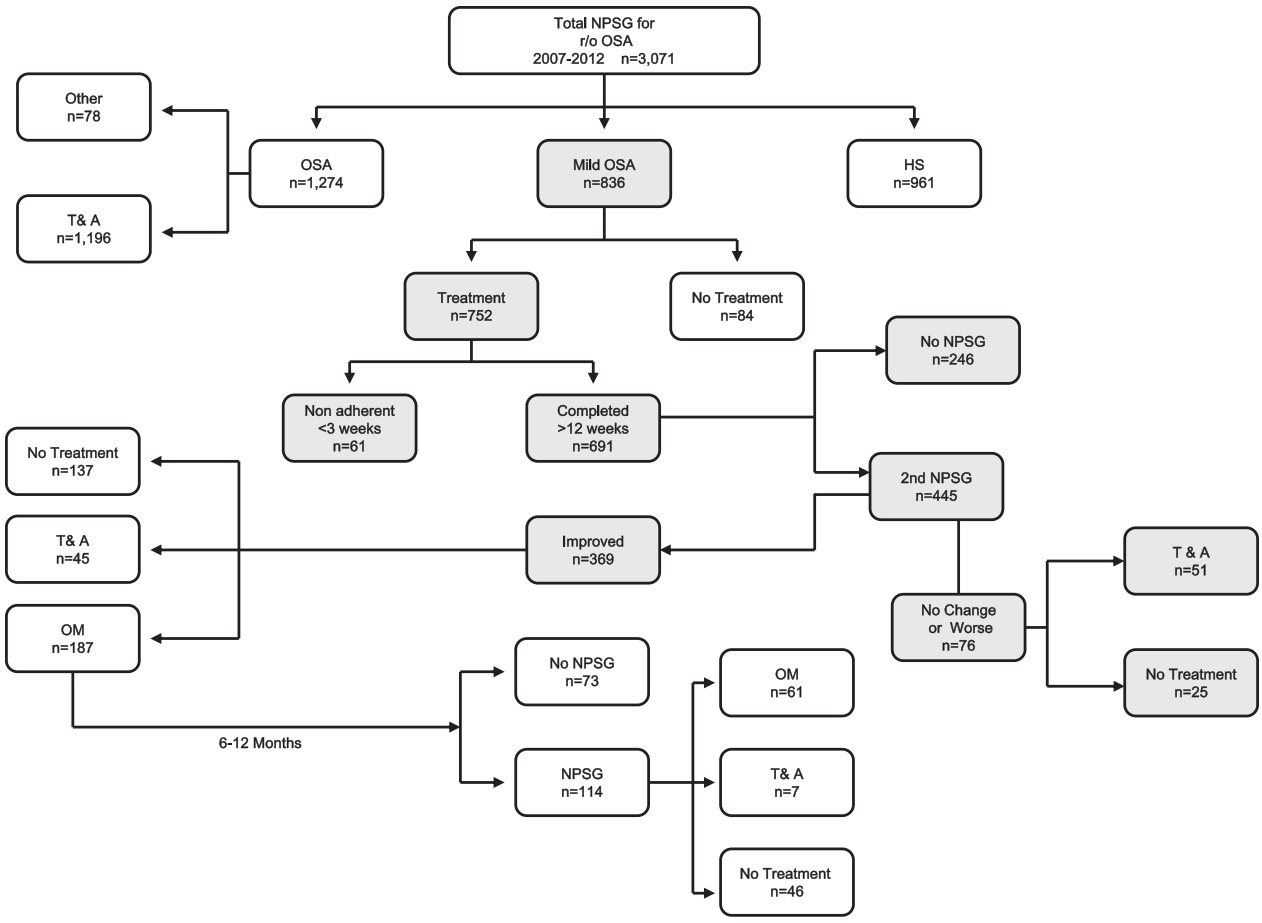

Figure 1 – *Schematic diagram of the overall clinical experience in treating 3,071 otherwise healthy children referred for evaluation of habitual snoring and suspected OSA. HS = habitual snoring; NPSG = nocturnal polysomnography; OM = oral montelukast; r/o = rule out; T&A = adenotonsillectomy.*

as a decrease in oronasal flow of > 50% on either the thermistor or nasal pressure transducer signal with a corresponding decrease in Spo_2 of > 3% or arousal. The obstructive AHI was defined as the number of apneas and hypopneas per hour of TST, and an AHI < 1/h TST was considered within normal limits.[25]

Data Analysis

Data are presented as mean ± SD unless stated otherwise. Data were assessed for kurtosis and confirmed as being normally distributed. Statistical analyses were conducted using SPSS, version 18.0 (IBM). A *P* value < .05 was considered to achieve statistical significance.

Results

A total of 3,071 otherwise healthy children between the ages of 2 to 14 years were referred for evaluation of habitual snoring and suspected OSA and underwent a diagnostic NPSG. Table 1 shows the demographic, anthropometric, and polysomnographic characteristics of these children based on their final diagnosis—namely, moderate to severe OSA, mild OSA, and habitual primary snoring. There were no significant differences in any of the demographic characteristics of the three groups or in the overall proportion of obesity across the groups. There were, however, small, albeit significantly higher, Mallampati scores in the children with more severe OSA when compared with the other two groups (*P* < .001). Similarly, the obstructive AHI and arousal indexes were increased in moderate to severe OSA, and lower nadir Spo_2 was also apparent compared with the other two groups. Mild OSA also differed from primary snoring in these polysomnographic measures (Table 1).

Of the 836 children with mild OSA, 84 parents (10%) refused ICS + OM treatment and sought alternative treatments, primarily consisting of surgical T&A (n = 72, 8.4%). Thus, 752 children began ICS + OM treatment, with 61 of these children (8.1%) discontinuing the treatment within the first 3 weeks or not adhering to the treatment as reported by parents. In the majority of these children (n = 52), parents decided to

TABLE 1] Demographic and Polysomnographic Characteristics of 3,071 Children Referred for Evaluation of Habitual Snoring

Characteristic	Moderate to Severe OSA (n = 1,274)	Mild OSA (n = 836)	Primary Snorers (n = 961)
Age, y	6.1 ± 1.3	6.4 ± 1.7	6.3 ± 1.9
Male sex, %	52.0	53.5	51.7
White, %	56.2	55.7	54.4
Black, %	27.7	26.3	25.8
BMI *z*-score	1.12 ± 0.76	1.17 ± 0.81	1.09 ± 0.87
Obese (BMI *z*-score > 1.65), %	37.3	38.2	34.8
Tonsillar size	2.37 ± 0.73	2.41 ± 0.82	2.29 ± 0.83
Adenoid size	2.3 ± 0.67	2.14 ± 0.71	2.13 ± 0.68
Mallampati score (n)	2.29 ± 0.54[a,b] (1,076)	1.87 ± 0.52[a] (789)	1.89 ± 0.58[b] (836)
TST, min	469.5 ± 47.7	472.3 ± 47.8	464.1 ± 49.1
Stage N1, %	7.4 ± 2.8[a,b]	4.4 ± 3.2[a]	4.6 ± 3.4[b]
Stage N2, %	38.1 ± 6.6	39.9 ± 7.5	39.2 ± 7.3
Stage N3, %	38.6 ± 14.1	41.4 ± 12.6	42.9 ± 12.3
REM sleep, %	19.3 ± 6.4	21.5 ± 7.8	26.7 ± 9.6[c]
Sleep latency, min	22.6 ± 14.3[b]	24.2 ± 15.2[d]	28.7 ± 11.8 [b,d]
REM latency, min	128.9 ± 51.0[a,b]	137.9 ± 65.1[a]	138.4 ± 55.2[b]
Total arousal index, events/h TST[e]	19.1 ± 7.8[a]	14.7 ± 7.1[a,d]	10.5 ± 5.7[a,d]
Respiratory arousal index, events/h TST[e]	5.9 ± 2.2[a,d]	2.8 ± 1.3[a,d]	0.6 ± 0.3[a,d]
Obstructive AHI, events/h TST[e]	13.5 ± 5.6[a,d]	4.4 ± 0.1.9[a,d]	0.7 ± 0.2[a,d]
Spo_2 nadir, %	82.6 ± 6.8[a,d]	87.3 ± 2.5[a,d]	94.8 ± 1.2[a,d]

Data given as mean ± SD unless otherwise indicated. AHI = apnea-hypopnea index; REM = rapid eye movement; Spo_2 = arterial oxygen saturation; TST = total sleep time.
[a]OSA vs mild OSA or primary snorer: $P < .01$.
[b]OSA vs primary snorer: $P < .01$.
[c]Primary snorer vs OSA or mild OSA: $P < .05$.
[d]Mild OSA vs OSA or primary snorer: $P < .01$.
[e]Time spent in the sleep state during the nocturnal polysomnography.

pursue T&A despite initiating the therapy but not adhering to it. However, six patients (0.7%) reported side effects that prompted them to discontinue therapy (three with headaches, one with nausea and vomiting, and two with epistaxis). Of the 691 children who presumably completed the 12-week treatment course, only 445 children (64.4%) returned for their follow-up NPSG. The changes in the sleep study between diagnosis and following ICS + OM treatment are shown in Table 2. Overall, significant improvements occurred with ICS + OM treatment in the magnitude of respiratory disturbances during sleep. More importantly, 62% of these 445 children exhibited normalization of their sleep studies (ie, they had an obstructive AHI < 1/h TST after completion of ICS + OM treatment). However, 17.1% (n = 76) showed either no improvement or worsening of their OSA. Table 3 shows the potential differences between responders who normalized breathing patterns during sleep after ICS + OM treatment and nonresponders. In general, no differences were apparent in either the sex, ethnicity, or sleep study measures between responders and nonresponders before initiation of ICS + OM treatment. However, younger children (ie, < 7 years of age) were 2.3 times more likely to normalize their sleep studies after ICS + OM treatment than obese children (95% CI, 1.43-4.13; $P < .001$), and nonobese children were 6.3 times more likely to normalize their sleep studies after ICS + OM treatment than obese children (BMI *z*-score > 1.65; 95% CI, 4.23-11.18; $P < .000001$). It is also worth mentioning that among the 396 patients in whom either improvements or normalization of the sleep study occurred with ICS + OM treatment, a subset of 45 patients (11.4%) opted to undergo T&A, while in 137 children (34.6%), no further treatment was prescribed (Fig 1). In the remaining 187 children (47.2%), OM was continued for

TABLE 2] Changes in Polysomnographic Findings Following 12-Wk Treatment With an Intranasal Corticosteroid and Oral Montelukast in 445 Children

Characteristic	Mild OSA Pretreatment (n = 445)	Mild OSA Posttreament (n = 445)	*P* Value
Age, y	6.2 ± 1.9	6.6 ± 1.9	...
Male sex, %	55.1	...	...
White, %	56.5	...	...
Black, %	26.8	...	...
BMI *z*-score	1.17 ± 0.81	...	...
Obese (BMI *z*-score > 1.65), %	33.8	...	...
Elapsed time between beginning treatment[a] and second NPSG, mean, d	...	114.8 ± 39.2	...
Tonsillar size	2.39 ± 0.77	1.87 ± 0.62	< .01
Adenoid size	2.17 ± 0.77	1.34 ± 0.68	< .001
Mallampati score (n)	1.89 ± 0.62 (412)	1.83 ± 0.64 (412)	...
Total sleep duration, min	472.1 ± 51.2	470.9 ± 49.1	...
Stage 1, %	4.7 ± 3.1	4.2 ± 3.4	...
Stage 2, %	37.8 ± 8.3	29.3 ± 9.7	...
Stage 3, %	40.6 ± 16.2	41.2 ± 15.8	...
REM sleep, %	19.3 ± 6.4	27.5 ± 7.8	< .01
Sleep latency, min	24.7 ± 16.1	27.9 ± 17.2	...
REM latency, min	138.1 ± 54.7	135.3 ± 62.9	...
Total arousal index, events/h TST	15.1 ± 9.3	12.2 ± 8.7	< .01
Respiratory arousal index, events/h TST	2.9 ± 1.7	0.8 ± 1.5	< .001
Obstructive AHI, events/h TST	4.5 ± 2.0	1.4 ± 0.0.9	< .01
Spo_2 nadir, %	87.5 ± 3.1	92.3 ± 2.1	< .001
Patients with normal NPSG, No. (%)	...	276 (62.0)	...

Data given as mean ± SD unless otherwise indicated. NPSG = nocturnal polysomnography. See Table 1 legend for expansion of other abbreviations.
[a]Intranasal corticosteroids plus oral montelukast for 12 wk.

6 to 12 months as consolidation therapy or with the intent to prevent recurrence of OSA, with such recommendation being consistently provided to parents who opted to either continue therapy or not. A third NPSG was obtained in 114 of these children (61%), with complete resolution of OSA being documented in 46 children (49.1%), persistently mild OSA being present in 61 children who elected to continue OM treatment (53.5%), and unchanged or worsening of OSA severity in seven children (6.2%) prompting surgical T&A. Thus, of the original cohort with mild OSA, a total of 175 children (20.9%) underwent T&A.

Discussion

This retrospective study on the clinical experience and long-term outcomes of combination therapy consisting of ICS + OM for management of mild OSA in children provides initial insights into the potential beneficial effects of this approach. Indeed, of the 836 children included in this clinical series with mild OSA, who would have normally undergone surgical removal of adenoids and tonsils in most centers in the United States as the first line of therapy, only 175 children (20.9%) ultimately required surgical intervention either based on a priori parental decision to refuse therapy or on response to therapy, with an additional 61 children (7.3%) being nonadherent to ICS + OM treatment and disappearing from follow-up. Thus, the overall success rate of the nonsurgical approach afforded by ICS and OM was 80.5%. Furthermore, we have now identified two readily identifiable patient characteristics that appear to adversely affect the favorable response to ICS + OM treatment: age > 7 years and the presence of obesity.

The rationale for implementing in our pediatric sleep center a clinical management paradigm consisting of nonsurgical treatment was twofold. First and foremost,

TABLE 3] Demographic, Anthropometric, and Polysomnographic Characteristics of Children Who Were "Cured" and "Nonresponders" After Treatment With Intranasal Corticosteroids and Oral Montelukast for 12 Wk

Characteristic	"Cured" AHI < 1/h TST (n = 276)	Nonresponders AHI > 5/h TST (n = 76)	*P* Value
Age, y	4.9 ± 2.1	8.1 ± 2.6	< .0001
Male sex, %	54.3	53.9	...
White, %	54.3	56.5	...
Black, %	27.1	27.6	...
BMI *z*-score	1.01 ± 0.51	1.47 ± 0.63	< .000001
Obese (BMI *z*-score > 1.65), %	13.0	48.7	...
Elapsed time between beginning treatment[a] and second NPSG, mean, d	107.8 ± 13.7	113.8 ± 17.4	...

All data are expressed as mean ± SD. See Table 1 and 2 legends for expansion of abbreviations.
[a]Intranasal corticosteroids plus oral montelukast for 12 wk.

the overall success rate of T&A resulting in normalization of NPSG abnormalities was found to be low in both our initial, prospective, single-center study and in a subsequent, multicenter, retrospective study.[2,26] Similar, albeit slightly more favorable, results have been reported by others, further providing compelling evidence that improved selection of those patients with OSA who are most likely to demonstrate complete resolution is highly desirable, but currently unavailable.[3,27] When these suboptimal outcomes are paired with the potential risks of T&A surgery,[28] it becomes readily apparent that nonsurgical options could be highly desirable, at least for patients with milder OSA.

Upon implementation of the clinical protocol in our center, the criteria for proposing ICS + OM treatment options to parents relied on the NPSG findings, the latter fulfilling the criteria of mild OSA. However, despite the uniformity of the clinical approaches implemented during the period of time covered in this study, we cannot infer whether differences in the duration of disease were present and affected the response to therapy. Of note, there is also evidence indicating that watchful waiting may result in improvements in the severity of OSA, and such naturally occurring improvements could have occurred in our cohort as well.[3] Second, the combined evidence from in vitro experiments showing marked reductions in tonsillar and adenoid tissue proliferation with application of corticosteroids or montelukast and the experience garnered from clinical trials using either ICS alone or OM alone further supported the rationale for implementation of nonsurgical options, even if appropriately RCTs are sorely lacking.[5-17] Notwithstanding the retrospective nature of the study and the potential for selection biases inherent to any retrospective study, current findings provide initial confirmation in the clinical setting that the combination of ICS and OM is a potentially effective intervention for treatment of mild OSA in children, and such findings need to be confirmed by prospective, multicenter, RCT approaches.

As mentioned, the subanalyses of the children presenting with worsening or unchanged polysomnographic findings after ICS + OM treatment raised the possibility that obese children and older children may not be as likely to respond to ICS + OM treatment. Although the specific reasons for such differences remain to be elucidated, there is some degree of plausibility to such findings. First, obesity is now a clearly established risk factor for OSA in children that not only imposes increased mass loading to the upper airway and respiratory system, but may also promote increased inflammation ultimately favoring proliferation of adenotonsillar tissues.[1,29-33] Therefore, similar to the poorer outcomes associated with T&A in obese children, administration of ICS + OM may have been less efficacious in alleviating the underlying processes that promoted the occurrence of OSA in these children. The putative explanations for the reduced likelihood of favorable results among older children are less apparent. It is possible that the presence of increased fibrotic and connective tissues in upper airway lymphadenoid tissues of older children may lead to better preservation of the overall structure of these tissues and reduced probability that such tissues will decrease in volume even if ICS + OM treatment effectively reduces the inflammatory cellularity component. Of course, we cannot exclude the possibility that these findings simply reflect a spurious association or, alternatively, reflect absence

of adherence to ICS + OM treatment, since no oversight of adherence was implemented in this clinical population.

There are multiple methodologic limitations that preclude assertive affirmations on the efficacy of ICS + OM treatment in mild pediatric OSA. The retrospective nature of the study and the uncontrolled and open-label approach that are inherent to the clinical practice setting in which ICS + OM was administered markedly reduce the level of evidence and of the strength of potential recommendations that can be derived from this study.[34,35] Nevertheless, the absence of significant side effects and the overall favorable safety profile associated with the use of either ICS[36-38] or OM[39] and the possibility that based on the current encouraging results reported herein ICS + OM may ultimately replace T&A as the first line of treatment in mild OSA, provides major impetus for future, large-scale, multicenter RCTs. In summary, the retrospective analysis of our clinical experience associated with the implementation of ICS and OM in the management of mild OSA in children as an alternative to T&A is highly encouraging and supports prospective evaluation of this treatment modality as a potential alternative to T&A.

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Author contributions: D. G. 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. L. K.-G. was principal author of the manuscript. L. K.-G. and D. G. contributed to the conceptual framework for the study; L. K.-G. and D. G. contributed to data analysis; L. K.-G., R. B., and H. P. R. B. contributed to data acquisition; L. K.-G., R. B., H. P. R. B., and D. G. contributed to data interpretation; L. K.-G. drafted the initial manuscript; R. B. and H. P. R. B. contributed to the revision of the manuscript; D. G. provided critical editing of the initial manuscript; D. G. is responsible for the financial support of the project; and L. K.-G., R. B., H. P. R. B., and D. G. approved the final manuscript.

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Clinical Practice Guideline: Polysomnography for Sleep-Disordered Breathing Prior to Tonsillectomy in Children

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Abstract

Objective. This guideline provides otolaryngologists with evidence-based recommendations for using polysomnography in assessing children, aged 2 to 18 years, with sleep-disordered breathing and are candidates for tonsillectomy, with or without adenoidectomy. Polysomnography is the electrographic recording of simultaneous physiologic variables during sleep and is currently considered the gold standard for objectively assessing sleep disorders.

Purpose. There is no current consensus or guideline on when children 2 to 18 years of age, who are candidates for tonsillectomy, are recommended to have polysomnography. The primary purpose of this guideline is to improve referral patterns for polysomnography among these patients. In creating this guideline, the American Academy of Otolaryngology—Head and Neck Surgery Foundation selected a panel representing the fields of anesthesiology, pulmonology medicine, otolaryngology–head and neck surgery, pediatrics, and sleep medicine.

Results. The committee made the following recommendations: (1) before determining the need for tonsillectomy, the clinician should refer children with sleep-disordered breathing for polysomnography if they exhibit certain complex medical conditions such as obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses. (2) The clinician should advocate for polysomnography prior to tonsillectomy for sleep-disordered breathing in children without any of the comorbidities listed in statement 1 for whom the need for surgery is uncertain or when there is discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing. (3) Clinicians should communicate polysomnography results to the anesthesiologist prior to the induction of anesthesia for tonsillectomy in a child with sleep-disordered breathing. (4) Clinicians should admit children with obstructive sleep apnea documented on polysomnography for inpatient, overnight monitoring after tonsillectomy if they are younger than age 3 or have severe obstructive sleep apnea (apnea-hypopnea index of 10 or more obstructive events/hour, oxygen saturation nadir less than 80%, or both). (5) In children for whom polysomnography is indicated to assess sleep-disordered breathing prior to tonsillectomy, clinicians should obtain laboratory-based polysomnography, when available.

Keywords

evidence-based medicine, polysomnography, practice guidelines, sleep, sleep-disordered breathing, obstructive sleep apnea, tonsillectomy, monitoring

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Polysomnography (PSG), commonly referred to as a "sleep study," is presently the gold standard for diagnosing and quantifying sleep-disordered breathing (SDB) in children.[1,2] SDB affects approximately 12% of children with manifestations ranging from simple snoring to potentially serious conditions, including sleep apnea.[3] SDB is also the most common indication for tonsillectomy with or without adenoidectomy in the United States.[4,5] Because more than 530,000 tonsillectomies are performed annually on

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children younger than age 15, primarily for SDB, clear and actionable guidance on optimal use of PSG is strongly needed.[6]

This guideline is intended to assist otolaryngologists–head and neck surgeons in making evidence-based decisions regarding PSG in children aged 2 to 18 years with a clinical diagnosis of SDB who are candidates for tonsillectomy and may benefit from PSG prior to surgery. The following definitions are used:

- *Polysomnography* is the electrographic recording of simultaneous physiologic variables during sleep and is currently considered the gold standard for objectively assessing sleep disorders. Physiologic parameters typically measured include gas exchange, respiratory effort, airflow, snoring, sleep stage, body position, limb movement, and heart rhythm. PSG may be performed in a sleep laboratory with continuous attendance as defined below.[7]
- *Sleep-disordered breathing* is characterized by an abnormal respiratory pattern during sleep and includes snoring, mouth breathing, and pauses in breathing. SDB encompasses a spectrum of disorders that increase in severity from snoring to obstructive sleep apnea. For example, *obstructive sleep apnea* (OSA) is diagnosed when SDB is accompanied by an abnormal PSG with obstructive events.
- *Tonsillectomy* is defined as a surgical procedure with or without adenoidectomy that completely removes the tonsil, including its capsule, by dissecting the peritonsillar space between the tonsil capsule and the muscular wall. For clarity, the term *tonsillectomy* is used instead of *adenotonsillectomy* in this guideline, recognizing that often, but not always, the adenoid is removed concurrently with the tonsils. A discussion on the merits of intracapsular versus complete tonsillectomy is beyond the scope of this guideline.

Although PSG can help guide medical decision making, assess surgical candidacy, and optimize perioperative monitoring after tonsillectomy, the test is time-consuming and often not readily available.[5] Additional obstacles to testing include lack of consensus on what constitutes an abnormal study and access to a qualified sleep center and specialist to obtain and interpret the results. Consequently, less than 10% of children undergo PSG prior to tonsillectomy, even though a clinical diagnosis of SDB in children is known to be a poor predictor of disease severity.[5,8] The decision to proceed with PSG is, therefore, often at the discretion of the physician or caregiver.[5]

There is increasing interest in portable monitoring (PM) devices, instead of formal PSG, to assess children with SDB. For the purposes of this guideline, the term *PM* is used to refer to home monitoring performed without a technologist present. PM devices will typically measure at least 4 physiologic parameters, including 2 respiratory variables (ie, respiratory effort and airflow), a cardiac variable (ie, heart rate or electrocardiogram), and arterial oxygen saturation via pulse oximetry. In contrast, PSG includes 7 or more channels of monitoring and evaluates sleep stages.

Guideline Scope and Purpose

The primary purpose of this guideline is to provide evidence-based recommendations for PSG prior to tonsillectomy in children aged 2 to 18 years with SDB as the primary indication for surgery. The target audience is otolaryngologists in any practice setting where a child would be evaluated. Although the guideline was developed with input from other specialties, the intent is to provide guidance specifically for otolaryngologists–head and neck surgeons.

Additional goals are to highlight the evidence for obtaining PSG in special populations or in children who have modifiable risk factors. A guideline is necessary given the evidence of practice variation between practitioners and in the literature. The guideline does not apply to children younger than age 2 or older than age 18, to those who have already undergone tonsillectomy, to children having adenoidectomy alone, or to children who are being considered for continuous positive airway pressure (CPAP) or other surgical therapy for SDB.

The guideline is intended to focus on a limited number of quality improvement opportunities, deemed most important by the working group, and is not intended to be a comprehensive, general guide for prescribing PSG for tonsillectomy candidates and patients with SDB. In this context, the purpose is to define actions that could be taken by otolaryngologists to deliver quality care. Conversely, statements in this guideline are not intended to limit or restrict care provided by clinicians based on assessment of individual patients.

The development panel concluded with 5 evidence-based action statements listed in **Table 1**, which are fully described later in the document with supporting evidence profiles.

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Table 1. Summary of Action Statements for PSG

Statement	Action	Evidence
1. Indications for PSG	Before performing tonsillectomy, the clinician should refer children with SDB for PSG if they exhibit any of the following: obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses.	Recommendation based on observational studies with a preponderance of benefit over harm.
2. Advocating for PSG	The clinician should advocate for PSG prior to tonsillectomy for SDB in children *without* any of the comorbidities listed in statement 1 for whom the need for surgery is uncertain or when there is discordance between tonsillar size on physical examination and the reported severity of SDB.	Recommendation based on observational and case-control studies with a preponderance of benefit over harm.
3. Communication with anesthesiologist	Clinicians should communicate PSG results to the anesthesiologist prior to the induction of anesthesia for tonsillectomy in a child with SDB.	Recommendation based on observational studies with a preponderance of benefit over harm.
4. Inpatient admission for children with OSA documented in results of PSG	Clinicians should admit children with OSA documented in results of PSG for inpatient, overnight monitoring after tonsillectomy if they are younger than age 3 or have severe OSA (apnea-hypopnea index of 10 or more obstructive events/hour, oxygen saturation nadir less than 80%, or both).	Recommendation based on observational studies with a preponderance of benefit over harm.
5. Unattended PSG with portable monitoring device	In children for whom PSG is indicated to assess SDB prior to tonsillectomy, clinicians should obtain laboratory-based PSG, when available.	Recommendation based on diagnostic studies with limitations and a preponderance of benefit over harm.

Abbreviations: OSA, obstructive sleep apnea; PSG, polysomnography; SDB, sleep-disordered breathing.

Background and Significance

SDB represents a spectrum of sleep disorders ranging in severity from snoring to OSA. In children, the estimated prevalence for habitual snoring is 10% to 12%, whereas the estimated prevalence of OSA is only 1% to 3 %.[3,9,10] In addition to nighttime symptoms, SDB also affects daytime behavior, including school performance, neurocognitive function, and quality of life.[11-13] Upper airway obstruction caused by the tonsils, adenoid, or both causes most SDB in children, making tonsillectomy (with or without adenoidectomy) the most common surgical intervention in managing the disorder. The prevalence of SDB as an indication for tonsillectomy is increasing.[14]

Collecting a patient history, with or without physical examination, fails to reliably predict the presence or severity of SDB or OSA in children. For example, in a systematic review of 10 diagnostic studies, only 55% of all children with suspected OSA, based on clinical evaluation, actually had OSA confirmed by PSG.[8] Another study, which stratified patients' symptoms by severity of OSA, failed to demonstrate a high positive predictive value for clinical history even when children with severe OSA (apnea-hypopnea index [AHI] of 10 or higher) were compared to primary snorers. Parents could report loud snoring, mouth breathing, or pauses, but their history was not consistently confirmed by PSG.[15]

The American Academy of Pediatrics (AAP) clinical practice guideline on diagnosis and management of childhood obstructive sleep apnea syndrome provides a nonspecific recommendation to obtain overnight PSG to confirm the diagnosis of SDB.[2] In addition to identifying the presence of SDB, PSG also helps define its severity, which can aid in perioperative planning. In addition, children with severe OSA documented by PSG are less likely to be cured by tonsillectomy[16,17] and are more likely to suffer perioperative complications.[18,19] Despite the AAP recommendations and documented utility of PSG, only about 10% of pediatric otolaryngologists obtain a preoperative PSG before tonsillectomy for SDB.[5] The variability in obtaining PSG prior to tonsillectomy in children with SDB may be due to lack of access, cost, time expended, and concern over the child's emotional distress.

The burden of PSG is emotional, practical, and logistical because of the prolonged wait times for the procedure and lack of "child-friendly" sleep laboratories. In a survey of pediatric otolaryngologists, 17% of respondents did not have access to a sleep laboratory, and only 60% had access to a dedicated pediatric center.[5] The typical wait time for the study was 6 weeks or longer. The emotional burden is increased when a reliable study is not obtained. On rare occasions, the child becomes combative and will not sleep, and no useful information is obtained. However, despite the foreign sleep environment, a good-quality study is obtained the vast majority of the time.

The role of PM, as an alternative to formal PSG, in assessing children with SDB is controversial. PM in the home may improve access and perhaps lower costs. The American Academy of Sleep Medicine (AASM) has endorsed PM as an alternative to PSG for diagnosing OSA in at-risk adults; however, the validity of PM among children is largely unknown.[20] Furthermore, the physiologic variables monitored during PM are inconsistent and may be as simple as oximetry alone or may include other measures, including chest wall movement, air flow, and sometimes electroencephalography (EEG). Including more variables increases the accuracy but also the complexity of the study. Simple oximetry is usually well tolerated but cannot detect (1) events that result in

arousal without desaturation, (2) how long the patient slept, (3) carbon dioxide elevation, (4) prolonged flow limitation without discrete desaturation, or (5) whether they achieved rapid eye movement (REM) sleep (the period when respiratory events are most common).[21]

Methods and Literature Search

This guideline was developed using an explicit and transparent a priori protocol for creating actionable statements based on supporting evidence and the associated balance of benefit and harm.[22] The guideline development panel was chosen to represent the fields of pediatric anesthesiology, pediatric pulmonology, otolaryngology–head and neck surgery, pediatrics, and sleep medicine. Despite the multidisciplinary nature of the development panel, the guideline target audience was defined to be otolaryngology–head and neck surgeons.

Several initial literature searches were performed through February 27, 2010, using MEDLINE, the National Guidelines Clearinghouse (NGC) (www.guideline.gov), The Cochrane Library, Guidelines International Network (GIN), the National Research Register (NRR), ClinicalTrials.gov, the International Clinical Trials Registry Platform, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and EMBASE. The initial search using "polysomnography" or "polysomnograph*" or "PSG" or "sleep apnea syndromes" or "apnea hypopnea index" or "respiratory disturbance index" or "AHI" or "RDI" or "sleep disorder*" or "sleep study*" or "sleep laboratory" in any field showed 5686 potential articles:

1. Clinical practice guidelines were identified by an EMBASE, CINAHL, and MEDLINE and GIN search using *guideline* as a publication type or title word. The search identified 206 guidelines with a topic of polysomnography. After eliminating articles that did not have polysomnography as the primary focus, 49 guidelines were selected for the panel's discussion.
2. Systematic reviews were identified using a validated filter strategy that initially yielded 234 potential articles. The final data set included 34 systematic reviews or meta-analyses on polysomnography that were distributed to the panel members.
3. Randomized controlled trials were identified through the Cochrane Library (Cochrane Controlled Trials Register), MEDLINE, EMBASE, and CINAHL and totaled 24 trials.
4. Original research studies were identified by limiting the MEDLINE, CINAHL, and EMBASE search to articles on humans published in English. The resulting data set of 92 articles yielded 47 related to indications for PSG, 69 to advocating for PSG, 48 to postoperative monitoring, 6 to anesthesiology, and 2 to portable devices.

Results of all literature searches were distributed to guideline panel members, including electronic listings with abstracts (if available) of the searches for randomized trials, systematic reviews, and other studies. This material was supplemented, as needed, with targeted searches to address specific needs identified in writing the guideline through July 2010.

In a series of conference calls, the working group defined the scope and objectives of the proposed guideline. During the 10 months devoted to guideline development ending in September 2010, the group met twice, with interval electronic review and feedback on each guideline draft to ensure accuracy of content and consistency with standardized criteria for reporting clinical practice guidelines.[23]

American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF) staff used GEM-COGS, the Guideline Implementability Appraisal and Extractor, to appraise adherence of the draft guideline to methodological standards, to improve clarity of recommendations, and to predict potential obstacles to implementation.[24] Guideline panel members received summary appraisals in September 2010 and modified an advanced draft of the guideline.

The final draft practice guideline underwent extensive external peer review. Comments were compiled and reviewed by the group chairpersons, and a modified version of the guideline was distributed and approved by the development panel. Recommendations contained in the practice guideline are based on the best available published data through July 2010. Where data were lacking, a combination of clinical experience and expert consensus was used. A scheduled review process will occur at 5 years from publication or sooner if new compelling evidence warrants earlier consideration.

Classification of Evidence-Based Statements

Guidelines are intended to produce optimal health outcomes for patients, to minimize harms, and to reduce inappropriate variations in clinical care. The evidence-based approach to guideline development requires that the evidence supporting a policy be identified, appraised, and summarized and an explicit link between evidence and statements be defined. Evidence-based statements reflect both the quality of evidence and the balance of benefit and harm anticipated when the statement is followed. Definitions of evidence-based statements (AAP SCIM 2004) are listed in **Tables 2** and **3**.

Guidelines are not intended to supersede professional judgment; rather, they may be viewed as a relative constraint on individual clinician discretion in a particular clinical circumstance. Less frequent variation in practice is expected for a "strong recommendation" than might be expected with a "recommendation." "Options" offer the most opportunity for practice variability.[25] Clinicians should always act and decide in a way that they believe will best serve their patients' interests and needs, regardless of guideline recommendations. They must also operate within their scope of practice and according to their training. Guidelines represent the best judgment from a team of experienced clinicians and methodologists addressing the scientific evidence for a particular topic.[26]

Making recommendations about health practices involves value judgments based on the desirability of various outcomes

*High-risk populations include children with obesity, neuromuscular or craniofacial disorders, Down syndrome, mucopolysaccharidoses, or sickle cell disease.

Table 2. Guideline Definitions for Evidence-Based Statements

Statement	Definition	Implication
Strong recommendation	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B).[a] In some clearly identified circumstances, strong recommendations may be made based on lesser evidence 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 means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C).[a] In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option	An option means that either the quality of evidence that exists is suspect (grade D)[a] or that well-done studies (grade A, B, or C)[a] show little clear advantage to one approach vs another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation	No recommendation means there is both a lack of pertinent evidence (grade D)[a] and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit vs harm; patient preference should have a substantial influencing role.

[a]See Table 3 for definition of evidence grades.

Table 3. Evidence Quality for Grades of Evidence

Grade	Evidence Quality
A	Well-designed randomized controlled trials or diagnostic studies performed on a population similar to the guideline's target population
B	Randomized controlled trials or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies
C	Observational studies (case control and cohort design)
D	Case reports, reasoning from first principles (bench research or animal studies)
X	Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit over harm

associated with management options. Values applied by the guideline panel sought to minimize harm and diminish unnecessary and inappropriate therapy. A major goal of the committee was to be transparent and explicit about how values were applied and to document the process.

Financial Disclosure and Conflicts of Interest

The cost of developing this guideline, including travel expenses of all panel members, was covered in full by the AAO-HNSF. Potential conflicts of interest for all panel members in the past 5 years were compiled and distributed before the first conference call. After review and discussion of these disclosures, the panel concluded that individuals with potential conflicts could remain on the panel if they (1) reminded the panel of potential conflicts before any related discussion, (2) recused themselves from a related discussion if asked by the panel, and (3) agreed not to discuss any aspect of the guideline with industry before publication.[27] Last, panelists were reminded that conflicts of interest extend beyond financial relationships and may include personal experiences, how a participant earns a living, and the participant's previously established "stake" in an issue.[28]

Guideline Key Action Statements

Each action statement is organized in a similar fashion: **statement in boldface type**, followed by *strength of the recommendation in italic*. Several paragraphs then discuss the evidence base supporting the statement, concluding with an "evidence profile" of aggregate evidence quality, benefit-harm assessment, and statement of costs. Last, there is an explicit statement of the value judgments, intentional vagueness, the role of patient preferences, potential exclusions, and a repeat statement of the strength of the recommendation. An overview of evidence-based statements in the guideline is shown in **Table 1**.

The role of patient preference in making decisions deserves further clarification. For some statements, the evidence base demonstrates clear benefit, which would minimize the role of patient preference. If the evidence is weak or benefits are

Table 4. Role of PSG in Assessing High-Risk Populations before Tonsillectomy for SDB

Role of PSG	Rationale
Avoid unnecessary or ineffective surgery in children with primarily nonobstructive events	Identify primarily nonobstructive events or central apnea that may not have been suspected prior to the study and may not benefit from surgery.
Confirm the presence of obstructive events that would benefit from surgery	The increased morbidity of surgery in high-risk children requires diagnostic certainty before proceeding.
Define the severity of SDB to assist in preoperative planning	Children with severely abnormal SDB may require preoperative cardiac assessment, pulmonary consultation, anesthesia evaluation, or postoperative inpatient monitoring in an intensive care setting.
Provide a baseline PSG for comparison after surgery	Persistent SDB or OSA despite surgery is more common in high-risk patients than in otherwise healthy children.
Document the baseline severity of SDB	High-risk patients are more prone to complications of surgery or anesthesia.

Abbreviations: OSA, obstructive sleep apnea; PSG, polysomnography; SDB, sleep-disordered breathing.

unclear, however, not all informed patients may opt to follow the suggestion. In such cases, the practice of shared decision making, where the management decision is made collaboratively between the clinician and the informed patient, becomes more useful. Factors related to patient preference include (but are not limited to) absolute benefits (number needed to treat), adverse effects (number needed to harm), cost of drugs or tests, frequency and duration of treatment, and desire to take or avoid antibiotics. Comorbidity can also affect patient preferences by several mechanisms, including the potential for drug-drug interactions when planning therapy.

STATEMENT 1. INDICATIONS FOR PSG: Before performing tonsillectomy, the clinician should refer children with SDB for PSG if they exhibit any of the following: obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses. *Recommendation based on observational studies with a preponderance of benefit over harm.*

Supporting Text

The purpose of this statement is to improve the quality of care and assist with clinical treatment plans in children with SDB who are at increased risk for surgical or anesthetic complications because of comorbid conditions that include obesity, neuromuscular or craniofacial disorders, Down syndrome, mucopolysaccharidoses, and sickle cell disease.[29-32] Obtaining PSG prior to tonsillectomy in children with any of the conditions mentioned above will benefit clinicians and patients by improving diagnostic accuracy in high-risk populations* and defining the severity of OSA to optimize perioperative planning (**Table 4**).

History and physical exam alone are poor predictors of OSA severity or risk of postoperative complication.[15,33,34] In children who are at high risk of postoperative respiratory compromise due to a comorbid medical condition, preoperative PSG helps determine postoperative level of care and the need for postoperative oximetry. In addition, overnight postoperative monitoring may identify children requiring further treatment of their residual OSA.[35]

Obesity is defined as body mass index (BMI) greater than or equal to the 95th percentile. The BMI-for-age percentile is used because the amount of body fat changes with age and differs between girls and boys.[36] Children are categorized into normal weight (BMI 5th to <85th percentile), overweight (BMI 85th to <95th percentile), and obese (BMI ≥95th percentile). For the purpose of the discussion in this guideline, recommendations are directed at obese (eg, an 8-year-old boy, height 4 foot 10 inches/1.4 meters, would have to weigh 100 lbs/45 kg or more), not overweight, children. BMI percentiles can be calculated by entering a child's height and weight into a calculator at http://apps.nccd.cdc.gov/dnpabmi/.

SDB has a prevalence of 25% to 40% in obese children.[37] Obese children are also more likely to have severe SDB[38-40] and respiratory complications following tonsillectomy.[41] Furthermore, Costa and Mitchell[42] reported in a meta-analysis of 4 studies that tonsillectomy significantly reduced the severity of SDB in obese children but was rarely curative: 60% to 88% of obese children had evidence of persistent SDB following tonsillectomy. Preoperative PSG, therefore, assists in planning perioperative care, and postoperative PSG assists with long-term management.

Neuromuscular diseases (neuropathies, congenital myopathies, muscular dystrophies, myotonias, and myasthenia gravis) form a heterogeneous group based on the etiology of the individual disorder. Neuromuscular disorders often include central apneas, obstructive apneas, and/or hypoventilation that are important to distinguish on preoperative PSG.[43] In children with predominantly nonobstructive events, tonsillectomy may not be indicated, and other management options should be explored.

Craniofacial deformities result from abnormal development of the brain, cranium, and facial skeleton. Premature fusion of cranial growth plates as well as abnormal facial bone development leads to craniofacial anomalies such as Apert, Crouzon, and Pfeiffer syndromes. Children with such craniofacial syndromes are at a high risk for SDB because of oropharyngeal and nasopharyngeal crowding and laryngeal abnormalities.[44] Similarly, children with Down syndrome have multiple anatomic and physiologic factors that predispose

them to SDB, including hypotonia, midfacial and mandibular hypoplasia, relative macroglossia, a narrow nasopharynx, and a shortened palate.[45] Craniofacial deformities of the maxilla and mandible (including Pierre Robin sequence, hemifacial microsomia, Treacher Collins syndrome, and Nager syndrome) fall under this definition.

Mucopolysaccharidoses are a group of genetic disorders characterized by enzyme deficiencies that lead to defective catabolism of lysosomal glycosaminoglycans and accumulation of mucopolysaccharides in the soft tissues of the body. SDB is common in children with mucopolysaccharidosis (>80%) because of upper airway narrowing caused by hypertrophy of the tongue, tonsils, adenoids, and mucous membranes. This narrowing is worsened by a physiological decrease in tone of the supporting muscles of the pharynx and increased airway resistance.[46]

Sickle cell anemia is an autosomal recessive disorder of hemoglobin that alters the properties of red blood cells and is associated with varying degrees of anemia.[47] Strokes, transient ischemic attacks, and seizures are common in sickle cell disease. Both episodic and continuous nocturnal hypoxemia are common in sickle cell disease, possibly because of upper airway obstruction secondary to adenotonsillar hypertrophy. Children with sickle cell anemia and a clinical history of SDB should have routine preoperative PSG. If hypoxemia is present, tonsillectomy is advisable as early as possible because SDB could be an important predisposing factor in the etiology of cerebrovascular accidents in these children.[48]

The conditions explained above demonstrate the need for individual assessment among those with neuromuscular disorders and craniofacial anomalies. A full discussion of each condition as it pertains to this statement is beyond the scope of this guideline.

Evidence Profile for Statement 1: Indications for PSG

- Aggregate evidence quality: grade C, observational studies; 1 systematic review of observational studies on obesity
- Benefit: PSG confirms indications and appropriateness of surgery, helps plan perioperative management, provides a baseline for postoperative PSG, and defines severity of sleep disturbance
- Harm: none
- Cost: procedural cost; indirect cost of missed work
- Benefits-harm assessment: preponderance of benefit over harm
- Value judgments: knowledge gained through PSG can assist in diagnosing those children with significant SDB; belief that PSG can improve surgical outcomes through improved perioperative planning
- Role of patient preferences: limited
- Intentional vagueness: the panel decided to use the broad categories of neuromuscular disorders and craniofacial anomalies, rather than a comprehensive list of diseases and syndromes, to emphasize the need for individualized assessment
- Exclusions: none
- Policy level: recommendation

STATEMENT 2. ADVOCATING FOR PSG: The clinician should advocate for PSG prior to tonsillectomy for SDB in children without any of the comorbidities listed in statement 1 for whom the need for surgery is uncertain or when there is discordance between tonsillar size on physical examination and the reported severity of SDB. *Recommendation based on observational and case-control studies with a preponderance of benefit over harm.*

Supporting Text

The purpose of this statement is to help clinicians decide when to request a polysomnogram prior to tonsillectomy in children *without* any of the conditions in statement 1. Advocating for PSG refers to encouraging, or arguing in favor of using, PSG to assist in decision making when the need for surgery is uncertain or there is discordance between the physical examination and the reported severity of SDB. Although the tonsil size does not predict the severity of OSA, one is less certain of the diagnosis when tonsil hypertrophy is absent. The clinician may fulfill the requirement of advocating for PSG by (*a*) documenting in the medical record that PSG was discussed and encouraged, (*b*) providing an informational brochure or handout that describes the benefits and rationale of PSG in this circumstance, or (*c*) referring the patient for PSG or to a sleep specialist.

In some children who are candidates for tonsillectomy to treat SDB, there may be controversy among clinicians, caregivers, or both regarding the need for surgical intervention. Examples include differing opinions or observations among parents, other family members, primary care clinicians, and surgeons. In addition, at times the severity of SDB by history is inconsistent with the physical examination by the clinician: children with small tonsils may have prominent symptoms suggesting SDB, or children without apparent SDB symptoms may have tonsillar hypertrophy or nasal airway obstruction that appears highly significant. In the above situations, information obtained from PSG should help clarify the diagnosis and severity of SDB, if present, and assist in decision making.

Recent investigations have demonstrated the potential for long-lasting health consequences if SDB remains untreated. A recent meta-analysis demonstrated a significant increase in height, weight, and growth biomarkers after tonsillectomy.[49] Although some children may not be experiencing growth failure, they also may not be meeting their full potential. The implications of untreated SDB may be worse for children with borderline neurocognitive functioning prior to developing a sleep disturbance. Multiple studies in younger children with SDB have shown an intelligence quotient (IQ) loss of more than 5 points.[50] For perspective, the exposure to lead-based paint is associated with an average IQ point loss of less than 4 points.[51]

Treatment of SDB has been shown to improve behavior,[39,52-54] attention,[53] quality of life (QOL),[39,55] neurocognitive functioning,[56] enuresis,[57,58] parasomnias (unusual events that occur while asleep),[59] and restless sleep.[60] Even when a

clinician strongly suspects SDB exists, some families require objective information to facilitate a clinical decision. In these situations, a PSG should be requested.

PSG can also assist in managing children who are tonsillectomy candidates when there is discordance between tonsillar size on physical examination and the reported severity of SDB. When a child with tonsils that do not appear hypertrophic nonetheless has symptoms of SDB, a normal PSG would lead to reassessing the need for surgery or performing more limited surgery if appropriate. Conversely, an abnormal PSG would support the need for surgery because tonsillectomy has been shown to improve PSG-documented SDB even when tonsils are not hypertrophic.[39]

Another clinical scenario involves a child with markedly hyperplastic tonsils and minimal to no symptoms of SDB reported by the caregiver. Caregiver reports of snoring, witnessed apnea, or other nocturnal symptoms may be unreliable if the caregiver does not directly observe the child while sleeping or only observes the child early in the evening. In this situation, PSG may help detect significant sleep disturbance that may otherwise have been overlooked and could be improved after tonsillectomy. Similarly, caregivers may be unaware of, or underappreciate, the impact of SDB on their child's daytime functioning or behavior (eg, hyperactivity, poor school performance) or nighttime symptoms (eg, enuresis, sleep terrors, sleep walking, frequent awakenings).

Until the clinical consequences of SDB and the threshold for intervention are established, clinicians must provide caretakers with the information necessary to make an informed decision. This requires advocating for a PSG when the diagnosis is uncertain. The objective information obtained from a PSG will help direct care and minimize the risk of overtreating or failing to accurately diagnose.

A minority of panelists felt strongly that PSG should be recommended for all children younger than age 2 prior to tonsillectomy. However, the majority of panelists noted there was insufficient evidence in the published, peer-reviewed literature to support such a recommendation.

Evidence Profile for Statement 2: Advocating for PSG

- Aggregate evidence quality: grade C, observational and case-control studies
- Benefit: selection of appropriate candidates for tonsillectomy
- Harm: none
- Cost: time spent counseling the patient or family; financial implications to the family and insurance industry; time commitment for the study and follow-up
- Benefit-harm assessment: preponderance of benefit over harm
- Value judgments: based on expert consensus, there are circumstances in which PSG will improve diagnostic certainty and help inform surgical decisions
- Intentional vagueness: the panel decided to "advocate for" PSG rather than to "recommend" PSG in these circumstances to avoid setting a legal standard for care and to recognize the role for individualized decisions based on needs of the child and caregiver(s). Furthermore, the word *uncertain* is used in the statement to encompass a variety of circumstances regarding the need for tonsillectomy that include, but are not limited to, disagreement among clinicians or caregivers, questions about the severity of SDB or validity of the SDB diagnosis, or any other situation where the additional information provided by PSG would facilitate shared decisions
- Role of patient preferences: limited role in advocating; significant role in deciding whether or not to proceed with PSG
- Exclusions: none

STATEMENT 3. COMMUNICATION WITH ANESTHESIOLOGIST: Clinicians should communicate PSG results to the anesthesiologist prior to the induction of anesthesia for tonsillectomy in a child with SDB. *Recommendation based on observational studies with a preponderance of benefit over harm.*

Supporting Text

The purpose of this statement is to allow the anesthesiologist advance notice of a child who may require a modified approach to anesthesia care. Children with SDB scheduled for tonsillectomy are at an increased risk of perioperative morbidity and mortality.[10,61,62] Patients may have a difficult airway, an abnormal central respiratory drive, or abnormal cardiopulmonary physiology.[63,64] In addition, patients with OSA may be more sensitive to the respiratory depressant effects of anesthetic medications.[65] Communication with the anesthesiologist will allow for early identification of a child who may require preoperative optimization, as well as a modified approach to the anesthetic management and postoperative care of the patient.

Early knowledge of a child's SDB status may alter the anesthetic plan as compared to a child without SDB. Anxious children are often administered an anxiolytic or sedative prior to anesthesia; however, children with OSA may be at a higher risk for oversedation and hypoventilation secondary to the effects of preoperative sedatives and opioids.[66,67] Children with OSA who receive a premedication before surgery may require monitoring to detect hypoventilation and hypoxemia, as well as access to supplemental oxygen, advanced airway equipment, and personnel trained in airway management.[10] Classification of a patient as having OSA by PSG will alert the anesthesiologist to an 8-fold increase in the probability that the patient may have a difficult airway.[61,64] The care of SDB patients, especially with comorbidities such as midfacial anomalies or Down syndrome, may benefit from the American Society of Anesthesiologists Practice Guidelines for Management of the Difficult Airway to aid in airway management and to have appropriate airway equipment and assistance available in the operating room.[68]

Recognition of a child with OSA may modify intraoperative management. The concentration of anesthetic gases must be carefully titrated because of increased susceptibility to

airway collapse and delayed emergence.[62,63,69] Nitrous oxide can increase pulmonary artery pressure and must be used with caution in patients with SDB who may be at risk for pulmonary hypertension and right ventricular dysfunction.[10,70]

Intraoperative opioids may be reduced or withheld because of the increased analgesic sensitivity to opiates found in children with OSA, who experience recurrent episodes of hypoxemia during sleep.[63,65,70] For example, when compared to children without OSA, children with OSA who received fentanyl had a higher incidence of central apnea and reduced spontaneous minute ventilation under general anesthesia with inhaled anesthetics.[71] Similarly, requirements of morphine were found to be 50% less in children with OSA.[65] Therefore, children with abnormalities on PSG may need changes in the choice of opioid as well as the dose and timing of administration. Because of the real or perceived risk of apnea and delayed emergence in SDB patients, an alternative approach would be to rely less on opioids and more on nonopioid analgesics such as dexmedetomidine or acetaminophen with the goal of minimizing adverse side effects of opioids.[63]

The anesthesiologist, in concert with the surgeon, may elect to escalate the level of postoperative care for a child with SDB, which may involve more intense nursing care and monitoring in the postoperative period compared to non-SDB children having the same procedure.[72] The presence of SDB is associated with an increased incidence of postoperative complications.[61,62,73,74] Anesthetic drugs may have a prolonged effect on the level of consciousness and respiratory function into the postoperative period.[63,75-79] Postoperative pain control may involve choosing a less potent opioid to administer in smaller divided doses or the use of a smaller dose of opioid in combination with a nonopioid analgesic to avoid oversedation and/or possible respiratory depression resulting in death.[63,80,81] Therefore, postoperative management may need to be modified for children with an abnormal PSG as discussed under statement 4.

Evidence Profile for Statement 3: Communication with Anesthesiologist

- Aggregate evidence quality: grade C observational studies and grade D panel consensus
- Benefit: improve communication, provide information to the anesthesiologist that may alter perioperative management, reduce perioperative morbidity
- Harm: none
- Cost: none
- Benefit-harm assessment: preponderance of benefit over harm
- Value judgments: promoting a team approach to patient care will result in improved patient outcomes
- Intentional vagueness: none
- Role of patient preferences: none
- Exclusions: none

STATEMENT 4. INPATIENT ADMISSION FOR CHILDREN WITH OSA DOCUMENTED IN RESULTS OF PSG: Clinicians should admit children with OSA documented in results of PSG for inpatient, overnight monitoring after tonsillectomy, if they are under age 3 years or have severe OSA (apnea-hypopnea index of 10 or more obstructive events/hour, oxygen saturation nadir less than 80%, or both). *Recommendation based on observational studies with a preponderance of benefit over harm.*

Supporting Text

The purpose of this statement is to promote an appropriate, monitored setting after tonsillectomy for children with SDB and abnormal PSG. Child age and OSA severity correlate with postoperative respiratory compromise, which may require medical intervention.[82,83] In particular, children who are younger than age 3 or have severe OSA benefit from inpatient hospital admission and monitoring after surgery. Postoperative care should include continuous pulse oximetry and the availability of more intensive levels of care, including respiratory support (intubation, supplemental O_2, CPAP). Although no widespread interdisciplinary consensus exists on the precise definition of "severe" OSA, many contributions to the literature use an AHI of 10 or an oxygen saturation nadir of 80%. The panel chose to be very specific in order to make this guideline as actionable as possible, based on the best available evidence. The panel, however, does acknowledge that opinions do differ among experienced clinicians as to what constitutes severe sleep apnea. The panel would like to be clear that if a clinician believes a child to have severe OSA based on other criteria, or if the sleep laboratory that performed the study interprets the OSA as severe, it would be prudent to admit the child for observation.

Whereas no validated severity scales are currently available for PSG in children, several publications[10,18,82,84] support defining *severe OSA as having an oxygen saturation nadir below 80% and an AHI of 10 or more obstructive events*. In contrast, a normal PSG has oxygen nadir saturation above 92% and an AHI of 1 or lower.

Children younger than age 3 with SDB symptoms are at increased risk of respiratory compromise after tonsillectomy compared to older children. In a review of 2315 children younger than age 6, 9.8% of children younger than age 3 experienced a respiratory complication postoperatively as compared to 4.9% of older children.[83] A report including 307 children younger than age 3 revealed outpatient tonsillectomy was less cost-effective than hospital admission, primarily due to prolonged recovery room stays in the outpatient group.[85]

Children with OSA confirmed by PSG are at increased risk of respiratory complications in the postoperative period.[18,82,86-88] Postoperative respiratory complications occur in up to 23% of children with OSA undergoing tonsillectomy[18,82] as compared to 1.3% in a general pediatric population.[89] Up to 25% of children with OSA require medical intervention, including supplemental oxygen, CPAP, and reintubation.[18,82,86,88,90]

There is no consensus in the literature on postoperative inpatient monitoring of children with OSA after tonsillectomy, and some controversy exists regarding the criteria for pediatric intensive care unit (PICU) admission. Oximetry monitoring in the recovery room during the initial postoperative period is reported as a routine part of postoperative care

among hospitalized children in many publications. In one study, children older than age 3, without severe OSA or other comorbidity requiring admission, were discharged home, whereas children younger than age 3, children with severe OSA, and children with comorbid conditions were admitted to the pediatric ward with oximetry. Admission to the PICU was reserved for children with very severe OSA, those with comorbidities that could not be managed on the floor, and those who demonstrated significant airway obstruction and desaturation in the initial postoperative period that required interventions beyond repositioning and/or oxygen supplementation.[10,18,82,86,88,90,91] Documentation of mild or moderate OSA should not prevent the clinician from overnight monitoring of a patient who retains clinically significant SDB after surgery. In addition, postoperative admission may be considered in children with comorbid conditions that, independent of OSA severity, increase their risk of postoperative complication.

The postoperative period is defined as the initial 24 hours following completion of surgery. Although tonsillectomy resolves or significantly improves OSA in the majority of children, they may continue to experience upper airway obstruction and oxygen desaturation in the postoperative period. Two studies have reported onset of respiratory compromise during sleep at least 5 hours postoperatively in children with OSA.[92,93] In another study, postoperative respiratory events were observed up to 14 hours postoperatively.[18] Obstructive apneas and desaturation occur primarily during REM sleep because of a greater hypoventilation and reduced responsiveness to hypoxemia or hypercapnia.[2] REM rebound may follow tonsillectomy for severe OSA and may not occur for 18 hours.[88] Most interventions required during the postoperative period include administration of oxygen or repositioning; however, in several studies, children with OSA required more significant interventions with PICU admission.[18,86,88]

One proposed mechanism for identifying potential postoperative upper airway obstruction and oxygen desaturation has been differences in neuromuscular control of the upper airway in children with OSA, which makes them more susceptible to residual effects of anesthetic and analgesic medications.[94,95] Children with OSA who are considered high risk for respiratory compromise require overnight inpatient monitoring postoperatively in a setting where signs of respiratory depression and airway obstruction can be recognized and prompt intervention can be implemented.[2,10,18,96]

Evidence Profile for Statement 4: Impact of PSG on Postoperative Monitoring

- Aggregate evidence quality: grade C, observational studies on age; diagnostic studies, guidelines, and panel consensus on what constitutes a severely abnormal PSG
- Benefit: PSG can help determine the appropriate setting for recovery after tonsillectomy that would allow prompt detection and management of respiratory complications among high-risk children
- Harm: unnecessary admission of children who do not have respiratory complications; occupying a hospital bed that might be better utilized; risk of iatrogenic injury (infection, parenteral narcotics causing respiratory depression, hyponatremia from hypotonic intravenous fluids, etc); reduced "family-centered care" during recovery process
- Cost: hospital admission; cost of monitoring
- Benefit-harm assessment: preponderance of benefit over harm
- Value judgments: despite the lack of consistent data on what constitutes severe OSA on PSG, the panel decided some criteria, based on consensus, should be provided to guide clinical decisions; perception by the panel that inpatient admission after tonsillectomy is underused for children with abnormal PSG and that obstacles exist in the health care system for precertifying inpatient admission, even when appropriate
- Intentional vagueness: none
- Role of patient preferences: limited
- Exclusions: none

STATEMENT 5. UNATTENDED PSG WITH PORTABLE MONITORING DEVICE: In children for whom PSG is indicated to assess SDB prior to tonsillectomy, clinicians should obtain laboratory-based PSG, when available. *Recommendation based on diagnostic studies with limitations and a preponderance of benefit over harm.*

Supporting Text

The purpose of this statement is to provide guidance when the clinician recognizes a need for PSG in a child prior to tonsillectomy, and consideration is given to using a portable monitoring (device) for home testing as a substitute for formal PSG in a sleep laboratory.

PSG in a sleep laboratory remains the gold standard for evaluating SDB in children. PSG not only confirms the diagnosis but also can differentiate OSA from snoring and can rule out other sleep disorders such as periodic limb movements, narcolepsy, and nocturnal seizures. It also quantifies the severity of OSA.

Because of the expense and inconvenience of laboratory-based PSG, there have been several attempts to use simpler, more limited studies to evaluate SDB. Studies in the home have the advantage of a more natural sleeping environment, which may be especially important for children; however, fewer measurements are made in an unmonitored setting, thus reducing its accuracy and precision. In addition, there is no technologist available to solve technical problems, so a percentage of home studies will need to be repeated.

In 1994, the AASM published clinical guidelines for using PM to diagnose OSA in adults. These guidelines were updated in 2007 to include a recommendation that PM record, at minimum, airflow, blood oxygenation, and respiratory effort, preferably including both oronasal thermisters and nasal pressure transducers to improve detection of hypopneas. A suggestion that PM only be used in conjunction with a comprehensive sleep evaluation in uncomplicated adult patients without comorbidities and with a

high pretest probability of OSA was also made. The updated guidelines also state studies should be scored and supervised by trained and accredited sleep technicians and physicians.[20]

The AASM recommendations in the preceding paragraph are based on studies in adults, so their relevance or validity for children is unknown. They highlight, however, the paucity of evidence on PM and restricted circumstances for which it may be of use.

Only 1 study has compared PM to PSG in children with possible OSA. Jacob and colleagues[97] performed both tests in 21 children aged 2 to 12 years using a home PM device that included inductance plethysmography, ECG, and pulse oximetry to assess respiratory events, with a camcorder and microphone to estimate sleep time. This device, in a selected population and in the hands of experienced investigators, was able to separate patients with an AHI greater or less than 5 events per hour of sleep. However, the Jacob study used a sophisticated testing apparatus not currently commercially available for home testing and was not able to define the severity of disease when compared to in-laboratory PSG.[97]

The guideline panel also considered the following issues regarding the suitability of PM devices as an alternative to laboratory-based PSG:

1. There are many PM devices on the market, and validation of one particular device cannot necessarily be extrapolated to others.
2. Few devices have been tested in children. Children are more difficult to study than adults, given the prevalence of shorter events and hypopneas, together with less cooperation. When, and if, comparison studies are performed, their accuracy in predicting the severity of OSA is as important as their ability to differentiate OSA from snoring.
3. Because every study of PM (adult and pediatric) the panel reviewed excluded patients with significant comorbidities, the panel concluded PM is not appropriate for high-risk children, including those with sickle cell disease, craniofacial or neurologic disorders, or Down syndrome.
4. The interpretation of PM results is likely as important as the hardware used in performing the test. If PM is used, the panel recommends that results are interpreted by an expert in sleep medicine who is aware of the differences in scoring for children. Although some commercial devices have a computerized scoring algorithm, these are usually based on adult criteria.

Laboratory-based PSG remains the gold standard for the diagnosis of OSA in children and should be used if a facility skilled in pediatric PSG is available. In areas where pediatric sleep centers are not accessible or in situations where there is strong parental preference for a home-based study, PM may be considered. However, given the paucity of data in this subject area, the panel recommends against the routine use of PM over laboratory-based PSG. Additional research is necessary to validate commercially available PM devices as alternatives to PSG and to clarify the relationship of benefit versus harm related to their use among children.

Evidence Profile for Statement 5: Unattended PSG with PM Device

- Aggregate evidence quality: grade C, 1 small diagnostic study in children and extrapolation from diagnostic studies and guidelines for adults
- Benefit: avoid inaccurate results or misdiagnosis of OSA because of limitations in the precision and accuracy of currently used PM devices
- Harm: potential for delays in testing based on access to PSG and availability of child-friendly test facilities
- Cost: procedure-related direct cost
- Benefit-harm assessment: preponderance of benefit over harm
- Value judgments: the panel chose to emphasize accuracy of test results over convenience of testing. The term “when available” was used to acknowledge that although home studies have limitations, there may be circumstances when the caregivers express a strong preference for home-based testing or when access to laboratory-based PSG is limited by geography, scheduling conflicts, or insurance restrictions
- Intentional vagueness: none
- Role of patient preferences: some role for patient preference in deciding whether or not a PM device would be an acceptable alternative to PSG
- Exclusions: none

Implementation Considerations

The complete guideline is published as a supplement to *Otolaryngology–Head and Neck Surgery* to facilitate reference and distribution. The guideline will be presented to AAO-HNS members as a mini-seminar at the AAO-HNS annual meeting following publication. Existing brochures and publications by the AAO-HNS will be updated to reflect the guideline recommendations. A full-text version of the guideline will also be accessible free of charge at www.entnet.org.

Research Needs

Significant gaps in research remain regarding our knowledge about OSA and its management. The guideline committee identified several areas where future studies could improve the ability of clinicians to manage SDB patients optimally.

1. The ability of PSG to predict the likelihood and time of onset of postoperative complications following tonsillectomy in children has yet to be determined. This is important not only for otherwise normal children but also for patients with Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, mucopolysaccharidoses,

and obesity. Studies are required to determine if the risk of postoperative complications can be stratified to the patient's disease severity as defined by PSG.
2. Determine the degree to which overweight and/or obesity correlates with OSA severity as measured by PSG. PSG parameters that correlate with respiratory compromise perioperatively in obese children undergoing tonsillectomy should also be examined.
3. Conduct a large-scale prospective study to determine the ability of PSG to predict surgical outcomes to determine whether abnormal PSG findings reliably predict the elimination of SDB after surgical intervention. This type of study would also be beneficial for predicting when tonsillectomy would be ineffective or potentially dangerous in the management of SDB.
4. Develop validated severity scales for PSG to benefit inpatient hospital admission and perioperative monitoring in children with severe OSA.
5. Examine the benefits of inpatient postoperative monitoring in children younger than age 3 with Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, mucopolysaccharidoses, or obesity where PSG identified only mild to moderate OSA.
6. Study the impact of PSG findings (severity, including normal) on the need for additional preoperative and postoperative evaluation and testing of children with SDB compared to those without SDB. Studies are needed to determine who would benefit from postoperative PSG.
7. Study the relationship between PSG findings (severity) and the perioperative management of children with SDB.
8. Conduct an outcomes study to determine the optimal anesthetic management to reduce the rate of postoperative complications in light of PSG findings (severity).
9. Study which parameters PM must measure to replicate laboratory findings and accurately predict children at risk for postoperative complications. This is of particular importance to patients who may lack access to a sleep laboratory and to those children who have difficulty sleeping in a foreign environment.
10. Additional studies of intraoperative anesthetic parameters such as end tidal CO_2 may show promise in predicting postoperative respiratory complications in patients with SDB.

Disclaimer

This clinical practice guideline is not intended as a sole source of guidance in prescribing polysomnography. Rather, it is designed to assist clinicians by providing an evidence-based framework for decision-making strategies. The guideline is not intended to replace clinical judgment or establish a protocol for all individuals who may benefit from polysomnography and may not provide the only approach to determining the appropriateness for polysomnography. Where data were lacking, a combination of clinical experience and expert consensus was used. A scheduled review process will occur 5 years from publication or sooner if compelling evidence warrants earlier consideration.

As medical knowledge expands and technology advances, clinical indicators and guidelines are promoted as conditional and provisional proposals of what is recommended under specific conditions but are not absolute. Guidelines are not mandates; these do not and should not purport to be a legal standard of care. The responsible physician, in light of all the circumstances presented by the individual patient, must determine the appropriate treatment. Adherence to these guidelines will not ensure successful patient outcomes in every situation. The American Academy of Otolaryngology–Head and Neck Surgery emphasizes that these clinical guidelines should not be deemed to include all proper treatment decisions or methods of care, or to exclude other treatment decisions or methods of care reasonably directed to obtaining the same results.

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Disclosures

Competing interests: Peter S. Roland: Advisory Board for MedE Corporation, Advisory Board for Entopica Therapeutics, and Advisory Board for Cochlear Corporation; consultant and speaker for Alcon Labs; consultant for Foresight Biotherapeutics; speaker for GlaxoSmithKline. Tae W. Kim: consultant for Cadence Pharmaceutical; advisory panel; and received funding for educational conference/course. Michael D. Seidman: director, Center for Integrative Medicine at Henry Ford Health System (HFHS); medical director, Wellness HFHS; founder, Body Language Vitamin Co; director, Product Development Visalus Sciences; minor shareholder, Arches Tinnitus Relief (<5%); author, *Save Your Hearing Now*; several patents; multiple National Institutes of Health and other sources of grant funding; scientific/medical adviser to major corporations (ie, Web MD, BASF, NFL, MLB), and several startup companies.

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The Laryngoscope

Contemporary Review

Juvenile Nasopharyngeal Angiofibroma: A Systematic Review and Comparison of Endoscopic, Endoscopic-Assisted, and Open Resection in 1047 Cases

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Objectives/Hypothesis: This study is a review of the treatment outcomes of juvenile nasopharyngeal angiofibroma (JNA) specifically comparing endoscopic, endoscopic-assisted, and open surgical approaches.

Study Design: Systematic review of studies using the MEDLINE database.

Methods: A systematic review of studies on JNA from 1990 to 2012 was conducted. A search for articles related to JNA, along with bibliographies of those articles, was performed. Articles were examined for individual patient data (IPD) and aggregate patient data (APD). Demographics, presenting symptoms, surgical approach, follow-up, and outcome were analyzed.

Results: Eighty-five articles were included, with IPD reported in 57 articles (345 cases) and APD in 28 articles (702 cases). For the IPD cohort, average follow-up was 33.4 months (range, 0.5–264 months). Average blood loss was 544.0 mL, 490.0 mL, and 1579.5 mL for endoscopic, endoscopic-assisted, and open surgical cases, respectively ($P < .05$). Recurrence rate following endoscopic surgery and open surgery were significantly less than endoscopic-assisted surgery ($P < .05$). In the APD cohort, the recurrence rate following endoscopic surgery was 4.7% compared to 20.6% in the endoscopic-assisted group and 22.6% in the open surgery group ($P < .05$). Among studies that reported Radkowski/Sessions grading, there was no significant difference in recurrence rates for both the IPD and APD cohorts across each stage between open and endoscopic surgery ($P > .05$).

Conclusions: In this study, endoscopic resection had a significantly lower intraoperative blood loss and lower recurrence rate when compared to open resection. However, there was no difference in recurrence rate when analyzing the IPD and controlling for Radkowski/Sessions grading. Therefore, further large-scale studies may be required to fully elucidate treatment options.

Key Words: Juvenile nasopharyngeal angiofibroma, sinonasal tumors, anterior skull base tumor, endoscopic anterior skull base tumor resection, skull base, infratemporal fossa, angiofibroma, vascular sinonasal tumor, sinonasal tumor.

Level of Evidence: 3a.

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INTRODUCTION

Juvenile nasopharyngeal angiofibroma (JNA) is a rare, benign, and highly vascular tumor that accounts for 0.05% to 0.5% of all head and neck neoplasms.[1] First classified by Chauveau et al.[2] and Friedberg et al.,[3] JNAs are nonencapsulated and composed of an irregular network of blood vessels set in fibroblastic stroma (Fig. 1).[4] Typically, JNA affects adolescent males. The most common presentation of this tumor includes painless nasal obstruction, recurrent unilateral epistaxis, and a nasopharyngeal mass.[5] These tumors originate in the nasopharynx and can be locally aggressive, causing extensive tissue destruction and bone remodeling.[1,6] Expansion of these tumors can occur anteriorly into the nasal cavity, laterally into the pterygopalatine fossa, and superiorly into the intracranial cavity.[7] Due to the vascular nature of these tumors, life-threatening epistaxis and massive intraoperative hemorrhage have been reported.[8]

Currently, there is limited consensus on the ideal staging system for JNAs and there are several criteria

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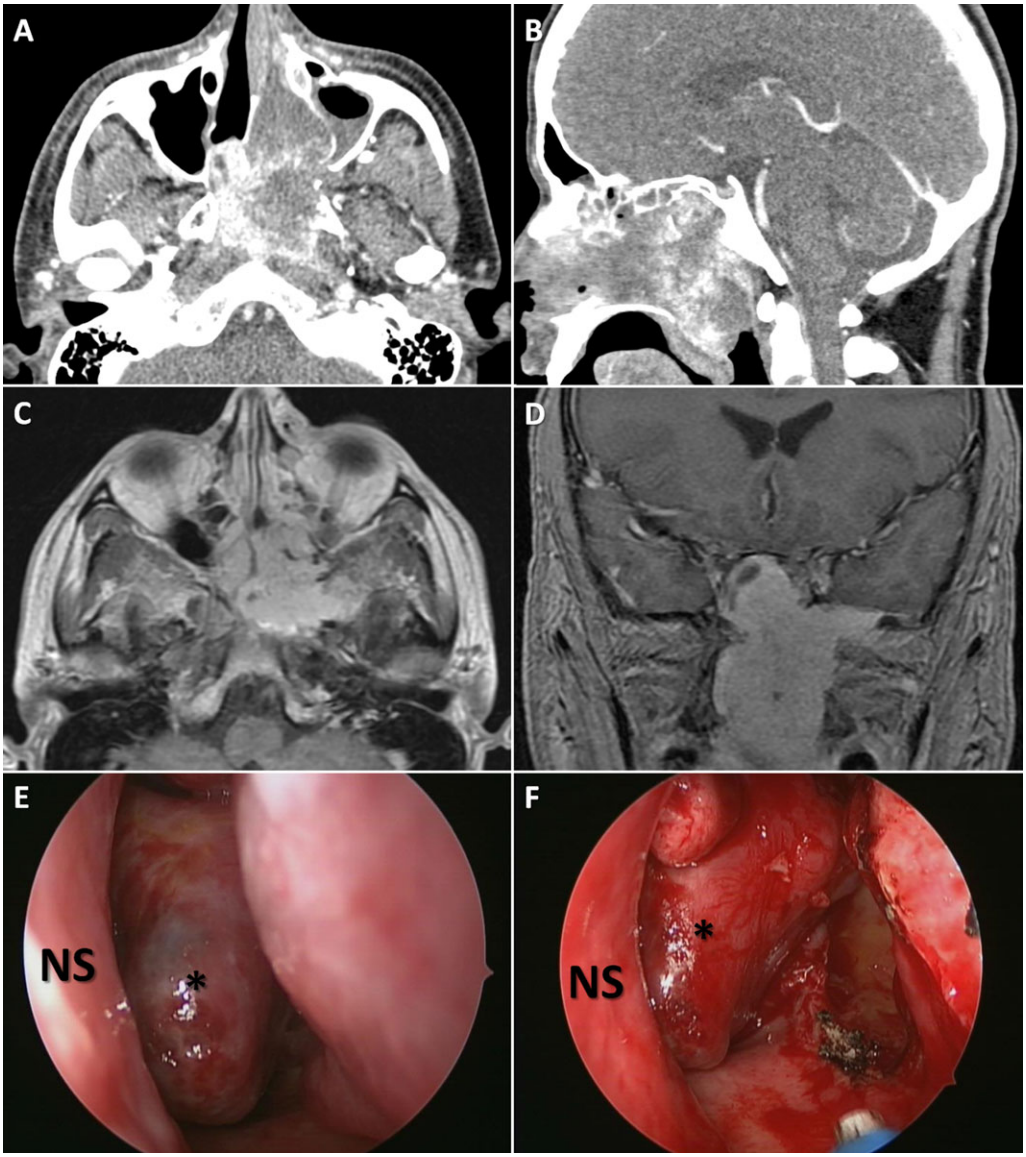

Fig. 1. Axial (A) and sagittal (B) contrast-enhanced computed tomography angiogram of a patient with a mostly left sinonasal juvenile nasopharyngeal angiofibroma. Axial (C) and coronal (D) T1-weighted gadolinium enhanced magnetic resonance imaging of the same patient demonstrating the nasopharyngeal angiofibroma. (E) Thirty-degree endoscopic view of the left sinonasal mass. (F) Endoscopic view of the lesion after endoscopic modified left medial maxillectomy. Asterisks depict lesion. NS = nasal septum.

utilized such as those established by Radkowski et al.,[9] Andrews et al.,[10] Sessions et al.,[11] Chandler et al.,[12] Fisch,[13] Onerci et al.,[14] and Snyderman et al.[15] Staging is based on tumor spread, which is frequently assessed by computed tomography (CT) and magnetic resonance imaging (MRI). CT is best utilized for determining bony changes and MRI for soft tissue destruction.[16] Due to the vascular nature of JNA, angiography is often performed to identify the primary vessels that feed the tumor and allow for embolization to reduce intraoperative blood loss.[17]

The primary treatment for JNA is surgical excision, either by endoscopic, endoscopic-assisted, or open surgical approaches.[7,18,19] Open approaches include lateral rhinotomy, transpalatal, transmaxillary, midfacial degloving, Le Fort I, Denker, infratemporal, and various combinations of approaches.[20–25] With the advent of minimally invasive endoscopic techniques, there have been several studies assessing the effectiveness of endoscopic resection of JNA.[26–28] Although prior studies have elucidated the benefits of the endoscopic approach, they have been limited by the number of patients. We present a systematic review of the literature on JNA, comparing endoscopic, endoscopic-assisted, and open surgical approaches for this rare but potentially life-threatening condition.

MATERIALS AND METHODS

Search Strategy

The MEDLINE database was searched for "nasopharyngeal angiofibroma," "sinonasal angiofibroma," and "nasal

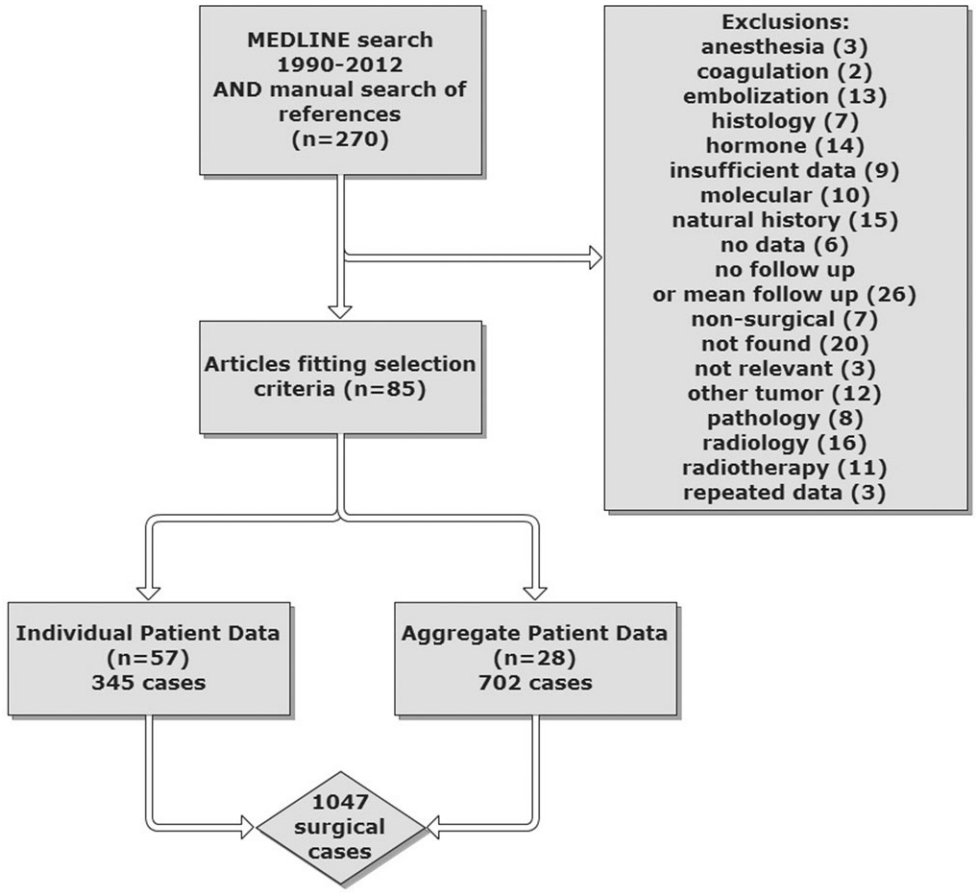

Fig. 2. Flow diagram of identified, excluded, and included studies.

angiofibroma," with a date range of January 1, 1990 to the present. Titles and abstracts were reviewed by two authors for pertinence to the topic of surgical management of JNA. Additionally, the references of included articles were searched manually to gather any studies that may not have been found through the initial search.

Inclusion Criteria

We included all English-language articles, which included case reports, case series, retrospective studies, and nonrandomized prospective studies that pertained to the surgical management of JNA. Patients of all ages and both sexes were included. Cases of recurrent JNA were also included in this review. Articles were included if they reported the diagnosis of JNA, surgical approach, outcome, and follow-up. The articles were then separated into two broad categories: aggregate patient data (APD) and individual patient data (IPD). Articles that presented outcome and follow-up for each individual patient (typically case reports and case series) were included in the IPD set. A second dataset, APD was constructed from articles that presented mean follow-up for an entire patient cohort (typical of larger case series, institutional reviews, or prospective studies).

Exclusion Criteria

Articles that were non-English or animal studies were excluded during the MEDLINE search. Articles pertaining to anesthesia, coagulation, embolization, histology, hormone, nonsurgical management, natural history, other tumors, pathology, radiology, and radiotherapy were excluded. Articles that had no data, insufficient data, and no follow-up or mean follow-up were also excluded. Articles from the same institution by the same set of authors were screened for study time-period overlap, and if repetitive information was presented, duplicated data were excluded. Articles with unobtainable full text were excluded.

Data Extraction

All data were extracted by two independent authors and included patient age, sex, presenting symptoms, tumor location, grading system utilized, grade, surgical approach (purely endoscopic, endoscopic-assisted, or open), outcome (remission/disease free, residual tumor/recurrence, or death), and follow-up. The data were reported per case, not per patient due JNA's tendency to recur and for patients to have repeat surgeries. Any discrepancies were addressed following discussion.

Data Analysis

This analysis utilized Microsoft Excel (Microsoft Corp., Redmond, WA) for data aggregation and analysis, and SAS Software (SAS Institute Inc., Cary, NC) for χ^2 tests, Fisher exact tests, and analysis of variance (ANOVA). Recurrence rates were compared with χ^2 tests or Fischer exact tests where appropriate. Intraoperative blood loss was compared using ANOVA.

RESULTS

Searching the MEDLINE database using the keywords and manual bibliography search identified 270 studies (Fig. 2). Exclusion criteria included no follow-up OR no mean follow-up (26), radiology (16), natural

history (15), hormone therapy (14), embolization (13), other tumors (12), radiotherapy (11), insufficient data (nine), pathology (eight), nonsurgical (seven), histology (seven), no data (six), anesthesia (three), not relevant (three), repeat data (three), and coagulation studies (two). Twenty articles were not found. After applying the aforementioned criteria, 85 articles were included in the systematic review.

These 85 studies were composed of 57 studies with IPD and 28 studies with APD (Table I). The studies with IPD spanned from 1992 to 2011, totaling 345 surgeries. Information on age, sex, location of tumor, associated symptoms, staging system, tumor stage, surgical approach, outcome, and follow-up were recorded if available. The aggregate studies spanned from 1996 to 2011, totaled 702 surgeries, and at minimum included the diagnosis, surgical approach, recurrence, and mean follow-up.

Patient Demographics

The average age of the individual patients in this review was 17.2 years (range, 1.25 to 64 years). The vast majority of patients in the IPD cohort were male (98.7%). Age was reported for 303 patients and gender was reported for 305 patients. Presenting symptoms were included in 130 cases; the most common presenting symptoms of JNA were nasal obstruction (76.2%), epistaxis (76.2%), headache (16.9%), vision changes (12.3%), eustachian tube dysfunction (9.2%), and cheek swelling (8.5%). JNAs were most commonly located in the nasopharynx (85.2%), followed by the nasal cavity (66.1%), sphenoid sinus (49.8%), pterygopalatine fossa (48.6%), and infratemporal fossa (29.2%) (Table II).

IPD Surgical Approaches and Recurrence Rates

We found 345 cases of JNA that were treated by either purely endoscopic, endoscopic-assisted, or open approaches (Table III). Of these 345 surgeries, 158 were purely endoscopic, 15 were endoscopic-assisted, and 172 were completed through an open surgical approach. The recurrence rate in the purely endoscopic approach was 10.8%, and there were no deaths reported in this group. The open surgical approach yielded a recurrence rate of 14.5%, and there were two deaths reported, both occurring intraoperatively. In total, 27 of the 172 (15.7%) surgeries completed by the open approach yielded a negative outcome (recurrence 14.5% or death 1.2%). Endoscopic-assisted cases had the highest recurrence rate at 46.7%. There was a significant difference in recurrence rates among these approaches ($P < .05$). Recurrence rates were significantly lower in cases completed by the purely endoscopic approach or open approach compared to endoscopic-assisted approaches ($P < .05$). There was no significant difference in recurrence rates between purely endoscopic and open surgical approaches ($P > .05$) (Table IV). The entire IPD cohort had a recurrence rate of 14.2% with an average follow-up of 33.4 months.

Of the 345 JNA included in the IPD cohort, 105 were staged using the Radkowski et al.[9] or Sessions et al.[11] staging criteria (Table V). There was no significant difference in recurrence rate when utilizing the purely endoscopic approach or open surgical approach regardless of stage ($P > .05$). There was only one case completed by the endoscopic-assisted approach, and as such it was excluded from the statistical analysis. The total recurrence rate for JNA resected by the purely endoscopic approach in this group was 6.7% compared to a recurrence rate of 18.2% when utilizing the open surgical approach ($P > .05$).

In the IPD, in those cases where Radkowski/Sessions staging was used (105/345 cases), there was no preference in surgical approach based on stage ($P > .05$). Within the APD, where Radkowski/Sessions staging was used (183/705 cases), there was also no preference in surgical approach used based on stage ($P > .05$).

Blood Loss and Preoperative Embolization

Blood loss was reported in 138 cases, 89 of these cases were completed purely endoscopically, five cases were endoscopic-assisted, and 44 cases were completed with an open surgical approach (Table VI). The mean blood loss for the purely endoscopic group was 544.0 mL (range, 20–2,000 mL) compared to 1,579.5 mL (range, 350–10,000 mL) in the open surgical group. Endoscopic-assisted cases had a mean blood loss of 490.0 mL (range, 100–950 mL). Using ANOVA, mean blood loss was found to be significantly different among these three groups ($P < .05$).

Of the 138 cases where blood loss was reported, data on preoperative embolization were available for 131 cases. Preoperative embolization was completed in 60 pure endoscopic cases, 29 open cases, and two endoscopic-assisted cases; no preoperative embolization was done in 40 cases. For usage of preoperative embolization, there was no statistical difference between open and pure endoscopic cases ($P > .05$). In purely endoscopic cases, preoperative embolization led to significantly lower amounts of blood loss with a mean estimated blood loss of 406.7 mL for embolized cases compared to 828.3 mL for nonembolized cases ($P < .05$). In open surgical cases, there was significantly more blood loss with preoperative embolization (1912.1 mL) compared to nonembolized cases (685.0 mL) ($P < .05$).

APD Surgical Approaches and Recurrence Rates

There were 702 total procedures reported in the APD cohort, of which 150 were completed purely endoscopically, 34 were endoscopic-assisted, and 518 were open surgical procedures (Table VII). Recurrence rate varied from 0.0% to 23.1% for purely endoscopic procedures, with a weighted average of 4.7% for all endoscopic cases. There were 34 endoscopic-assisted cases with a weighted average recurrence rate of 20.6% (range, 15.0%–50.0%). Open surgical procedures had a recurrence rate that ranged from 0.0% to 50.0%, with a weighted average of 22.6%. Analysis revealed that there was a significant difference among recurrence rates in

TABLE I.
Studies Meeting Criteria for Systematic Review.

Author	Year	No. of Patients
Individual patient data		
Ahmad[41]	2008	5
Albuquerque[42]	2009	1
Antoniades[43]	2002	1
Avelar[44]	2011	2
Aziz Sultan[45]	2011	1
Borghei[46]	2006	23
Browne[47]	2000	1
Browne[48]	1994	5
Dare[49]	2003	2
de Brito[50]	2006	9
Donald[51]	2004	5
Dubey[52]	2011	16
Eloy[53]	2007	6
Fagan[54]	1997	16
Fonseca[55]	2008	15
Gaffney[56]	1997	1
Gallia[57]	2010	1
Goel[58]	1994	1
Gullane[20]	1992	14
Gupta[8]	1997	7
Handa[59]	2001	1
Hardillo[23]	2004	28
Hazarika[60]	2002	9
Hofmann[61]	2005	25
Kamel[62]	1996	1
Khalifa[63]	2001	1
Koshy[64]	2008	1
Lin[22]	2008	6
Mair[65]	2003	7
Moschos[66]	1998	1
Murray[67]	2000	1
Nakamura[68]	1999	1
Naraghi[69]	2003	12
Newlands[70]	1999	12
Nicolai[71]	2003	15
Nomura[72]	2006	1
Ochi[73]	2002	1
Patrocinio[74]	2002	1
Patrocinio[75]	2005	1
Peloquin[76]	1997	1
Powell[77]	2002	5
Ramos[78]	2011	2
Reddy[79]	2002	1
Rha[80]	2003	1
Riggs[81]	2010	1
Robinson[82]	2005	4
Romani[83]	2010	1
Rong[84]	2008	3
Schick[85]	1998	1
Schick[86]	1999	5
Scholtz[5]	2001	14
Sinha[87]	2008	2
Szymanska[88]	2006	1
Tosun[21]	2006	24
Tseng[89]	1997	1
Yi[90]	2007	2
Yiotakis[40]	2008	19
Total individual patient data		345
Aggregate patient data		
Andrade[91]	2007	12
Bales[92]	2002	5
Bleier[93]	2009	18
Bosraty[94]	2011	42
Chen[33]	2006	8
Cherekaev[95]	2011	29
Danesi[96]	2008	85
de Mello-Filho[97]	2004	19
Elsharkawy[98]	2010	23
Gaillard[99]	2010	16
Hackman[18]	2009	31
Herman[34]	2011	4
Hosseini[100]	2005	37
Howard[36]	2001	39
Huang[101]	2009	19
Margalit[25]	2009	7
Mattei[102]	2011	20
Midilli[103]	2009	42
Paris[6]	2001	33
Pryor[19]	2005	58
Radkowski[9]	1996	23
Roger[35]	2002	20
Singh[104]	2011	12
Tewfik[105]	1999	14
Ungkanont[106]	1996	36
Wormald[107]	2003	7
Ye[26]	2011	23
Zhang[108]	1998	20
Total aggregate patient data		702

this cohort ($P < .05$). There was significantly lower recurrence in the purely endoscopic group compared to endoscopic-assisted ($P < .05$) and open surgical approaches ($P < 0.05$) (Table IV). There was no significant difference between recurrence rates of endoscopic-assisted and open surgical cases ($P > .05$).

DISCUSSION

JNA is a rare entity, making prospective, randomized, double-blind analysis difficult. Therefore, systematic review of the existing literature can provide valuable information when these optimal studies are not feasible. We conducted a systemic review with the

TABLE II.
Summary of Individual Patient Data: Patient Demographics, Presenting Symptoms, and Tumor Extent From the Sphenopalatine Region.

Presenting Symptoms (n = 130 Cases)	No. Reported	% Reported	Location (n = 257 Cases)	No. Reported	% Reported
Nasal obstruction	99	76.2	Nasopharynx	219	85.2
Epistaxis	99	76.2	Nasal cavity	170	66.1
Headache	22	16.9	Sphenoid sinus	128	49.8
Vision changes	16	12.3	Pterygopalatine fossa	125	48.6
Hyponasality	13	10.0	Infratemporal fossa	75	29.2
Eustachian tube dysfunction	12	9.2	Ethmoid sinus	47	18.3
Cheek swelling	11	8.5	Pterygomaxillary fissure	32	12.5
Proptosis	9	6.9	Maxillary sinus	28	10.9
Nasal discharge	8	6.2	Orbit	26	10.1
Pain	4	3.1	Cavernous sinus	26	10.1
Snoring	4	3.1	Middle cranial fossa	22	8.6
Hearing changes	3	2.3	Cheek	17	6.6
Smell changes	3	2.3	Pterygoid process/plate	16	6.2
Posterior nasal drip	2	1.5	Pterygoid base	14	5.4
Respiratory distress	2	1.5	Clivus	11	4.3
Alopecia	1	0.8	Sella turcica	9	3.5
Epiphora	1	0.8	Basisphenoid	8	3.1
Weight loss	1	0.8	Intracranial (unspecified)	6	2.3
Insomnia	1	0.8	Skull base	6	2.3
Dizziness	1	0.8	Orbital apex	6	2.3
Facial numbness	1	0.8	Parasellar region	5	1.9
Dry eye	1	0.8	Sphenoid bone	5	1.9
			Vomer	3	1.2
Average age (n = 303 patients), yr	17.2		Inferior orbital fissure	2	0.8
Range (1.25–64 years)			Anterior cranial fossa	1	0.4
			Oropharynx	1	0.4
Sex (n = 305 patients), N			Optic chiasm	1	0.4
Male	301	98.7	Optic canal	1	0.4
Female	4	1.3	Vidian canal	1	0.4
			Temporal fossa	1	0.4
			Lacrimal sac	1	0.4
			Superior orbital fissure	1	0.4

largest single series of JNA to apply acquired clinically relevant information toward its current and future management.

Incidence and Demographics

There have been few studies on the incidence of JNA. Glad et al.[1] reported an incidence rate of 0.4 cases per million inhabitants per year, with a median age at diagnosis of 15 years. When considering the population at risk, the incidence rose to 3.7 cases per million. The population that is affected by JNA is overwhelming consisting of adolescent males. In our study, we found 301 males out of the 305 cases where sex was reported. The mean age of this patient cohort was 17.2 (range, 1.25–64

TABLE III.
Individual Patient Data Cohort.

All Surgeries (n = 345)	Total Cases	Remission (%)	Recurrence (%)	Death (%)
Endoscopic	158	141 (89.2)	17 (10.8)	0 (0.0)
Endoscopic-assisted	15	8 (53.3)	7 (46.7)	0 (0.0)
Open surgery	172	145 (84.3)	25 (14.5)	2 (1.2)

Mean follow-up = 33.4, $P < .05$ (χ^2).
Two by three χ^2 analysis revealed that there was a significant difference among recurrence rates based on approach ($P < .05$).

TABLE IV.
The Results of χ^2 or Fisher Exact Tests Comparing Recurrence Rates Between Treatment Groups in the IPD and APD Cohorts.

	IPD	APD
ES vs. OS	$P = .323$ (NS)	$P < .05$ (S)
ES vs. EA	$P < .05$ (S)	$P < .05$ (S)
OS vs. EA	$P < .05$ (S)	$P = 1.000$ (NS)

APD = aggregate patient data; EA = endoscopic assisted group; ES = endoscopic group; IPD = individual patient data; NS = not significant; OS = open surgery group; S = significant.

TABLE V.
Individual Patient Data Cohort That Included Staging by Radkowski or Sessions Staging Criteria.

	Radkowski or Sessions Graded Patients (n = 105 Patients)			
	Stage I	Stage II	Stage III	Total
Endoscopic (ES)	29	28	3	60
ES recurrences (%)	1 (3.4%)	3 (10.7%)	0 (0.0%)	4 (6.7%)
Endoscopic-assisted (EA)	0	1	0	1
EA recurrences (%)	—	0 (0.0%)	—	0 (0.0%)
Open surgery (OS)	13	27	4	44
OS recurrences (%)	1 (7.7%)	6 (22.2%)	1 (25.0%)	8 (18.2%)
ES vs. OS	$P = 1.000$	$P = .295$	$P = 1.000$	$P = .118$

Fisher exact tests were completed to compare recurrence between the endoscopic and open surgery groups; no significant difference was found.

EA = endoscopic assisted group; ES = endoscopic group; OS = open surgery group.

years). Interestingly, four cases of JNA were women with the ages of 14, 31, 57, and 64 years, which may call into question the diagnosis. The tendency for this tumor to occur in adolescent males has led to the hypothesis that sex hormone receptors are present in JNA, although evidence to support this claim remains equivocal.[29–31]

Presenting Symptoms

There are a wide variety of symptoms, including extranasopharyngeal symptoms that can manifest as a result of JNA due to its locally destructive nature. However, there is an agreement on the classic clinical presentation of JNA: an adolescent male with recurrent epistaxis, nasal obstruction, and a nasopharyngeal mass.[20] Our findings were consistent with the current paradigm; 76.2% of patients presented with nasal obstruction and recurrent epistaxis. Prior studies have demonstrated similar proportions of patients who present with these symptoms.[19,21,23,32]

Location and Staging

Advances in imaging have allowed for more accurate localization and staging of JNA, which are essential for selection of the correct approach for resection. CT and MRI are the two most commonly utilized modalities for assessing JNAs. Biopsies can be an effective alternative, but surgeons remain wary due to the vascular nature of JNA and possibility of causing severe epistaxis. The location of JNA is classically in the nose and pterygopalatine fossa, with erosion of bone posteriorly, and the diagnosis can be made solely on the basis of CT.[16] In our study, the most common locations for JNA were the nasopharynx, nasal cavity, sphenoid sinus, and the pterygopalatine fossa. The middle cranial fossa (8.6%) was the most common location for intracranial manifestation of JNA. Most patients with JNA manifest prior to intracranial extension. We found that only seven cases of the 105 with available staging manifested as Radkowski stage IIIa or stage IIIb (with intracranial extension).

Treatment and Recurrence

Consensus has not been reached as to which approach is most appropriate with respect to complications, morbidity, and mortality. With the introduction of endoscopic techniques, both purely endoscopic and endoscope-assisted, further procedures have been developed, but not extensively evaluated. Some may note that a predilection for treating stage I and stage II neoplasms with an endoscopic approach may distort outcome measures. However, when we analyzed for a preference based on stage (albeit only with a subset of the data), we found no significant difference in both the IPD and APD cohorts.

From the individual patient cohort, we found that there is no statistically significant difference between the recurrence rate of JNA after purely endoscopic and open surgery. Both of these approaches had lower recurrence rates compared to the endoscopic-assisted group. Yet, the comparison is of limited value, because only 15 cases were completed with the endoscopic-assisted approach. Purely endoscopic and open surgical techniques were equally as effective regardless of stage. Prior studies have demonstrated that endoscopic approaches may have lower recurrence rate, but statistical analysis is limited by the small power of these studies.[33,34] For example, Pryor et al.[19] found that a purely endoscopic approach had a recurrence rate of 0.0% in five patients, compared to a recurrence rate of 26.4% after open surgical approaches. Renkonen and colleagues[7] demonstrated that a 33.3% recurrence rate was achieved following endoscopic surgery compared to 37.5% in the open surgical group; three patients participated in the endoscopic group. Both of these studies suffer from a limited number of patients included in the endoscopic group. Standardization of staging criteria and multi-institute studies are required to fully elucidate when the endoscopic approach is indicated for resection.

Although the individual patient cohort suggests that purely endoscopic and open surgical approaches are equally as effective, the aggregate patient cohort leads to a different conclusion. In the aggregate patient cohort of 702 cases, we found that purely endoscopic resection had a significantly lower rate of recurrence/residual disease compared to both endoscopic-assisted and open surgical approaches. Recent studies that focus solely on the purely endoscopic approach have come to similar conclusions.[35] Nicolai et al.[27] conducted one of the largest studies that focused on purely endoscopic approaches, consisting of 46 consecutive patients. The authors of this study found that the recurrence rate was

TABLE VI.
Blood Loss Compared Among Endoscopic, Endoscopic-Assisted, and Open Surgery Groups in the Individual Patient Data Cohort.

Blood Loss (n = 138 Patients)	Patients Reported	Mean Blood Loss (mL)	Range (mL)
Endoscopic	89	544.0	20–2,000
Endoscopic-assisted	5	490.0	100–950
Open surgery	44	1579.5	100–10,000

Analysis of variance revealed a statistically significant difference in mean blood loss ($P < .05$).

TABLE VII.
Aggregate Patient Data Cohort of Studies Comparing Endoscopic, Endoscopic-Assisted, and Open Surgery Groups.

All Aggregate Data												
Study	Year	Total Patients	ES Patients	ES Recurrence	ES % Recurrence	EA Patients	EA Recurrence	EA % Recurrence	OS Patients	OS Recurrence	OS % Recurrence	Follow-up
Ye	2011	23	23	0	0.0	0	—	—	0	—	—	58.0
Singh	2011	12	0	—	—	0	—	—	12	0	0.0	12.0
Mattei	2011	20	0	—	—	20	3	15.0%	0	—	—	60.0
Herman	2011	4	4	0	0.0	0	—	—	0	—	—	11.3
Cherekaev	2011	29	0	—	—	0	—	—	29	5	17.2	48.0
Bosraty	2011	42	13	3	23.1	0	—	—	29	9	31.0	43.4
Gaillard	2010	16	2	0	0.0	2	1	50.0%	12	6	50.0	27.6
Elsharkawy	2010	23	0	—	—	0	—	—	23	4	17.4	21.0
Midilli	2009	42	12	0	0.0	0	—	—	30	7	23.3	92.0
Margalit	2009	7	0	—	—	0	—	—	7	0	0.0	42.0
Huang	2009	19	19	0	0.0	0	—	—	0	—	—	34.0
Hackman	2009	31	15	1	6.7	12	3	25.0%	4	1	25.0	48.0
Bleier	2009	18	10	0	0.0	0	—	—	8	4	50.0	24.4
Danesi	2008	85	0	—	—	0	—	—	85	13	15.3	54.9
Andrade	2007	12	12	0	0.0	0	—	—	0	—	—	24.0
Chen	2006	8	8	1	12.5	0	—	—	0	—	—	54.0
Pryor	2005	58	5	0	0.0	0	—	—	53	14	26.4	13.0 ES, 48.0 OS
Hosseini	2005	37	0	—	—	0	—	—	37	10	27.0	46.5
de Mello-Filho	2004	19	0	—	—	0	—	—	19	0	0.0	116.4
Wormald	2003	7	7	0	0.0	0	—	—	0	—	—	45.0
Roger	2002	20	20	2	10.0	0	—	—	0	—	—	22.0
Bales	2002	5	0	—	—	0	—	—	5	1	20.0	38.0
Paris	2001	33	0	—	—	0	—	—	33	8	24.2	56.0
Howard	2001	39	0	—	—	0	—	—	39	8	20.5	24.0
Tewfik	1999	14	0	—	—	0	—	—	14	4	28.6	63.0
Zhang	1998	20	0	—	—	0	—	—	20	5	25.0	25.0
Ungkanont	1996	36	0	—	—	0	—	—	36	13	36.1	61.8
Radkowski	1996	23	0	—	—	0	—	—	23	5	21.7	72.0
Total		702	150	7	4.7	34	7	20.6	518	117	22.6	—

EA = endoscopic assisted group; ES = endoscopic group; OS = open surgery group.

8.7% and suggest that endoscopic techniques can be utilized even in cases of intracranial involvement. Indications for open surgical approaches may include instances when there is significant involvement of internal carotid artery, cavernous sinus, or optic nerve.[27] Ardehali et al.[32] also came to similar conclusion following a study of 47 patients treated by endoscopic or endoscopic-assisted resection; recurrence rate in this cohort was 19.1%. The authors of this study similarly suggested that endoscopic approaches may be utilized in cases of minimal intracranial involvement, but cases where there is a large intracranial component should be reserved for open surgery. Drawing on their experiences with endoscopic resection, the authors recounted one case of a Radkowski stage IIIb JNA. Due to cavernous sinus injury, significant intraoperative hemorrhage occurred leading to 8,500 mL of blood loss.[32]

The primary measure of success in the treatment of JNA is the recurrence rate.[16] Howard et al.[36] found that the recurrence rate was reduced from 35.0% to 0.0% when macroscopic removal of JNA was combined with drilling out of the basisphenoid. The working hypothesis in this study was that most recurrences occur as a result of invasion of the sphenoid and incomplete excision. Lund et al.[37] put forth the concept that JNA undergoes a period of rapid growth followed by a stable phase. Therefore, the recurrence of JNA may be due to an incomplete resection during the aggressive growth phase of the JNA.[36] Recognizing this and the fact that not all studies report residual tumor separately from recurrence, we combined residual tumor and recurrence into one category. Comparing the IPD and APD, the total recurrence rates of these series were 14.2% and 18.7%, respectively. The recurrence rates in this study are similar to what has been reported in the literature.[14,18]

The conflicting results between IPD and APD cohorts with respect to recurrence rate is interesting and should be commented on. IPD provides the most effective data when provided in large quantities, as it allows for complete and accurate analysis of outcome measures as well

as demographic data. The risk of bias in IPD, however, is introduced when it is provided by case reports and case series, as these are low in quality and therefore high in variability. Meta-analyses are highly effective in high-quality data and most useful in randomized controlled studies. Meta-analyses would also be more rigorous in terms of statistical independence and hidden biases than the techniques used in this study. However, given the rare nature of this tumor, there were not sufficient studies that satisfied the requirements for meta-analyses. The APD group, therefore, was used to examine recurrence rate across studies that generally provided a higher n (average of 25.1 [range, 4–85] cases per study vs. 6.1 [range, 1–28] for IPD studies). Although APD typically only report summary data, the value of these data is higher than that provided by case reports and small case series, as temporal, regional, and interinstitutional biases are not introduced. In addition, smaller studies do not take into account the experience of the surgeon or group of surgeons over time. Because the endoscope is a relatively new tool, there is a learning curve associated with it.[38] This may demonstrate that in larger APD studies, where the surgeons were more experienced with endoscopic techniques, there might be a higher benefit in using the endoscope. This could possibly explain the significance obtained in the APD cohort compared to the IPD cohort.

Recurrence Rates in Endoscopic-Assisted Surgery

Recurrence rate in endoscopic-assisted surgery is of particular interest due to the novelty of this approach. This hybrid technique combines the superior visualization provided by the endoscope with increased maneuverability due to surgical incision. These added benefits make the endoscopic-assisted approach particularly well suited for resection of larger and more technically challenging JNAs. The data from our study suggest that the endoscopic-assisted approach provides limited benefits in terms of recurrence rates. In the IPD cohort, the recurrence rate was significantly higher, and in the APD cohort there was no significant difference between endoscopic-assisted and open surgical approaches. Yet, it is of note that endoscopic-assisted approaches constituted only 49 of 1047 cases reviewed in our study. Other studies by Carrau et al.[39] and Hackman et al.[18] have found that recurrence rates of endoscopic-assisted surgery are higher than purely endoscopic surgery. Yet, endoscopic-assisted approaches are reserved for cases where the purely endoscopic approach would not suffice due size, spread, or complexity of the JNA that must be resected. In all, more studies are required to compare open surgery and endoscopic-assisted surgery.

Blood Loss

Blood loss was found to be significantly less in the purely endoscopic approach compared to the open approach.[32] In our study, the average blood loss from the purely endoscopic approach was 544.0 mL (range, 20–2000 mL) compared to 1579.5 mL (range, 350–10,000 mL) for the open approach. Endoscopic-assisted cases had an average blood loss of 490.0 mL (range, 100–950 mL). Several studies have come to similar conclusions regarding blood loss.[19,32,40] Diminished blood loss leads to fewer transfusions and decreased morbidity and mortality. Intraoperative hemorrhage still occurs with purely endoscopic techniques, especially in cases with significant intracranial extension.[32] In addition, preoperative embolization was found to make a significant impact on blood loss when used in purely endoscopic cases. Preoperative embolization increased blood loss in open surgeries, but there were a limited number of cases with both values included. Additionally, it is possible that the significantly increased blood loss noted in the embolized cases in the open approach may be due to selection bias based on larger tumors being embolized.

Limitations

There are several limitations in this study that should be noted. Assessing studies that span a significant time frame introduces biases with respect to the advancements in diagnosis and treatment. The quality of the data available in the literature was inconsistent, and much of it was taken from case reports and case studies, thus introducing allocation and selection biases. In addition, due to the nonuniform staging systems utilized and heterogeneous reporting of follow-up, recurrence, and residual tumor, the quality of the data was affected. Ideally, there would be a uniform staging method so the endoscopic and open approaches could be effectively compared across stages with respect to outcome measures (recurrence and blood loss). Additionally, the number of endoscopic-assisted cases was limited in the literature both in the IPD and APD cohorts. In the data collection, there were some patients in which the diagnosis of JNA was questioned as they affected individuals who did not fall into the typical affected population (female gender, advanced age). Last, because APD was used, it is possible that there was heterogeneity in these studies and inconsistencies in those datasets that were unknown due to the summation of data.

CONCLUSION

JNA is a rare tumor with aggressive growth, tendency for recurrence, and local tissue destruction, making it particularly difficult to treat. In select cases, purely endoscopic surgery may be more effective than open techniques in resecting JNA, as it may lead to decreased recurrence and blood loss. Because IPD and APD results varied, however, further analysis in large-scale studies should be undertaken to further elucidate treatment modalities.

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Clinical Consensus Statement: Pediatric Chronic Rhinosinusitis

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Abstract

Objective. To develop a clinical consensus statement on the optimal diagnosis and management of pediatric chronic rhinosinusitis (PCRS).

Methods. A representative 9-member panel of otolaryngologists with no relevant conflicts of interest was assembled to consider opportunities to optimize the diagnosis and management of PCRS. A working definition of PCRS and the scope of pertinent otolaryngologic practice were first established. Patients of ages 6 months to 18 years without craniofacial syndromes or immunodeficiency were defined as the targeted population of interest. A modified Delphi method was then used to distill expert opinion into clinical statements that met a standardized definition of consensus.

Results. After 2 iterative Delphi method surveys, 22 statements met the standardized definition of consensus while 12 statements did not. Four statements were omitted due to redundancy. The clinical statements were grouped into 4 categories for presentation and discussion: (1) definition and diagnosis of PCRS, (2) medical treatment of PCRS, (3) adenoiditis/adenoidectomy, and (4) endoscopic sinus surgery (ESS)/turbinoplasty.

Conclusion. Expert panel consensus may provide helpful information for the otolaryngologist in the diagnosis and management of PCRS in uncomplicated pediatric patients.

Keywords

pediatric otolaryngology, rhinosinusitis, chronic rhinosinusitis, evidence-based medicine, review, Delphi method

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Introduction

Pediatric chronic rhinosinusitis (PCRS) is a commonly encountered condition in otolaryngological practice. Five percent to 13% of childhood viral upper respiratory tract infections may progress to acute rhinosinusitis,[1-4] with a proportion of these progressing to a chronic condition. PCRS may also coexist and/or be exacerbated by other widespread conditions such as allergic rhinitis and adenoid disease,[5-9] and some suggest the incidence of PCRS may be rising.[10] In addition, PCRS has a meaningful impact on quality of life,[11] with its related adverse effects potentially exceeding that of chronic respiratory and arthritic disease.[12] PRCS also has the potential to exacerbate asthma,[13,14] a condition that negatively affects 2% to 20% of children.[15-17]

In spite of its prevalence and impact on affected families, many aspects of PCRS remain ill-defined. At the most basic level, even the diagnostic definition of PCRS has not been concretely elucidated among our specialty societies, creating challenges in discussing clinical presentations or establishing human study protocols. Similarly, while performing nasal endoscopy and obtaining site-specific cultures may be routine in the cooperative adult population, their role in the evaluation of children has not been clearly established. Likewise, the concept of maximal medical therapy has yet to be specifically delineated, although there is a broad spectrum

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of options, ranging from topical irrigations to longstanding intravenous antibiotic therapy. Both adenoidectomy and endoscopic sinus surgery (ESS) have been reported to produce associated improvements,[18,19] thus raising practical questions regarding whether these procedures are best done in tandem or concomitantly and whether that choice should depend on age, comorbidities, or additional patient factors. In addition, other related aspects of PCRS remain controversial, such as the potential impact of gastroesophageal reflux (GER), the effect of ESS on facial growth, the role of postoperative debridement, and emerging techniques such as balloon sinuplasty in children.

Nonetheless, PCRS occurs with sufficient frequency that otolaryngologists regularly encounter it in their practice, creating opportunities for optimizing practice patterns. While experience regarding the epidemiology, diagnosis, and management of PCRS is burgeoning, the associated evidence regarding optimal medical and surgical management has clear limits. Thus, the American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF) Guidelines Task Force selected this topic for clinical consensus statement (CCS) development. The expert panel convened with the objectives of addressing opportunities to promote appropriate care, reduce inappropriate variations in care, and educate and empower clinicians and patients toward the optimal management of PCRS. This document describes the result of this process and focuses on diagnosis, medical therapy, and surgical interventions.

Methods

This clinical consensus statement was developed in discrete, predetermined steps: (1) evaluation of the suitability of PCRS as the subject of a clinical consensus statement; (2) panel recruitment; (3) vetting potential conflict of interests among proposed panel members; (4) systematic literature review; (5) determination of working definition of PCRS, intended scope of practice, and population of interest for the consensus statement; (6) modified Delphi survey development and completion; (7) iterative revision of clinical statements based on survey results; and (8) data aggregation, analysis, and presentation. The pertinent details of each of these steps will be briefly described.

Determination of PCRS as the Topic of a Consensus Statement, Panel Recruitment, and Vetting

PCRS was first considered as the subject of a clinical consensus statement based on suggestion from an American Academy of Otolaryngology—Head and Neck Surgery member. After deliberation, the Guidelines Task Force supported the suggestion, and consensus panel leadership was selected and administrative support allocated. Panel membership was strategically developed to ensure appropriate representation of all relevant subgroups within the specialty of otolaryngology. The various subgroups were contacted about the consensus statement project with the requirements and desired qualifications for panel membership,s and each subgroup then selected their own representative expert to participate. Participating subgroups include the American Society of Pediatric Otolaryngology (JJS), the American Academy of Otolaryngic Allergy (MV), the American Rhinologic Society (HHR), the Triologic Society (SC), and the appropriate committees within the American Academy of Otolaryngology—Head and Neck Surgery including the Board of Governors (SP), the Outcomes Research and Evidence Based Medicine Subcommittee (SEB), the Rhinology and Paranasal Sinus Committee (JL), the Pediatric Otolaryngology Committee (MP), and the Young Physicians Section (JP). Each member of the panel is either a fellowship-trained pediatric otolaryngologist or rhinologist in active clinical practice. Once the panel was assembled, complete disclosure of potential conflicts of interest were reported and vetted within the group. A panel vote was used to determine whether a disclosed conflict of interest necessitated disqualification from panel participation. The panel chair (SEB) and panel co-chair (JJS) led the development of the clinical statements and the Delphi process with input from a senior consultant/methodologist from the Academy leadership in the Guidelines Task Force (RMR) and administrative support from an Academy staff liaison (MC).

Literature Review and Determination of the Scope of the Consensus Statement

A systematic biomedical literature review was performed to identify current high-level evidence regarding the diagnosis and medical and surgical management of PCRS. The purpose of this literature search was to guide the CCS panel in developing clinical statements for standardized consensus evaluation that could help fill evidence gaps and assist otolaryngologists in the diagnosis and management of PCRS. The literature search was conducted in January 2014 with the assistance of a professional database search consultant. The systematic search included systematic reviews (including meta-analyses), clinical practice guidelines, and other relevant clinical consensus statements in English from Medline; National Guidelines Clearinghouse; CMA Infobase; National Library of Guidelines; National Institute for Health and Clinical Excellence (NICE); Scottish Intercollegiate Guidelines Network (SIGN); New Zealand Guidelines Group; Australian National Health and Medical Research Council; Trip Database; Guidelines International Network (G-I-N); Cochrane Database of Systematic Reviews; Excerpta Medica database (EMBASE); Cumulative Index to Nursing and Allied Health (CINAHL); Allied and Complementary Medicine Database (AMED); BIOSIS Citation Index; Web of Science; Agency for Healthcare Research and Quality (AHRQ) Research Summaries, Reviews, and Reports; and Health Services/Technology Assessment Texts (HSTAT) from 2003 using the search string: ''(chronic disease OR chronic) AND (sinusitis OR rhinosinusitis) AND (child OR adolescent OR teen).'' The gaps in literature were used as a framework for the qualitative survey.

The panel evaluated the recent AAO-HNSF CCS regarding the Appropriate Use of Computed Tomography for Paranasal Sinus Disease[20] and made an early decision to

accept the statements within this document regarding use of CT for the diagnosis of PCRS in children rather than readdress this topic within the current consensus statement.

The panel made several decisions regarding the scope of this clinical consensus statement before formally beginning the Delphi process. It was decided that the target audience of the statement would be specifically otolaryngologists. A working definition of PCRS was determined and consensus on this definition was confirmed using the Delphi process (see statement 1). The target population was defined as children ages 6 months to 18 years old with PCRS, although it was acknowledged that children of different ages have different factors in regards to the diagnosis and management of PCRS (statement 3). Children with craniofacial syndromes (eg, Trisomy 21) or relative immunodeficiency (eg, cystic fibrosis) were excluded as it was felt the treatment of this subgroup is very different from the typical PCRS patient. Once the target population and scope of practice were determined, the panel used the results of the literature review to prioritize the clinical areas that could most benefit from potential consensus from an expert panel. These areas were then used as the basis for the formulation of the initial statements that were then evaluated through the Delphi survey method.

Delphi Survey Method Process and Administration

A modified Delphi survey method was utilized to distill expert opinion into concise clinical consensus statements. The Delphi method involves using multiple anonymous surveys to assess for objective consensus within an expert panel.[21] This rigorous and standardized approach minimizes bias and facilitates expert consensus.

Web-based software (www.surveymonkey.com) was used to administer confidential surveys to panel members. The survey period was broken down into 3 iterations: 1 qualitative survey with free text boxes for responses and 2 subsequent Delphi rounds. All answers were de-identified and remained confidential; however, names were collected to ensure proper follow-up if needed. The qualitative survey included 54 questions on the definition and clinical areas of chronic pediatric sinusitis. The purpose of the qualitative survey was to narrow the scope and provide a framework for the subsequent Delphi rounds.

Based on the outcomes of the qualitative survey and resulting discussion, the panel chair developed the first Delphi survey, which consisted of 37 statements. Prior to dissemination to the panel, the Delphi surveys were reviewed by the consultant for content and clarity. Questions in the survey were answered using a 9-point Likert scale where 1 = strongly disagree, 3 = disagree, 5 = neutral, 7 = agree, and 9 = strongly agree. The surveys were distributed, and responses were aggregated, distributed back to the panel, discussed via teleconference, and revised if warranted. The purpose of the teleconference was to provide an opportunity to clarify any ambiguity, propose revisions, or drop any statements recommended by the panel.

The criterion for consensus was established a priori with reference to previous consensus statements[20,22] and followed the following criteria (outliers are defined as any rating at least 2 Likert points away from the mean):

- **consensus**: statements achieving a mean score of 7.00 or higher and have no more than 1 outlier,
- **near consensus**: statements achieving a mean score of 6.50 or higher and have no more than 2 outliers,
- **no consensus**: statements that did not meet the criteria of consensus or near consensus.

Additionally for the purposes of emphasis within the discussion, strong consensus was subsequently defined as a mean Likert score of 8.00 or higher with no outliers.

Two iterations of the Delphi survey were performed. The panel extensively discussed (via teleconference) the results of each item after the first Delphi survey. Items that reached consensus were accepted, and items that did not meet consensus were discussed to determine if wording or specific language was pivotal in the item not reaching consensus. Four items were found to be essentially redundant to other items and were omitted at this point. The second iteration of the survey was used to reassess items for which there was near consensus or for items for which there was suggestion of significant alterations in wording that could have affected survey results. The entire panel also extensively discussed the results of the second Delphi survey. All items reaching consensus were accepted. A third iteration of the Delphi process was considered but was not felt to be necessary. The factors leading to the remaining items not reaching consensus were not attributed to wording or other modifiable factors but rather a true lack of consensus.

The final version of the clinical consensus statements were grouped into 4 specific areas: (1) definition and diagnosis of PCRS, (2) medical treatment of PCRS, (3) adenoiditis/adenoidectomy, and (4) ESS/turbinoplasty. The final manuscript was drafted with participation and final review from each panel member.

Results

Thirty-eight clinical statements were developed for assessment with the Delphi survey method. All panelists completed all survey items. After 2 iterations of the Delphi survey, 22 statements (58%) met the standardized definition for consensus. Twelve clinical statements (31%) did not meet the criteria for consensus. Four clinical statements (11%) were omitted due to redundancy. The clinical statements were organized into 4 specific subject areas, and the results of each will be individually considered in the following.

Definition and Diagnosis of Pediatric Chronic Rhinosinusitis

In the area of definition and diagnosis of PCRS, 7 statements reached objective clinical consensus (see **Table 1**). The panel reached consensus on a working definition of PCRS that included both subjective symptoms and objective features. PCRS is defined as at least 90 continuous days of

Table 1. Definition and Diagnosis of Pediatric Chronic Rhinosinusitis Statements Reaching Consensus.

Number	Statement	Mean	Outliers	Quality Improvement Opportunity
1	Chronic rhinosinusitis (PCRS) is defined as at least 90 continuous days of 2 or more symptoms of purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough *and* either endoscopic signs of mucosal edema, purulent drainage, or nasal polyposis and/or CT scan changes showing mucosal changes within the ostiomeatal complex and/or sinuses in a pediatric patient aged 18 years or younger (Adapted from European Position Paper on Rhinosinusitis and Nasal Polyps 2012[23]).	7.56	0	Promoting appropriate care
2	Management of children aged 12 years and younger with CRS is distinctly different than management of children aged 13 to 18 years old with CRS.	7	0	Promoting appropriate care
3	Nasal endoscopy (flexible or rigid) is appropriate in evaluating a child with CRS to document purulent drainage, mucosal edema, nasal polyps, and/or adenoid pathology (hyperplasia, infection).	7.67	1	Promoting appropriate care
4	Management of the children with nasal polyps and CRS is distinctly different than management of children with CRS unaccompanied by nasal polyps.	8.22	0	Reducing inappropriate or harmful care
5	Allergic rhinitis is an important contributing factor to PCRS, especially in older children.	7.56	0	Promoting appropriate care
6	Adenoiditis is an important contributing factor to PCRS, especially in younger children.	7.67	1	Promoting appropriate care
7	The ability of adenoids to serve as a bacterial reservoir for PCRS is independent of adenoid size.	7.67	1	Reducing inappropriate or harmful care

symptoms of purulent rhinorrhea, nasal obstruction, facial pressure/pain, or cough with corresponding endoscopic and/or CT findings in a patient who is 18 years of age or younger (statement 1). Strong consensus (mean Likert score above 8.00) was achieved for the statement that pediatric patients with nasal polyps should be managed differently than those without polyps (statement 4). The panel reached consensus that age was an important distinguishing factor in the diagnosis of PCRS, with adenoid disease (independent of adenoid size) being a prominent factor in younger children and allergic rhinitis being a more important contributing factor in older children (statements 2, 5-7). Lastly, consensus was also reached that nasal endoscopic (flexible or rigid) is appropriate and useful in the diagnosis of PCRS (statement 3). There was no consensus regarding the contribution of gastroesophageal reflux disease (GERD) to PCRS (**Table 2**, statement 8).

Medical Treatment of PCRS

For medical management of PCRS, 5 statements reached consensus by the panel and 4 statements failed to reach consensus (see **Table 3**). Consensus was reached that daily, topical nasal steroid spray as well as daily, topical nasal irrigations are beneficial adjunctive medical therapies for PCRS (statements 11 and 12). Regarding antibiotic therapy, the panel failed to reach consensus on the statement that appropriate antibiotic therapy for PCRS includes a minimum of 10 consecutive days of an antimicrobial medication that is effective against typical rhinosinusitis pathogens (statement 14). However, the panel did reach consensus that 20 consecutive days of antibiotic therapy may produce a superior clinical response in PCRS patients compared to 10 days of antibiotic therapy (**Table 2**, statement 9). The panel also reached consensus that culture-directed antibiotic therapy may improve outcomes for PCRS patients who have not responded to empiric antibiotic therapy (statement 10).

The panel did not agree that medical therapy for PCRS should include treatment for GERD when signs or symptoms of GERD are present (**Table 2**, statement 15), instead agreeing that empiric treatment for GERD is not a beneficial adjunctive medical therapy for PCRS (statement 13). Additionally, the panel did not reach consensus that the current evidence supports a role for topical antibiotic therapy or antral irrigation in managing children with PCRS (**Table 2**, statements 16, 17).

Adenoiditis/Adenoidectomy

For adenoiditis/adenoidectomy, 4 statements reached consensus by the panel and 1 did not (see **Table 4**). Strong consensus was reached regarding the effectiveness of adenoidectomy as the initial surgical therapy for patients aged up to 6 years, and measurably less consensus was obtained for patients age 6 to 12 years (statements 18, 19). However, the panel could not reach consensus on whether adenoidectomy was an effective first-line procedure for patients aged 13 years and older with CRS (**Table 2**, statement 22). The panel agreed that adenoidectomy can have a beneficial effect in pediatric patients with PCRS that is independent of ESS (statement 20). There was strong consensus, in fact the highest Likert score of any statement in

Table 2. Clinical Statements that Did Not Meet the Criteria for Consensus.

Number	Statement	Subgroup	Status	Mean	Outliers
8	Gastroesophageal reflux disease (GERD) can contribute to pediatric chronic rhinosinusitis (PCRS).	Definition and Diagnosis of PCRS	No consensus	6.11	1
14	Appropriate antibiotic therapy for PCRS includes a minimum of 10 consecutive days of an antimicrobial medication that is effective against typical rhinosinusitis pathogens.	Medical Management of PCRS	No consensus	6.22	3
15	Medical therapy for PCRS should include treatment for GERD when signs or symptoms of GERD are present.	Medical Management of PCRS	No consensus	6.22	2
16	Current evidence supports a role for topical antibiotic therapy in managing selected children with CRS.	Medical Management of PCRS	No consensus	4.67	2
17	Current evidence supports a role for antral irrigation in managing selected children with CRS.	Medical Management of PCRS	No consensus	4.56	2
22	Adenoidectomy is an effective first-line surgical procedure for children aged 13 years and older with CRS.	Adenoidectomy/ Adenoiditis	No consensus	3.89	3
29	Balloon sinuplasty is safe for treating children with PCRS.	Endoscopic Sinus Surgery/ Turbinoplasty	Near consensus	6.56	2
30	Balloon sinuplasty is effective for treating patients with PCRS.	Endoscopic Sinus Surgery/ Turbinoplasty	No consensus	5.33	0
31	Inferior turbinate reduction can benefit children with CRS by reducing nasal congestion and improving penetration of topical medications.	Endoscopic Sinus Surgery/ Turbinoplasty	No consensus	6.22	1
32	Inferior turbinate reduction is a safe and minimally invasive adjunctive procedure for treating PCRS.	Endoscopic Sinus Surgery/ Turbinoplasty	No consensus	6.11	1
33	Children with swollen, enlarged inferior turbinates on preoperative assessment that have not responded to medical therapy are most likely to benefit from bilateral inferior turbinate reduction.	Endoscopic Sinus Surgery/ Turbinoplasty	No consensus	6.33	1
34	Reduction or removal of an obstructive middle turbinate concha bullosa when present is a valuable component of the surgical management of PCRS.	Endoscopic Sinus Surgery/ Turbinoplasty	Near consensus	6.78	0

Table 3. Medical Management of Pediatric Chronic Rhinosinusitis (PCRS) Statements Reaching Consensus.

Number	Statement	Mean	Outliers	Quality Improvement Opportunity
9	Twenty consecutive days of antibiotic therapy may produce a superior clinical response in PCRS patients compared to 10 days of antibiotic therapy.	7.44	0	Promoting appropriate care
10	Culture-directed antibiotic therapy may improve outcomes for PCRS patients who have not responded to empiric antibiotic therapy.	8	0	Promoting appropriate care
11	Daily, topical nasal steroids are a beneficial adjunctive medical therapy for PCRS.	7.44	0	Promoting appropriate care
12	Daily, topical nasal saline irrigations are a beneficial adjunctive medical therapy for PCRS.	7.78	0	Promoting appropriate care
13	Empiric treatment for gastroesophageal reflux disease (GERD) is not a beneficial adjunctive medical therapy for PCRS.	7	0	Reducing inappropriate or harmful care

Table 4. Adenoidectomy/Adenoiditis Statements Reaching Consensus.

Number	Statement	Mean	Outliers	Quality Improvement Opportunity
18	Adenoidectomy is an effective first line surgical procedure for children up to 6 years of age with chronic rhinosinusitis (CRS).	8.33	0	Promoting appropriate care
19	Adenoidectomy is an effective first-line surgical procedure for children aged 6 to 12 years with CRS.	7.11	1	Promoting appropriate care
20	Adenoidectomy can have a beneficial effect in patients with pediatric CRS that is independent of endoscopic sinus surgery (ESS).	7.33	1	Educating and empowering clinicians and patients
21	Tonsillectomy (without adenoidectomy) is ineffective treatment for PCRS.	8.56	0	Reducing inappropriate or harmful care

Table 5. Endoscopic Sinus Surgery/Turbinoplasty Statements Reaching Consensus.

	Statement	Mean	Outliers	Quality Improvement Opportunity
23	Endoscopic sinus surgery (ESS) is an effective procedure for treating pediatric chronic rhinosinusitis (PCRS) that is best performed after medical therapy, adenoidectomy, or both have failed.	7.89	0	Promoting appropriate care
24	A CT scan of the paranasal sinuses is indicated prior to ESS to assess structure, development, and extent of disease.	8.56	0	Promoting appropriate care
25	Image-guided ESS is useful for revision ESS cases and/or for patients with extensive nasal polyposis that can distort anatomical landmarks.	8.22	1	Promoting appropriate care
26	There is a lack of convincing evidence that ESS causes a clinically significant impairment of facial growth when performed in children with CRS.	7	0	Educating and empowering clinicians and patients
27	Postoperative debridement after ESS for PCRS is not essential for treatment success.	7	1	Reducing inappropriate or harmful care
28	The effectiveness of balloon sinuplasty compared to traditional ESS for PCRS cannot be determined based on current evidence	7.89	0	Reducing inappropriate or harmful care

the entire clinical consensus statement, that tonsillectomy (without adenoidectomy) is an ineffective treatment for PCRS (statement 21).

Endoscopic Sinus Surgery/Turbinoplasty

For the specific area of ESS/turbinoplasty, 6 statements reached consensus and 6 did not (see **Table 5**). Consensus was reached that ESS is an effective procedure for treating PCRS and that it is best performed when medical management, adenoidectomy, or both have failed to control the symptoms of PCRS (statement 23). Strong consensus was reached that a CT scan of the paranasal sinuses is indicated prior to ESS to assess the anatomy of the sinuses and development, extent, and severity of sinus disease and also that image-guided surgery is useful in revision cases and in patients with extensive nasal polyposis that can distort anatomical landmarks (statements 24, 25). There was consensus by the panel about the lack of convincing evidence that ESS causes a clinically significant impairment of facial growth when performed in children with CRS (statement 26). There was also consensus that postoperative debridement after ESS for PCRS is not an essential component for treatment success (statement 27).

The panel considered balloon sinuplasty for PCRS at length as it is a topic that receives a great deal of attention. The panel decided to assess an initial statement regarding the comparative effectiveness of balloon sinuplasty versus ESS in pediatric patients. Consensus was reached that there was insufficient current evidence to compare balloon sinuplasty to ESS for PCRS (statement 28). Not unexpectedly, the panel subsequently could not reach consensus regarding the effectiveness of balloon sinuplasty in treating PCRS although there was near consensus (mean Likert score = 6.56) regarding the safety of balloon sinuplasty (**Table 2**, statements 29, 30).

Turbinoplasty was extensively deliberated by the panel as consensus was actively sought for the appropriate role for this commonly performed, simple, noninvasive procedure. Unfortunately, the panel could not reach any consensus regarding the indications, potential benefits, or optimal candidates for inferior turbinoplasty (**Table 2**, statements 31-33). The primary reason noted in the panel discussion for this result was lack of pediatric-specific data. Near consensus (mean Likert score 6.78) was reached regarding the potential benefits of reducing an obstructive concha bullosa in PCRS patients (**Table 2**, statement 34).

Discussion

The purpose of this clinical consensus statement is to formulate evidence-enriched expert opinion into distinct clinical statements to promote high-quality care, reduce variations in care, and educate and empower clinicians and patients toward the goal of optimal management of PCRS. Specific discussion of the key elements in each of the 4 distinct clinical areas follows.

Definition and Diagnosis of PCRS

The definition of CRS that reached expert panel consensus for the pediatric population is similar to what has been accepted in adults.[23] Like the definition of CRS in adults, the panel agreed that an ideal definition of PCRS should include both subjective symptoms and objective signs. Specifically, the consensus definition specifies 2 or more symptoms of nasal congestion, nasal discharge, facial pressure/pain, or cough accompanied either by clinical signs on endoscopy such as nasal polyps, mucosal edema, or mucopurulent discharge or relevant findings on sinus CT scan over a 90-day continuous time span (statement 1). The chronicity requirement of 90 days is somewhat arbitrary but was felt to clearly represent a benchmark that distinguished PCRS from acute and subacute presentations of rhinosinusitis and is aligned with parallel adult definitions.[23-25]

The panel considered various pediatric age ranges to use as the target of this consensus statement. Clearly the typical medical-legal division between the pediatric and adult realms of 18 years old is not necessarily a physiologic threshold. Yet, since adult-based literature targets age 18 years and greater, the panel felt this was likely the appropriate limit to use for practical reasons. It is well known that sinus anatomic development continues throughout childhood and into adulthood.[26] Likewise, it would be expected that the pathophysiology of PCRS also evolves throughout childhood into adulthood. The age at which the frontal sinuses (the last to fully develop) reach an adult size is approximately age 19.[27] Similarly, the management CRS in children 13 to 18 may more closely approximate that of adults compared to children 12 years or younger, as the anatomic space and physiologic mechanisms incrementally approach that of adults. The panel's actions highlighted this concept of an age continuum by reaching consensus on a statement indicating patients 12 and under are typically managed differently than patients 13 to 18 years old (statement 2).

Although it may not always be feasible in the uncooperative pediatric patient, the use of nasal endoscopy to evaluate CRS is ideal and should be attempted. The panel reached consensus that either flexible or rigid nasal endoscopy is advantageous as it allows for direct assessment for the presence of purulence, mucosal edema, nasal polyps, and adenoid hypertrophy/adenoiditis (statement 3). Alternatively, lateral plain film x-ray or CT is less invasive but can only indirectly assess for some of these same vital factors, albeit with the requisite radiation exposure to the skull and brain, which carries a postulated risk of malignancy. Radiologic imaging studies (eg, lateral plain films) are not recommended to assess the adenoid in children with CRS because they provide limited information on adenoid size alone, which does not necessarily correlate with ability to serve as a bacterial reservoir for infection (statement 7). Moreover, imaging studies involve radiation of the skull and brain, which carries a postulated risk of malignancy. Although the relative risk ratios of cancer from childhood radiation exposure can be eye-catching, the absolute risk of malignancy from radiation exposure is extremely small. Specifically, the estimated absolute risk difference is approximately 1 resultant case of leukemia or brain tumor per 10,000 head CT scans obtained in childhood although this carries an imposing relative risk ratio of approximately 3.18 (95% CI, 1.46-6.94) for leukemia and 2.82 (95% CI, 1.33-6.03) for brain tumors.[28]

The panel reached strong consensus (mean Likert score = 8.22) that children who present with polyps as a component of PCRS represent a distinct patient subgroup (statement 4). Similar to adults, the presence of polyps in children constitutes a different subtype of CRS with differing pathophysiology and distinct optimal management.[23-25,29] Specifically, children presenting with nasal polyps carry a substantially increased risk of underlying cystic fibrosis and should be specifically assessed for this and other serious comorbid disorders such as allergic fungal sinusitis or antrochoanal polyps.[30]

Although some studies have shown possible association of allergic rhinitis (AR) to the development of PCRS, other studies suggest that allergy is not a significant factor in pediatric sinus disease. A study by Sedaghat et al[31] reported on a large series of 4044 pediatric patients with PCRS and found that AR was the most common comorbidity with 26.9% of patients carrying a diagnosis of AR. The authors concluded, ''formal allergy testing, guided by clinical history and regional allergen sensitivity prevalence, should be strongly considered in all children with CRS.''[31]

Interestingly, a later study from the same author group reported on a cohort of patients with allergic rhinitis with or without development of subsequent PCRS. They found that patients who developed subsequent PCRS did not have more severe subjective AR or more severe objective quantitative atopy measurements.[32] The only factor associated with development of PCRS was exposure to tobacco smoke (OR = 3.96, 95% CI, 1.50-10.48), and the authors concluded ''the degree of atopy, as reflected by the number of aeroallergen sensitivities or the presence of atopic comorbidities, is not associated with progression to CRS in the pediatric age group.''[32] Although this study does not directly contradict a possible causal relationship between AR and PCRS, it does suggest there is a not a measurable dose-dependent relationship between them. Clearly the association between AR and PCRS is complex and multifarious, and further study into this important question is required. The panel weighed this issue and the available evidence along with their own experience, and ultimately the majority felt that there was indeed a clinically relevant association between

AR and PCRS. This led to consensus being achieved for a statement supporting the association of AR as a contributing factor for PCRS, particularly in older children (statement 5).

Medical Treatment of PCRS

Published recommendations advocate the use of antibiotic therapy in PCRS as an essential element in the treatment of this disease.[23] Although no specific high-level evidence supports the effectiveness of broad-spectrum antibiotics in chronic rhinosinusitis in children, their use is understandably widespread. The optimal duration of antimicrobial therapy or duration that would constitute ''maximal medical therapy'' remains unclear. The panel struggled with the question of antibiotic duration in PCRS to be highly nuanced, as demonstrated by statement 9 achieving consensus while statement 14 did not (see **Table 3**). While guidelines from professional organizations have recommended 10 to 14 days of therapy for acute uncomplicated rhinosinusitis in children,[33,34] longer courses have generally been recommended for chronic rhinosinusitis with the inference that PCRS is a more advanced infection requiring more extended therapy.[23] As an extension of this concept, topical antibiotic therapy has been purported as a direct therapy that might be utilized over extended periods for the treatment of chronic rhinosinusitis.[35] However, based on the current limited body of related evidence, the panel did not reach consensus regarding a role for topical antimicrobials.

CRS is increasingly understood as a multifactorial process in which bacteria may play only 1 role of many.[36] Accordingly, therapies beyond antimicrobials have been utilized in PCRS, and there was more agreement among the panel regarding other topical adjuvant medical therapies. Intranasal topical corticosteroids suppress mucosal inflammation and have been widely prescribed. These anti-inflammatory agents have demonstrated efficacy in the adult population for chronic rhinosinusitis and are included in the consensus statement addressing adult sinusitis.[37] Evidence is more limited in the pediatric literature but supports topical steroid use in PCRS either alone or in combination with antibiotic therapy.[38] Nasal saline irrigations are thought to help primarily in the clearance of secretions, pathogens, and debris. Wei and colleagues demonstrated significant improvement in both quality of life and CT scan Lund-Mackay scores after 6 weeks of once-daily nasal saline irrigation[39] as well as long-term efficacy as a first-line treatment in PCRS and subsequent nasal symptoms.[40]

The panel directed special attention on the topic of gastroesophageal reflux disease and PCRS due to persistent controversy and uncertainty on this topic. An association between GERD and sinusitis has been repeatedly suggested in the pediatric population. However, no definitive causal relationship has been demonstrated in randomized, controlled studies in the PCRS patient.[41] The question has not been answered conclusively, but there is a lack of evidence to support a strong relationship between GERD and PCRS. This fact was reflected in the panel reaching consensus that empiric therapy for GERD in the context of PCRS is not indicated (statement 13). Similarly, consensus was not reached regarding a contribution of GERD in the pathogenesis of PCRS (**Table 2**, statement 8) and in the routine treatment of GERD as part of the comprehensive therapy of PCRS (**Table 2**, statement 15).

Adenoidectomy/Adenoiditis

Adenoidectomy is a simple, well-tolerated procedure that has always been an attractive surgical option to consider for the treatment of PCRS. Yet, the ideal role of adenoidectomy in the treatment of PCRS has been somewhat elusive. The panel desired to address this issue as part of the consensus statement. Although high-level, randomized sham surgery controlled studies are not available or even feasible, solid evidence supports the benefit of adenoidectomy in managing PCRS. From the microbiologic viewpoint, adenoidectomy (regardless of adenoid hypertrophy) has been shown to produce a dramatic decrease in nasopharyngeal pathogens that have been implicated in pediatric CRS.[8,42] From a clinical outcomes standpoint, a meta-analysis of 8 studies investigating the efficacy of adenoidectomy alone in pediatric CRS patients (mean age 5.8 years; range, 4.4-6.9 years) that failed medical management demonstrated that the majority of patients significantly improved sinusitis symptoms after adenoidectomy (subjective success rate = 69.3%, 95% CI, 56.8%-81.7%, $P < .001$).[43] The data from these studies helped the panel reach consensus that adenoidectomy is an effective first-line surgical procedure for younger children (statements 18, 19). The panel was unable to reach consensus on the utility of adenoidectomy in patients age 13 years and older due to the absence of supporting data for adolescent patients (**Table 2**, statement 23).

The panel reached agreement that adenoidectomy can have a beneficial effect on pediatric CRS independent of ESS (statement 24). This consensus was based in part on the highly published success rate of adenoidectomy in managing pediatric CRS[44] and the data from one prospective investigation that recommended adenoidectomy prior to ESS as part of a stepped treatment algorithm for the management of pediatric CRS.[45] It is recognized that adenoidectomy is frequently coupled with other minimally invasive procedures such as sinus irrigation. However, due to the practical limitations of the clinical consensus statement process, the panel chose to consider procedures on their own individual merit as opposed to in combination with other procedures. Panel consensus was achieved regarding the value of adenoidectomy by itself (statements 18, 19, 20) but not for antral irrigation by itself (statement 17).

Despite the general belief that infection in 1 part of the pharyngeal lymphoid tissue can spread to another part of Waldeyer's ring and that the bacteriology in the adenoid and palatine tonsils are similar,[46] the consensus panel strongly agreed that tonsillectomy is an ineffective treatment for pediatric CRS (statement 25). This was due to the lack

of any direct evidence supporting tonsillectomy for the management pediatric CRS.

Endoscopic Sinus Surgery and Turbinoplasty

ESS has been shown to be an effective mode of therapy in children with PCRS who have failed maximal medical management.[18,19] In a Cochrane/PubMed database review (1990-2012) conducted by Makary and Ramadan, success rates of 82% to 100% were reported for pediatric ESS with an overall complication rate of only 1.4%.[18] Similarly, in a meta-analysis of 15 interventional studies (levels II-IV, n = 1301), Vlastarakos et al[19] concluded that ESS improved sinus-related symptoms and quality of life in PCRS patients, giving the procedure a grade B strength of recommendation. PCRS patients undergoing ESS have also been found to harbor more severe disease than those treated with adenoidectomy or medical therapy.[18] Given such evidence, the panel reached consensus that ESS is an effective procedure for treating PCRS and is best performed when medical therapy, adenoidectomy, or both have proven unsuccessful (statement 23).

A comprehensive clinical consensus statement regarding the appropriate use of computed tomography in the context of PCRS has been published previously[20] and was not further addressed by the current panel. However, the panel did agree that CT scan of the paranasal sinuses is indicated prior to ESS to assess structure, development, and extent of disease (statement 24). Image guidance was also deemed particularly useful for revision ESS cases and in children with extensive nasal polyposis that could obscure typical anatomical landmarks (statement 25). Data regarding post-ESS debridement in pediatric patients differ from the related data in adults. Multiple level 1b studies have shown that sinus cavity debridement significantly improved symptoms and endoscopic outcomes in adult CRS patients following ESS.[47-50] Based on the available evidence, debridement has been recommended in the early postoperative care of adult ESS patients.[51] However, no corresponding studies have been published investigating the impact of postoperative debridement on PCRS patients. In fact, several studies have shown that postoperative debridement was not necessary in children.[52,53] Consequently, the panel agreed that debridement is not essential for the successful outcome of pediatric ESS (statement 27).

Based on findings primarily from animal studies, there has been concern that pediatric ESS may lead to adverse sequelae on pediatric facial skeletal development. Both Mair et al[54] and Carpenter et al[55] reported significant alterations in midface and sinus growth following ESS in a piglet model. In humans, Kosko et al[56] presented a series of 5 patients who developed maxillary sinus hypoplasia after ESS but no clinically apparent facial asymmetry or midface hypoplasia. Three longitudinal studies of human children with follow-up times ranging from 6.9 to 13.2 years reported no deleterious effects on facial growth after pediatric ESS using both volumetric and anthropomorphic measurements.[57-59] Therefore, after reviewing the evidence, the panel reached consensus that there is a lack of convincing evidence that ESS causes clinically significant impairment of facial growth when performed in children with CRS (statement 26).

Balloon catheter sinuplasty (BCS) has recently emerged as another therapeutic option in the surgical management of PCRS, having been more extensively studied in adult patients to this point. In a nonrandomized prospective review of 30 PCRS patients who failed medical therapy, 80% treated with BCS showed symptomatic improvement.[60] Likewise, in a follow-up study by the same author, a success rate of 81% was reported in children with CRS who underwent BCS after adenoidectomy failure.[61] However, no studies have directly compared the efficacy of BCS to ESS in the treatment of PCRS. Therefore, the panel reached consensus that the effectiveness of BCS versus traditional ESS for PCRS cannot be determined with the current evidence (statement 28). The further evaluation of BCS in children as a simple, potentially less traumatic procedure in the management of PCRS would be an appropriate research priority for the near future.

With respect to inferior turbinoplasty, no consensus could be reached regarding its role in the treatment of PCRS. The panel explored this issue extensively as turbinoplasty is a commonly performed procedure whose precise clinical role remains ill defined. Although some panelists agreed that inferior turbinate reduction is a safe, minimally invasive procedure that could potentially benefit children with PCRS, others disagreed due to the lack of supportive evidence in the literature. To date, no clinical studies specifically investigating the efficacy of inferior turbinoplasty in the context of PCRS have been reported. Moreover, there is also no data to determine that PCRS patients would derive the most benefit from inferior turbinate reduction or what the potential mechanisms of improvement might be. Thus, no consensus statements pertaining to inferior turbinoplasty in the management of PCRS could be made by the panel (**Table 2**, statements 31-33). Given the attractiveness of turbinoplasty as an adjunctive procedure to adenoidectomy and/or ESS, further investigation into potential role of inferior turbinoplasty in the management of PCRS should be a research priority.

Similar to inferior turbinoplasty, there were no studies found in children examining whether reduction of a concha bullosa has any positive impact on the treatment of PCRS. Again similar to inferior turbinoplasty, reduction of a concha bullosa is also an attractive, simple, minimally invasive procedure that could be plausibly expected to improve nasal airflow and mucociliary clearance and potentially increase the permeation of topical medications. However, there is a dearth of evidence on the topic, so the panel only reached a near consensus that reduction of concha bullosa, when present, is a valuable component of the surgical management of PCRS (**Table 2**, statement 34).

Conclusion

This clinical consensus statement was developed by and for otolaryngologists and is intended to promote appropriate, and when possible, evidence-based care for pediatric patients with chronic rhinosinusitis. A series of clinical statements were developed by an expert panel using an objective survey method. A complete definition of PCRS was first developed, and additional statements addressing the diagnosis of PCRS, the medical management of PCRS, the appropriate role of adenoidectomy in the management of PCRS, and the appropriate role of endoscopic sinus surgery in the management of PCRS were subsequently produced and evaluated. It is anticipated that the application of these principles will result in decreased variations in the care of PCRS patients and an increase in the quality of care.

Disclaimers

The views herein are the private views of the authors and do not reflect the official views of the Department of the Army or the Department of Defense.

Clinical consensus statements are based on the opinions of carefully chosen expert panels and provided for informational and educational purposes only. The purpose of the expert panel is to synthesize information, along with possible conflicting interpretations of the data, into clear and accurate answers to the question of interest. Clinical consensus statements may reflect uncertainties, gaps in knowledge, opinions, or minority view points, but through a consensus development process, many of the uncertainties are overcome, a consensual opinion is reached, and statements are formed. Clinical consensus statements are not clinical practice guidelines and do not follow the same procedures as clinical practice guidelines. Clinical consensus statements do not purport to be a legal standard of care. The responsible physician, in light of all the circumstances presented by the individual patient, must determine the appropriate treatment, diagnosis, and management. Consideration of clinical consensus statements will not ensure successful patient outcomes in every situation. The AAO-HNSF emphasizes that these clinical consensus statements should not be deemed to include all proper diagnosis/management/treatment decisions or methods of care or to exclude other treatment decisions or methods of care reasonably directed to obtaining the same results.

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Sinusitis and Pneumonia Hospitalization After Introduction of Pneumococcal Conjugate Vaccine

WHAT'S KNOWN ON THIS SUBJECT: Pneumococcal conjugated vaccines (PCVs) are known to decrease invasive pneumococcal disease in children, but their effect on pneumonia necessitating hospitalization is more variable across study sites, and effects on hospitalization for sinusitis have not been shown previously.

WHAT THIS STUDY ADDS: There was a significant decrease in hospitalizations for sinusitis in children <2 years of age, and hospitalization for pneumonia decreased in children aged <5 years after sequential introduction of PCV7 and PCV13.

abstract

FREE

BACKGROUND AND OBJECTIVE: *Streptococcus pneumoniae* is a major cause of pneumonia and sinusitis. Pneumonia kills >1 million children annually, and sinusitis is a potentially serious pediatric disease that increases the risk of orbital and intracranial complications. Although pneumococcal conjugate vaccine (PCV) is effective against invasive pneumococcal disease, its effectiveness against pneumonia is less consistent, and its effect on sinusitis is not known. We compared hospitalization rates due to sinusitis, pneumonia, and empyema before and after sequential introduction of PCV7 and PCV13.

METHOD: All children 0 to <18 years old hospitalized for sinusitis, pneumonia, or empyema in Stockholm County, Sweden, from 2003 to 2012 were included in a population-based study of hospital registry data on hospitalizations due to sinusitis, pneumonia, or empyema. Trend analysis, incidence rates, and rate ratios (RRs) were calculated comparing July 2003 to June 2007 with July 2008 to June 2012, excluding the year of PCV7 introduction.

RESULTS: Hospitalizations for sinusitis decreased significantly in children aged 0 to <2 years, from 70 to 24 cases per 100 000 population (RR = 0.34, $P < .001$). Hospitalizations for pneumonia decreased significantly in children aged 0 to <2 years, from 450 to 366 per 100 000 population (RR = 0.81, $P < .001$) and in those aged 2 to <5 years from 250 to 212 per 100 000 population (RR = 0.85, $P = .002$). Hospitalization for empyema increased nonsignificantly. Trend analyses showed increasing hospitalization for pneumonia in children 0 to <2 years before intervention and confirmed a decrease in hospitalizations for sinusitis and pneumonia in children aged 0 to <5 years after intervention.

CONCLUSIONS: PCV7 and PCV13 vaccination led to a 66% lower risk of hospitalization for sinusitis and 19% lower risk of hospitalization for pneumonia in children aged 0 to <2 years, in a comparison of 4 years before and 4 years after vaccine introduction. *Pediatrics* 2014;134:e1528–e1536

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KEY WORDS

Streptococcus pneumoniae, sinusitis, pneumonia, pneumococcal conjugated vaccine

ABBREVIATIONS

CI—confidence interval
ICD-10—International Classification of Diseases, 10th Revision
PCV—pneumococcal conjugate vaccine
RR—rate ratio
RSV—respiratory syncytial virus

Drs Örtqvist and Alfvén made equal contributions to this article. Dr Lindstrand conceptualized and designed the study, carried out data collection and analyzed the data, and drafted and revised the manuscript; Dr Bennet conceptualized and designed the study, carried out data collection, and reviewed and revised the manuscript; Mr Galanis performed statistical analysis and reviewed and revised the manuscript; Drs Blennow, Rinder, Eriksson, Henriques-Normark, Örtqvist, and Alfvén conceptualized and designed the study and reviewed and revised the manuscript; Drs Ask and Dennison revised medical records of the sinusitis patients and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Streptococcus pneumoniae is a common cause of invasive infections in children, such as bacteremic pneumonia, septicemia, and meningitis, but also of noninvasive infections such as nonbacteremic pneumonia, sinusitis, and otitis. Pneumococcal disease is the vaccine-preventable disease that currently causes most child deaths worldwide. Every year 826 000 deaths in children 1 to 59 months old are caused by *S. pneumoniae,* corresponding to 7% of all deaths in this age group.[1] Pneumonia makes up 90% of these deaths.[2–4]

Sinusitis in preschool children is a potentially serious disease because of anatomic closeness to the orbita and the brain. Complications include periorbital and orbital cellulitis, abscesses, and meningitis. The most commonly isolated pathogens in pediatric sinusitis are *S. pneumoniae* (30%), *Haemophilus influenzae* (30%), and *Moraxella catarrhalis* (10%).[5] The disease is more severe in patients infected with pneumococci than in those infected with *H. influenzae*.[6]

Pneumococci may be divided into >90 serotypes, depending on the structure of their polysaccharide capsules. Effective pneumococcal conjugate vaccines (PCVs) targeting an increasing number of serotypes (PCV7, PCV10, and PCV13) have been developed for children <2 years of age. Meta-analyses of randomized placebo-controlled clinical trials in children <2 years show that PCVs have a vaccine efficacy against vaccine-type invasive pneumococcal disease (80% [58%–90%]), radiologically verified pneumonia (27% [15% to 36%]), and clinical pneumonia (6% [2%–9%]).[7] Since 2000 global use of PCVs has increased and has consistently led to reductions of 79% to 100% in the incidence of vaccine-type invasive pneumococcal disease. Effectiveness of PCVs in reducing hospitalization rates for pneumonia seems less consistent, with a decrease ranging from 13% to 65% in all-cause pneumonia hospitalizations in children.[8,9] However, some studies show decreased risk only in infants and increasing risk in older children.[10–12] To our knowledge PCV effectiveness against hospitalizations due to sinusitis in children has not been clarified previously.[13–15]

In Stockholm County, Sweden, PCV7 was offered on a 2+1 schedule at 3, 5, and 12 months of age to all children born since July 1, 2007. PCV7 was changed to PCV13 in January 2010, even for children who had received 1 or 2 doses of PCV7. No catch-up program was implemented. High coverage with the vaccine was reached early on, and by 2 years of age 96% of children born in 2008 and 98% of those born in 2010 had received 3 doses of PCV.[16]

The aim of this study was to evaluate the impact of PCV7 and PCV13 on the incidence of hospitalization due to pediatric sinusitis, pneumonia coded as bacterial pneumonia, and empyema. We compared hospital discharge diagnoses during the 4-year periods before and after introduction of PCV7.

METHODS

A retrospective population-based study was performed using International Classification of Diseases, 10th Revision (ICD-10) coded hospital registries to identify all children hospitalized with sinusitis, pneumonia, and empyema in Stockholm County between July 2003 and June 2012. The year of introduction of PCV7, from July 1, 2007 to June 30, 2008, was excluded from the analysis. The study years included cases from July 1 through June 30, to keep winter's higher infection rates within 1 study year.

Study Population and Data Collection

In 2012 Stockholm County had a population of ~2 million, of whom 22% were <18 years (458 000) and 7% (144 000) were <5 years old.[17] Data on hospitalizations were collected from the 3 children's hospitals in the county. For the diagnosis of sinusitis, data were also included from the only otorhinopharyngeal clinic where children are treated as inpatients in Stockholm. Children 0 to <18 years with the diagnoses being studied were hospitalized exclusively in these 4 places. All children with ICD-10 discharge diagnosis codes J13–J18 (pneumonia coded as bacterial pneumonia, or pneumonia unspecified), J86 (empyema), and J01 (sinusitis) were included. In Sweden children with sinusitis are treated as inpatients only when they have complications, either with orbital or periorbital cellulitis, or are in need of drainage or other surgical procedures.

We used pyelonephritis as a control for the effect of PCV on number of admissions (N10.9). To control for possible changes in diagnosis routines we also recorded the number of children admitted with asthma and obstructive bronchitis (J45.1, J20.9), respiratory syncytial virus (RSV) (J21, J20.5, J12.1), and viral pneumonia (J09–12, except for J12.1 respiratory syncytial pneumonia, J10.1 influenza, and J09 H1N1) during the same time period.

Data on age, gender, and date of admission were recorded for all children. Patients readmitted with the same diagnoses within 30 days of discharge were excluded. The children were divided into the age groups 0 to <2, 2 to <5, and 5 to <18 years for analysis.

To validate the ICD-10 diagnoses we reviewed the medical records of all children with a discharge diagnosis of sinusitis (N = 678) and 100 children with pneumonia coded as bacterial pneumonia (50 before and 50 after vaccination). Information on signs and symptoms, radiographic findings, treatment, risk factors, and outcome

was collected. Sinusitis cases were considered valid if there was a previous or ongoing respiratory infection, signs of orbital or periorbital swelling or redness, or a positive computed tomography scan. Pneumonia cases were considered valid if there was ongoing respiratory infection or radiographic verification, or they were judged by the attending pediatrician to be of bacterial origin and antibiotics were given.

Statistical Analysis

Segmented regression analysis was applied to evaluate the effect of the PCV7 vaccination program on monthly hospital admission rates of sinusitis and pneumonia, comparing the periods before and after vaccination, excluding the in-between year.[18,19] Generalized linear models assuming a Poisson distribution for the monthly admission rates were fitted, and negative binomial distribution was preferred in the presence of overdispersion. Generalized additive models were used instead of generalized linear models to adjust for a seasonal effect when necessary. All models contained 3 basic parameters accounting for the preintervention trend, the change in level from the last preintervention point to the first postintervention point, and the difference in trend between the 2 periods. The postintervention trend and its SE were derived from a combination of the first and third parameters. Correlograms were used to check for autocorrelation in the residuals, and the models were adjusted for first-order autocorrelation when necessary.

Rate ratios (RRs) and their respective 95% confidence intervals (CIs) were calculated to compare the prevaccination and postvaccine periods. We conducted all analyses by using the statistical software R, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria), and *P* values $<.05$ were considered statistically significant.

Ethical Permission

Ethical approval was obtained from the Stockholm Regional Ethics Committee.

RESULTS

Sinusitis

Between July 2003 and June 2012, 678 children <18 years old were discharged from the hospital with a diagnosis of sinusitis. Validation of medical records using preset criteria led to exclusion of 76 cases because of incorrect diagnosis without signs of concomitant sinusitis, such as skin infection, conjunctivitis, or insect bite ($n = 46$), or because there were no clinical signs of sinusitis ($n = 30$). Of the 602 remaining validated sinusitis cases, 234 (39%) patients were aged <2 years and 159 (26%) 2 to <5 years. Of the 393 children <5 years of age, 62% were boys.

The incidence of hospitalization for sinusitis in children <2 years of age decreased significantly from the prevaccination to the postvaccination period, from 70 to 24 per 100 000 person-years (RR = 0.34; 95% CI, 0.25–0.47, $P < .001$). A decrease, although not significant, was also seen in children 2 to <5 years of age (RR = 0.72; 95% CI, 0.51–1.02; $P = .06$), whereas the incidence remained stable in older children (Table 1).

Trend analysis showed that before PCV7 introduction there was no significant month-to-month change in the incidence of hospitalization due to sinusitis in children <5 years old (Fig 1 and Table 2). Immediately after the first year of vaccination (July 2008) there was a decrease in hospitalization in the younger age group (0 to <2 years); however, this was not significant ($P = .055$). For this age group and for those aged 2 to <5 years, a significant month-to-month decrease in incidence was observed after vaccination ($P = .018$ and .004, respectively). No change was observed for those aged 5 to 18 years. There were no changes in gender distribution or in proportion of children with risk factors or chronic illnesses after introduction of PCVs (data not shown).

Pneumonia

From July 2003 to June 2012, 5018 children <18 years of age with a discharge diagnosis of pneumonia coded as bacterial pneumonia were included; 2034 (41%) were <2 years of age, and 1555 (31%) were 2 to <5 years of age. Of the 3589 children <5 years of age, 54% were boys.

The incidence of hospitalization for pneumonia in children <2 years of age decreased significantly, from 450 to 366 per 100 000 person-years ($P < .001$), in a comparison of the prevaccination and postvaccination periods (Table 1). A significant decrease in incidence ($P = .002$) was also seen in the age group 2 to <5 years, whereas the incidence remained stable in older children.

Trend analysis showed that before PCV7 introduction there was a significant increase in month-to-month hospitalizations for pneumonia in children aged 0 to <2 years ($P = .001$), but there was no significant change in children aged 2 to <5 years. Soon after the first year of vaccination (July 2008) there was a significant decrease in hospitalizations in children aged 0 to <2 years ($P = .002$). However, a significant month-to-month decrease in the postvaccination period was seen only in those aged 2 to <5 years ($P = .02$). For the age group 5 to 18 years there was an increasing trend in month-to-month hospitalization both before and after vaccination, but there was no difference in the incidence RR (Fig 1, Tables 1 and 2).

When we compared the 50 validated pneumonia cases coded as bacterial pneumonia before PCV7 introduction

TABLE 1 Number of Hospitalizations and Incidence of Pneumonia, Sinusitis, Empyema, Pyelonephritis, Asthma and Obstructive Bronchitis, RSV Infection, and Viral Pneumonia in Children 0 to <18 y Before and After Sequential PCV7 and PCV13 Introduction in Stockholm

Diagnosis	No. of Cases		Incidence Rate per 100 000 Person-Years		RR (95% CI)	*P*
	Before July 2003–June 2007	After July 2008–June 2012	Before July 2003–June 2007	After July 2008–June 2012		
Pneumonia						
0–<2 y	914	836	450	366	0.81 (0.74–0.89)	<.001
2–<5 y	687	694	250	212	0.85 (0.76–0.94)	.002
5–<18 y	604	683	51	56	1.10 (0.99–1.23)	.09
Sinusitis						
0–<2 y	142	55	70	24	0.34 (0.25–0.47)	<.001
2–<5 y	70	60	25	18	0.72 (0.51–1.02)	.06
5–<18 y	82	98	7	8	1.16 (0.87–1.56)	.31
Empyema						
0–<2 y	5	10	2.5	4.4	1.78 (0.55–6.63)	.42
2–<5 y	5	10	1.8	3.1	1.68 (0.52–6.26)	.49
5–<18 y	11	19	0.9	1.6	1.68 (0.80–3.53)	.17
Pyelonephritis						
0–<2 y	598	757	294	331	1.13 (1.01–1.25)	.03
2–<5 y	123	156	45	48	1.06 (0.84–1.35)	.61
5–<18 y	167	233	14	19	1.36 (1.11–1.66)	.002
Asthma and obstructive bronchitis						
0–<2 y	2136	2493	1051	1090	1.04 (0.98–1.10)	.21
2–<5 y	709	902	258	275	1.07 (0.97–1.18)	.20
5–<18 y	334	323	28	27	0.94 (0.81–1.10)	.44
RSV infection						
0–<2 y	1711	2647	842	1158	1.37 (1.29–1.46)	<.001
2–<5 y	58	137	21	42	1.98 (1.46–2.69)	<.001
5–<18 y	7	28	0.6	2.3	3.89 (1.66–10.56)	<.001
Viral pneumonia						
0–<2 y	70	115	34	50	1.46 (1.08–1.97)	.01
2–<5 y	42	60	15	18	1.20 (0.81–1.78)	.37
5–<18 y	24	58	2.0	4.8	2.35 (1.46–3.78)	<.001

(in 2005) with 50 cases after vaccine introduction (in 2009), no differences were observed in frequency of chest radiographs on admission (100% in 2005, 98% in 2009). Chronic conditions (mainly asthma, prematurity, or neurologic disease) were found in 36% of children in 2005 and 31% in 2009 (P = .82). The clinical severity of pneumonia, measured using mean C-reactive protein, oxygen saturation, and need for oxygen or intensive care, was comparable in 2005 and in 2009 (data not shown).

Empyema

For children <2 years old there was a nonsignificant increased incidence of hospitalization for empyema in the period after compared with the period before PCV7 and PCV13 vaccination (4.4 vs 2.5 per 100 000 person-years; RR = 1.78; 95% CI, 0.55–6.63; P = .42) (Table 1).

Hospitalization for Control Diagnosis

Pyelonephritis was used as an indicator disease for general hospitalization trends during the study period. There was a slight increase in hospitalizations during the study period in the age group 0 to <2 years but not among children aged 2 to <5 years (Table 1). However, in the time trend analysis (Fig 1) the month-to-month incidence remained stable in the prevaccination and postvaccination period for both age groups (Fig 1 and Table 2).

The incidence of hospitalizations for asthma and obstructive bronchitis remained stable during the study period (Table 1). However, the incidence of hospitalization for RSV infections and viral pneumonia increased significantly in children <2 years old between the prevaccination and postvaccination periods (RR = 1.37; 95% CI, 1.29–1.46; P < .001 and RR = 1.46; 95% CI, 1.08–1.97; P = .01, respectively) (Table 1).

DISCUSSION

To our knowledge this is the first study showing that introduction of PCV7 and PCV13 in the childhood vaccination program significantly reduces hospitalizations for sinusitis in children <5 years of age. We also found a significant reduction in hospitalization rates for pneumonia in children <5 years old. However, there was an increase in empyema in children <2 years of age in the postvaccination compared with the prevaccination period, but this was not statistically significant.

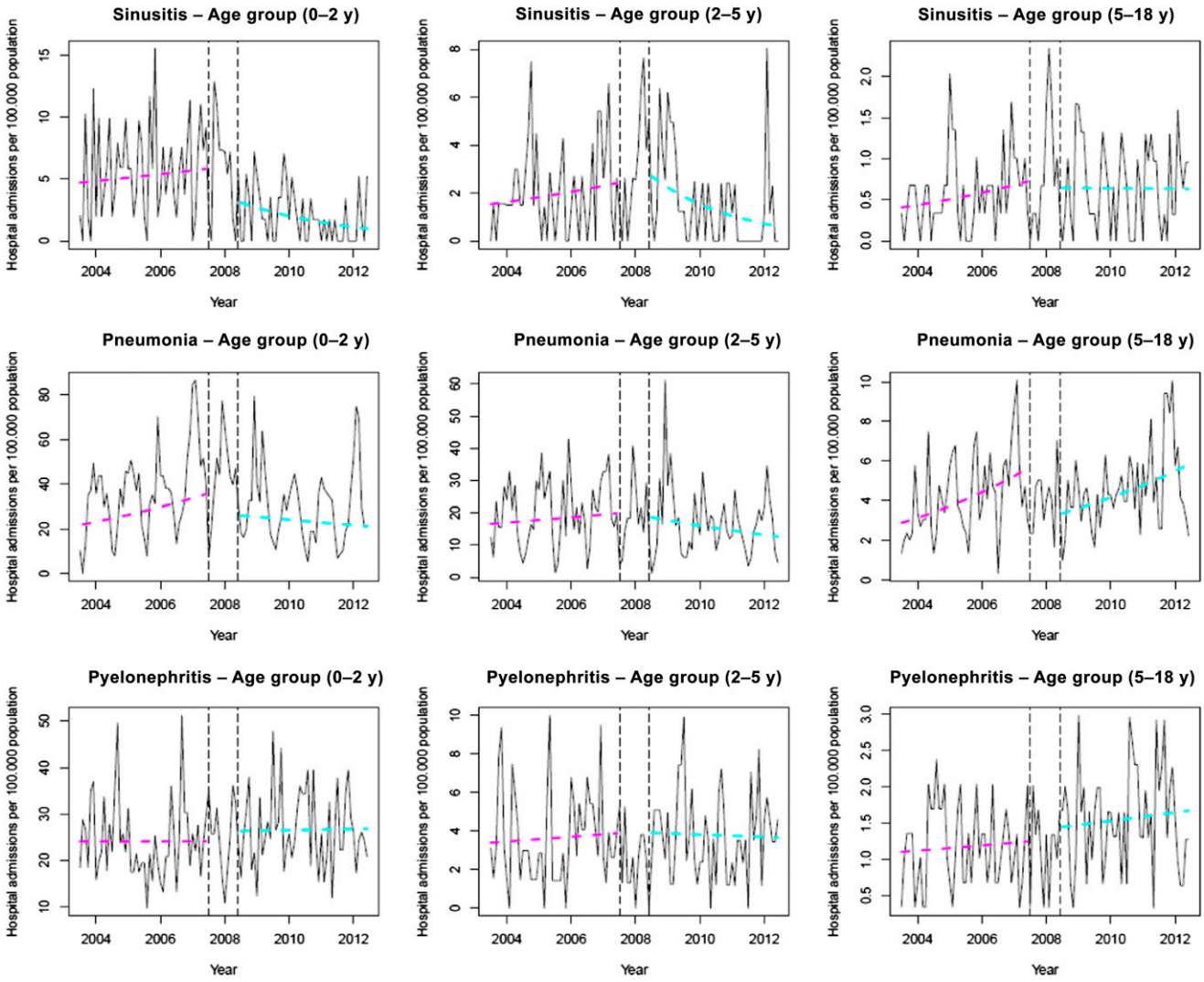

FIGURE 1

Trend analysis of hospitalizations by discharge diagnosis per 100 000 population, by age groups 0 to <2 years, 2 to <5 years, and 5 to <18 years in Stockholm County, Sweden, 2003–2012.

Our finding of a decreased incidence of sinusitis after introduction of PCV7 and PCV13 is supported by a recent study by Peña et al[20] showing that *S. pneumoniae* was nearly eliminated as an etiological agent of complicated sinusitis in children after PCV introduction in the United States. Moreover, they observed a significant increase in *S. aureus* as a cause of complicated sinusitis. Benninger[21] described a change in serotype distribution in both acute otitis media and acute rhinosinusitis in children after PCV7 introduction. McNeil et al[22] showed that in the period when PCV7 was used in the United States, 50% of the pneumococcal isolates recovered from children with chronic sinusitis were serotype 19A, probably because of serotype replacement. So an overall decline in sinusitis after PCV7 and PCV13 vaccination in children may be followed by both serotype replacement and expansion of other bacteria, similar to the experience with invasive pneumococcal disease and otitis media.[8,23,24]

The effect of PCV on the incidence of pneumonia necessitating hospitalization has varied between studies. A meta-analysis by Fitzwater et al[8] showed a 13% to 65% reduction in hospitalizations for pneumonia in children. In Norway, Magnus et al[25] showed a 22% decrease in pneumonia among PCV7-vaccinated children of 12 to 18 months of age. This is comparable to the 19% decrease in hospitalization for pneumonia in children aged <2 years and the 15% decreased risk of pneumonia hospitalization in children 2 to <5 years that we observed in this study.

Nelson et al[10] observed an effect on pneumonia rates in outpatients in the

TABLE 2 Trend Analysis of Monthly Hospitalizations by Discharge Diagnosis per 100 000 Person-Years by Age Group in Stockholm County, Sweden, 2003–2012

Disease (Age Group)	RR (95% CI)[a]	*P*	Disease (Age Group)	RR (95% CI)	*P*	Disease (Age Group)	RR (95% CI)	*P*
Sinusitis (0–2 y)			Sinusitis (2–5 y)			Sinusitis (5–18 y)		
Preintervention trend	1.00 (0.992–1.017)	.47	Preintervention trend	1.01 (0.991–1.029)	.32	Preintervention trend	1.01 (0.996–1.029)	.13
Change in level	0.52 (0.265–1.014)	.055	Change in level	1.026 (0.434–2.425)	.95	Change in level	0.77 (0.381–1.561)	.47
Postintervention trend	0.976 (0.957–0.996)	.018	Postintervention trend	0.969 (0.949–0.990)	.004	Postintervention trend	1.00 (0.985–1.014)	.96
Pneumonia (0–2 y)			Pneumonia (2–5 y)			Pneumonia (5–18 y)		
Preintervention trend	1.01 (1.004–1.017)	.001	Preintervention trend	1.004 (0.997–1.011)	.29	Preintervention trend	1.01 (1.007–1.022)	<.001
Change in level	0.65 (0.494–0.856)	.002	Change in level	0.90 (0.647–1.255)	.54	Change in level	0.50 (0.357–0.70)	<.001
Postintervention trend	0.996 (0.990–1.001)	.13	Postintervention trend	0.992 (0.985–0.999)	.02	Postintervention trend	1.01 (1.005–1.019)	.001
Pyelonephritis (0–2 y)			Pyelonephritis (2–5 y)			Pyelonephritis (5–18 y)		
Preintervention trend	1.00 (0.994–1.007)	.99	Preintervention trend	1.00 (0.990–1.016)	.67	Preintervention trend	1.003 (0.992–1.014)	.64
Change in level	1.09 (0.809–1.474)	.57	Change in level	0.974 (0.551–1.740)	.93	Change in level	1.123 (0.681–1.849)	.65
Postintervention trend	1.00 (0.994–1.006)	.90	Postintervention trend	0.999 (0.987–1.010)	.82	Postintervention trend	1.003 (0.994–1.013)	.52

[a] When referring to the preintervention and postintervention trend, the RR expresses the month-to-month change in hospitalization rates. For the change in level it expresses comparison of the hospitalization rate of the first postintervention month to the last preintervention one.

United States but only a nonsignificant reduction in confirmed hospitalization events in children aged <1 year. In contrast, a recent study from the United States showed a sustained decrease in hospitalizations for pneumonia in children and a decrease in people >65 years old, possibly a herd effect.[26] Our use of a discharge diagnosis of pneumonia coded as bacterial pneumonia as an endpoint was motivated by the difficulty of establishing an etiological diagnosis of pneumonia, especially in small children.

Interestingly, we observed an increasing incidence of admissions to the hospital for pneumonia among children <2 years and from 5 to <18 years old before vaccine introduction, from 2003 to 2007 (Fig 1). The reason for this increase is unclear, but natural fluctuations caused by expansion of certain pneumococcal serotypes or clones might have contributed. A similar increase in 2004 to 2006 was seen in a national time trend (1997 to 2008) study on hospitalizations for pneumonia among children in England.[9] This might have led to an underestimation of the real effect of the PCV vaccination, because we did not calculate expected rates assuming a continued increasing trend and comparing those with the observed rates, as was done in other studies.[27]

Previous influenza virus infection has been shown to increase the risk of developing pneumococcal pneumonia.[28,29] Recent data from the United States showed excess risk of pneumococcal pneumonia during the H1N1 influenza pandemic in 2009.[30] In our study we observed only an increase in hospitalizations for pneumonia, coded as bacterial pneumonia, in children aged 2 to <5 years during this pandemic. There was a high coverage rate (50% of children aged 6 months to 2 years, 70% of children

aged 3–18 years) of AS03-adjuvanted monovalent vaccine against influenza A(H1N1)pdm09 in Sweden. This vaccine was about 90% effective in preventing the need for hospitalization for pandemic influenza,[31] which may have lowered the excess risk for pneumococcal pneumonia.

A decrease in RSV infections was seen in South Africa during a PCV trial, and an increase in RSV activity was associated with an increased incidence of pneumonia in children in Israel, indicating mixed infections with RSV and pneumococci.[32,33] In contrast, we noted an increase in RSV after PCV introduction, which may be explained by 3 consecutive seasons with unusually high circulations of RSV and increasing use of viral respiratory polymerase chain reaction diagnostics on nasopharyngeal samples in the last 10 years. Thus, the higher burden of influenza and RSV after PCV may have lowered the effect of the vaccine on pneumonia, as we found.

Empyema is a rare complication of pneumonia. Grijalva et al[34,35] showed a twofold increase in hospitalizations for parapneumonic empyema after vaccine introduction in children in the United States. Serotypes 1 and 3 have been associated with empyema, and because they are not included in PCV7, serotype replacement may cause increased rates of empyema after vaccine introduction.[36] An increase in staphylococcal empyema or empyema of unknown etiology has been described, as well as an increase in pneumonia complicated by empyema, from 3.7 cases per 100 000 children to 10.3 after vaccine introduction in the United States.[35–37] As was found in earlier studies, we found a nearly twofold increase in hospitalizations for empyema in children aged <2 years; this was nonsignificant, probably because of low numbers. The highest incidence of empyema was observed in 2007 to 2009, immediately after introduction of PCV7, indicating that factors other than the vaccine may have contributed.

A major strength of this population-based study is inclusion of 100% of the relevant hospitalizations registered in the area. This is also the main weakness, because the result depends on doctors assigning the correct ICD diagnosis and not changing coding practices over time. However, we validated all cases of sinusitis and a selection of cases of pneumonia, finding no major changes in ICD coding. Another weakness is that we could not link clinical cases to bacterial strains or serotypes of pneumococci with this study design. However, in prospective studies it is also difficult to isolate the causative microbe in children with pneumonia, sinusitis, or empyema.

Except for introduction of PCV in the vaccination programs, there were no changes or interventions that should have affected pneumonia or sinusitis case management or hospital care or that could have explained the decrease in hospitalizations for sinusitis and pneumonia. This finding is supported by the fact that the hospitalization rates for asthma or obstructive bronchitis and pyelonephritis were stable during the postvaccination period. However, a clear limitation is that data on outpatient care are not available.

Our data come from Sweden, a country with 98% PCV coverage, >80% day care attendance, very low levels of HIV infection and tuberculosis, and low antibiotic consumption compared with most countries, all of which play a role in the results. Therefore, it is not only pneumococcal vaccines that affect the rate of hospitalization for pneumonia and sinusitis in children; fluctuations in other bacterial and viral pathogens, socioeconomic status, hygiene in day care centers, and antibiotic pressure in society may also affect pneumococcal transmission.

CONCLUSIONS

Pneumococcal disease is the most important vaccine-preventable disease in children, because it causes most child deaths. Many low- and middle-income countries are implementing PCV vaccination programs. This study adds evidence that PCV vaccine (PCV7 and PCV13) prevents severe sinusitis and pneumonia, with implications for global child survival.[38–40] Specifically, we are the first to show great effectiveness against sinusitis in children aged <5 years.

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Impact of the 13-valent Pneumococcal Conjugate Vaccine on Chronic Sinusitis Associated With *Streptococcus pneumoniae* in Children

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Background: The widespread use of the 7-valent pneumococcal conjugate vaccine has been associated with epidemiologic changes of mucosal and invasive pneumococcal disease. No study describes the impact of 13-valent pneumococcal conjugate vaccine (PCV13) on chronic sinusitis in children. We describe changes in epidemiology of *Streptococcus pneumoniae* chronic sinusitis after the introduction of PCV13 at Texas Children's Hospital.

Methods: We identified patients <18 years with positive sinus culture for *S. pneumoniae* who underwent endoscopic sinus surgery because of chronic sinusitis from August 2008 to December 2013 at Texas Children's Hospital. Isolates were serotyped by the capsular swelling method. Demographic and clinical information was collected retrospectively. The χ^2 test and Fisher's exact test were used to analyze dichotomous variables.

Results: We identified 91 cases of chronic sinusitis with positive sinus culture for *S. pneumoniae*. Sixty-one (67%) isolates were non-PCV13 serotypes. PCV13 cases decreased 31% in the post-PCV13 period ($P = 0.003$). Serotype 19A decreased 27% in the post-PCV13 period ($P = 0.007$), but accounted for all the isolates with penicillin minimal inhibitory concentration ≥ 4 μg/mL and ceftriaxone minimal inhibitory concentration ≥ 2 μg/mL. Serotypes 19A (38%) and 15C (17%) were the most common in the pre- and post-PCV13 periods, respectively. The most common organism co-isolated was *Haemophilus influenzae* (52%). Isolation of *Prevotella* spp. increased in the post-PCV13 period ($P = 0.02$).

Conclusions: *S. pneumoniae* continues to represent an important pathogen in chronic sinusitis in children <5 years of age. After the introduction of PCV13, *S. pneumoniae* isolation declined in children with chronic sinusitis at Texas Children's Hospital. We also observed a substantial reduction of PCV13 serotypes, predominantly serotype 19A.

Key Words: *Streptococcus pneumoniae*, sinusitis, pneumococcal conjugate vaccine

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Streptococcus pneumoniae (~30%) has been described as the most common pathogen in acute bacterial sinusitis in children followed by *Haemophilus influenza*e and *Moraxella catarrhalis* (~20% each).[1] Studies describing the pathogenesis of chronic sinusitis report a predominance of anaerobes in adults.[2,3] However, results are variable in children,[4,5] with some studies reporting bacteriologic characteristics of chronic sinusitis similar to acute sinusitis.[4] Nevertheless, *S. pneumoniae* continues to represent an important pathogen among the aerobic isolates in chronic sinusitis, particularly in acute exacerbations of chronic sinusitis and in younger children.[2,4]

After the licensure of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2000, a sustained decrease in the incidence of invasive pneumococcal disease and acute otitis media (AOM) was observed.[6–8] As the isolation of *S. pneumoniae* declined in patients with AOM, an increase of *H. influenzae* isolations was described.[8,9] A similar shift in the organisms isolated from patients with acute bacterial sinusitis was reported after the introduction of PCV7.[10,11] Brook et al[10] reported a decrease of *S. pneumoniae* isolated from nasopharyngeal cultures obtained from children with acute sinusitis from 43% during 1996–2000 to 25% during 2001–2005 ($P = 0.0014$).[10] Similar results were obtained from patients with acute sinusitis who underwent endoscopic sinus surgery (ESS).[11]

The widespread use of PCV7 not only altered the pathogenesis of bacterial sinusitis with respect to the causative pathogens, but also the serotype distribution within the pneumococcal isolates. Serotype 19A, which is not included on PCV7, was described as the most common pneumococcal serotype isolated from pediatric patients with chronic sinusitis during 2007–2008 undergoing endoscopic sinus surgery at Texas Children's Hospital (TCH)[12], a finding that likely reflected the overall high prevalence of serotype 19A during that time.[13]

The 13-valent pneumococcal conjugate vaccine (PCV13) that added serotypes 1, 3, 5, 6A, 7F and 19A to PCV7 was licensed in 2010. A multicenter surveillance study showed an early trend in a decrease of invasive pneumococcal disease in the year after the introduction of PCV13.[14] To our knowledge, there are no studies describing the impact of PCV13 on chronic sinusitis in children to date. The purpose of this study was to compare the distribution of pneumococcal serotypes, antibiotic susceptibilities of pneumococcal isolates and the distribution of co-isolated organisms from pediatric patients with chronic sinusitis at TCH before and after the introduction of PCV13.

MATERIALS AND METHODS

Paranasal sinuses cultures positive for *S. pneumoniae* have been prospectively identified at TCH as part of a pneumococcal surveillance study that has been approved by the Institutional Review Board of the Baylor College of Medicine.

Patients with a positive sinus culture for *S. pneumoniae* obtained during ESS because of chronic sinusitis from August 2008 to December 2013 at TCH were included. All patients were evaluated by an otorhinolaryngologist in the outpatient setting and diagnosed with chronic sinusitis. Under endoscopic visualization, patients' sinuses were cannulated, suctioned and irrigated with saline solution. A sample of each aspirate obtained was sent for culture in the TCH Microbiology Laboratory. Pneumococcal isolates were then serotyped by the capsular swelling method using commercially available antisera (Statens Seruminstitut, Copenhagen,

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Denmark; Daco, Inc, Carpinteria, CA) in the Infectious Disease Research Laboratory.

Antimicrobial susceptibility testing for penicillin and ceftriaxone was performed by standard microbroth dilution with Mueller-Hinton media supplemented with 3% lysed horse blood in the Infectious Disease Research Laboratory. Susceptibilities for erythromycin, clindamycin and trimethoprim-sulfamethoxazole were determined by standard disk diffusion testing in the TCH Clinical Microbiology Laboratory. Susceptibility categories were "susceptible," "intermediate" or "resistant" as defined by the 2012 Clinical and Laboratory Standards Institute.[15]

Demographic and clinical information was collected retrospectively and recorded on a case report form. Administration of PCV7 or PCV13 was documented through the medical records or by contacting the patient's healthcare provider.

We defined the prevaccine period as August 2008 through December 2010 (29 months). We defined the postvaccine period as January 2011 through December 2013 (36 months). PCV13 was licensed in the United States in February 2010, overlapping the endmost part of the prevaccine period; however, patients included in the prevaccine period had not received any PCV13 doses.

To estimate the proportion of chronic sinusitis cases attributable to *S. pneumoniae*, we used ICD-9 (*International Classification of Diseases, 9th Revision*) codes to identify the total number of patients with chronic sinusitis (ICD-9 code 473) who underwent ESS (ICD-9 code 31231 or 31000) during the study period. Descriptive statistics were used to characterize the study population. The χ^2 test and Fisher's exact test were used to compare the characteristics of patients with chronic sinusitis before and after introduction of PCV13. IBM SPSS statistics V22.0.0 was the statistical program used. $P \leq 0.05$ was considered significant.

RESULTS

During the study period, 652 patients (245 in the pre-PCV13 period and 407 in the post-PCV13 period) with chronic sinusitis who underwent ESS were identified based on ICD-9 codes. Of these, 91 of 652 (14%) had a positive sinus culture for *S. pneumoniae*; 55 of 245 (22%) and 36 of 407 (9%) were identified in the pre- and post-PCV13 periods, respectively ($P < 0.0001$). The total number of annual pneumococcal sinusitis cases was: 19 in 2009; 26 in 2010; 11 in 2011; 20 in 2012 and only 5 in 2013.

The median age of the patients was 24 months (range: 5 months to 17 years). Sixty-one (67%) patients were male. No differences were noted in the age distribution and gender of the patients in the pre and postvaccine periods. Fifty-nine (65%) patients were white. All the patients presented with chronic nasal congestion/drainage and chronic cough. Information regarding antibiotic therapy before surgery was only available in 43 patients (47%); of those 40 had received an antibiotic in the 4 weeks before surgery.

The most common comorbid conditions were chronic otitis media (67%), allergic rhinitis (37%), reactive airway disease/asthma (30%) and gastroesophageal reflux (15%). Of 91 patients, 23 (25%) had a significant underlying condition: 5 patients with cardiovascular disorder, 3 with central nervous system disorder, 3 with cystic fibrosis, 2 with Trisomy 21, 2 with malignancy, 2 with renal disorders and 1 each with Kartagener syndrome, Cri-du-chat, status post lung transplant secondary to bronchiolitis obliterans, Turner syndrome, juvenile osteochondrosis or thalassemia trait. No statistical difference in the type or frequency of comorbid or underlying medical conditions was observed between the pre- and post-PCV13 periods.

Eleven (12%) patients had not received any doses of pneumococcal vaccine. Eighty (88%) patients received at least 1 dose of pneumococcal vaccine; of those 30 patients received at least 1 dose of PCV13. Seventy-two (79%) patients received 3 or more doses of pneumococcal vaccine; of those 14 patients received 3 or more doses of PCV13. No statistical difference was observed in the pneumococcal immunization status of the patients between the pre- and post-PCV13 periods. All 91 pneumococcal isolates were serotyped. Nineteen different serotypes were identified.

Thirty isolates (33%) were PCV13 serotypes and 61 (67%) isolates were non-PCV13 serotypes. The percentage of PCV13 cases decreased 31% in the post-PCV13 era ($P = 0.003$) when compared with the pre-PCV13 era (Fig. 1). This decrease was driven by a reduction of 27% of serotype 19A cases in the post-PCV13 period ($P = 0.007$). No serotype 19A cases were identified in 2013. Serotype 19A (38%) and serotype 15C (17%) were the most common serotypes in the pre- and post-PCV13 periods, respectively (Table 1). All the cases in 2013 were because of non-PCV13 serotypes.

Five patients developed sinusitis because of PCV13 serotypes (serotype 19A in 4 patients and serotype 3 in 1 patient) despite being fully immunized for *S. pneumoniae* by age including at least 1 PCV13 dose. Of these patients, 2 had an underlying condition: 1 patient had Trisomy 21 and Lennox-Gastaut syndrome and the other had asthma.

All of the pneumococcal isolates were tested for antimicrobial susceptibility. The percentages of isolates with penicillin minimal inhibitory concentration (MIC) ≥ 2 μg/mL and ceftriaxone MIC ≥ 1 μg/mL were similar in the pre- and post-PCV13 periods. Serotype 19A accounted for all the isolates with penicillin MIC ≥4 μg/mL and ceftriaxone MIC ≥ 2 μg/mL. Isolates with a penicillin MIC ≥ 2 μg/mL and ceftriaxone MIC ≥ 1 μg/mL were more commonly associated with serotype 19A ($P < 0.001$ for both). Clindamycin and trimethoprim-sulfamethoxazole nonsusceptibility also was seen more commonly in serotype 19A isolates ($P < 0.01$ for both).

Sixteen cases (18%) were positive for *S. pneumoniae* only and 75 cases (82%) represented polymicrobial infections. *S. pneumoniae*-only infections were not associated with any particular pneumococcal serotype. The most common co-isolated organisms were nontypeable *H. influenzae* (52%), *Moraxella catarrhalis* (36%) and *Staphylococcus aureus* (11%; Table 2). Of the nontypeable *H. influenzae* isolates, 10 of 47 were β-lactamase positive. All *M. catarrhalis* isolates were β-lactamase positive with the exception of one. Three methicillin-resistant *S. aureus* isolates were identified. No specific age group was more affected by *S. pneumoniae*-only or

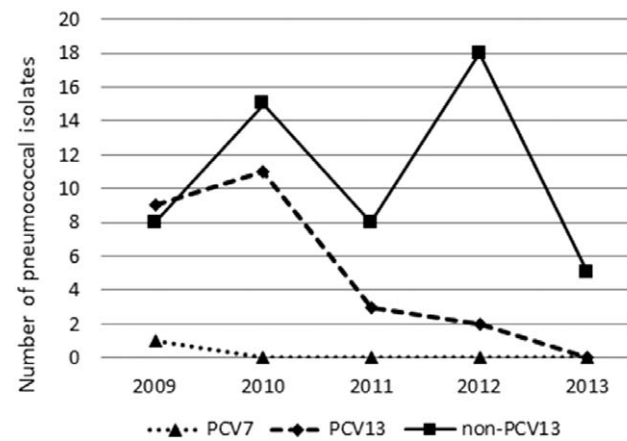

FIGURE 1. Serotype distribution of pneumococcal isolates recovered from children undergoing endoscopic sinus surgery 2009–2013. PCV7-serotypes included in the 7-valent PCV; PCV13-serotypes included only in the 13-valent PCV; non-PCV13-serotypes not included in the 13-valent PCV.

TABLE 1. Serotype Distribution of Pneumococcal Isolates Recovered From Children Undergoing Endoscopic Sinus Surgery

	Pre-PCV13	Post-PCV13	Total	*P*
PCV13				
19A	21	4	25	0.0074
19F	2	0	2	NS
3	2	1	3	NS
Non-PCV13				
35B	7	5	12	NS
15C	3	6	9	NS
6C	4	4	8	NS
23A	5	2	7	NS
11	1	4	5	NS
15B	2	3	5	NS
15A	1	2	3	NS
22F	2	0	2	NS
23B	1	1	2	NS
33F	0	2	2	NS
10	1	0	1	NS
16	0	1	1	NS
17	1	0	1	NS
21	0	1	1	NS
33A	1	0	1	NS
34	1	0	1	NS

Pre-PCV13 versus post-PCV13 periods.
NS, no significant.

polymicrobial infections. An increase in the isolation of *Prevotella* spp. was noted in the post-PCV13 period ($P = 0.02$) among patients with pneumococcal isolates.

None of the patients developed intracranial complications. Two patients were treated for allergic fungal sinusitis and pneumococcal (serotype 10 and 15C) sinusitis with antibiotics and steroids. One patient (serotype 23A) developed mastoiditis 3 months after completing antibiotic therapy for sinusitis. Seven patients had a second episode of pneumococcal sinusitis during the study period; all of them underwent repeat ESS and intraoperative cultures were obtained. Data for the pneumococcal serotype for the second episode were not available in 3 patients. None of the other 4 patients had the same pneumococcal serotype that was isolated during the first surgical procedure. The most common prescribed antibiotics post-surgery were cephalosporins (46%) and amoxicillin-clavulanate (17%).

TABLE 2. Other Organisms in Addition to *S. pneumoniae* Isolated From Children Undergoing Endoscopic Sinus Surgery

Species	Pre-PCV13	Post-PCV13	Total	*P*
Nontypeable *H. influenzae*	28	19	47	NS
Moraxella catarrhalis	22	11	33	NS
S. aureus	7	3	10	NS
Fungal species*	6	1	7	NS
Haemophilus parainfluenzae	3	2	5	NS
Prevotella spp.	0	4	4	0.02
Pseudomonas aureginosa	3	1	4	NS
Coagulase-negative Staphylococcus	3	0	3	NS
Stenotrophomonas maltophilia	2	0	2	NS
Other organisms†	5	1	6	NS

*Two isolates each of *Candida* spp. and *Aspergillus flavus*. One isolate each of *Fusobacterium* spp., *Bipolaris* spp. and *Curvularia* spp.
†One isolate each of *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Corynebacterium* spp., *Neisseria* spp. and alpha-hemolytic *Streptococcus* spp.

DISCUSSION

Our study revealed important changes in the epidemiology of *S. pneumoniae* among children with chronic sinusitis after the introduction of PCV13 in 2010. The proportion of cases of chronic sinusitis attributable to *S. pneumoniae* showed a significant decline in the 3 years after the introduction of PCV13. Isolation of PCV13 serotypes from children with chronic sinusitis also decreased significantly, mostly related to a substantial decrease of serotype 19A.

In our study, the overall isolation rate of *S. pneumoniae* was 14%. This result is similar to previous studies from Brook et al[2] and Merino et al[16] who reported a pneumococcal isolation rate of 13% among adolescents and adults with chronic sinusitis during 1987–2004 and pre-PCV7 period, respectively. However, Tinkelman et al[4] reported a higher pneumococcal isolation rate of 23% among young children (mean age 4.9 years) with chronic sinusitis before the introduction of PCVs; this rate is similar to our results (22%) from the pre-PCV13 period, which suggests that *S. pneumoniae* might play a more important role in chronic sinusitis in younger children.

Despite a similar overall isolation rate of *S. pneumoniae* to studies conducted in the pre- and early post-PCV7 period, we demonstrated a decrease of 13% ($P < 0.0001$) in the proportion of chronic sinusitis cases attributable to *S. pneumoniae* after the introduction of PCV13. We also found that the proportion of chronic sinusitis cases because of PCV13 serotypes decreased 31% ($P = 0.003$) in the post-PCV13 period, which is consistent with the impact of PCV13 in invasive pneumococcal disease in US children.[14,17] Our findings also provide evidence of indirect protection of PCV13 given the substantial decline in chronic sinusitis attributable to *S. pneumoniae* despite an incomplete vaccination rate. A recent study reported a 50% decline in nasopharyngeal colonization by PCV13 serotypes in non-PCV13 immunized children in Massachusetts by 2012.[18]

Pneumococcal serotype 19A was described as the most common serotype isolated from children with invasive pneumococcal disease[13] as well as chronic sinusitis[12] after the introduction of PCV7. In our study, we demonstrated a pronounced decline of serotype 19A (38% vs. 11%; −27% $P = 0.007$) after the introduction of PCV13. Moreover, serotype 19A was not responsible for any of the cases of chronic sinusitis in 2013. Non-PCV13 serotypes represented 86% of all the isolates in the post-PCV13 period; and serotype 15C became the most common serotype during the same period. Similarly, Lee et al[19] evaluated rates of pneumococcal colonization in children after PCV13 introduction and reported that serotype 15B/C has emerged as the most common isolate, whereas serotype 19A remained the second most common serotype in 2011. Despite these changes in serotype distribution, we did not observe an early emergence of replacement non-PCV13 serotypes. A significantly greater number of serotype 19A isolates showed high MIC for penicillin and ceftriaxone than non-19A serotypes, as described in previous studies.[12,13]

In our study, 18% of children with chronic sinusitis had *S. pneumoniae*-only infections; the remainder had polymicrobial infections. Similar results among patients with chronic sinusitis have been described.[10,12] Results from an AOM study in children described that *S. pneumoniae*-only infections were associated with serotypes identified as having higher disease potential, whereas mixed *S. pneumonia*e and *H. influenzae* infections were associated with serotypes identified as having low disease potential.[20] Similarly, Xu et al[21] reported when *S. pneumoniae* co-colonized the nasopharynx with *H. influenzae*, the latter predominated over all *S. pneumoniae* strains except for serotype 19A to cause AOM.

We did not identify an association with a particular pneumococcal serotype and *S. pneumoniae*-only infections. Moreover, we did not observe a higher rate of recurrence or complications in patients with *S. pneumoniae*-only infections. *H. influenzae* (52%) was overall the most common organism co-isolated with *S. pneumoniae*. The proportion of sinus cultures positive for *S. pneumonia*e and *H. influenzae* remained unchanged in the post-PCV13 era. However, we found an increase of *Prevotella* spp. (+11%; $P = 0.02$) after the introduction of PCV13. The importance of anaerobes in chronic sinusitis has been previously described[2,3,5] and their role in pediatric sinusitis seems to be controversial.[4] A recent study from Netherlands[22] reported that vaccination with PCV7 resulted in a shift in bacterial composition of the nasopharyngeal microbiota of vaccinated healthy children, with an increase in abundance of anaerobic bacteria, especially *Prevotella* spp. The change in the isolation rate of *Prevotella* spp. that we observed could be related to variations in the nasopharyngeal microbiota as a result of the introduction of PCVs or secondary to sampling techniques and improved isolation of anaerobic organisms.

Some limitations of our study should be recognized. First, we only studied children with chronic sinusitis, mainly because pediatric patients with acute sinusitis do not usually undergo a sinus tap or endoscopic sinus procedure unless their presentation is complicated with an orbital abscess or an intracranial process that requires surgical drainage. Therefore, we cannot extrapolate these results to patients with acute sinusitis. Second, 3 patients had recurrence of pneumococcal sinusitis during the study period, but their isolates were not available. Thus, it is possible that we missed some cases of chronic sinusitis positive for *S. pneumoniae*, underestimating the prevalence of pneumococcal chronic sinusitis. Third, it is possible that cultures positive for *S. pneumoniae* reflect inadvertent contamination of sinus specimen with nasopharyngeal flora and not a true pathogen.

In conclusion, our study provides evidence of important epidemiologic changes of pneumococcal chronic sinusitis among children after the introduction of PCV13. We reported a significant decline of *S. pneumoniae* isolation rate in children with chronic sinusitis at TCH. This decrease of pneumococcal chronic sinusitis cases was driven by a substantial reduction of PCV13 serotypes, predominantly serotype 19A. *S. pneumoniae* continues to represent an important pathogen in chronic sinusitis especially in children <5 years of age; however, additional studies are needed to fully understand the microbiology of chronic sinusitis in children, particularly in the PCV13 era.

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Do you need to operate following recovery from complications of pediatric acute sinusitis?

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ABSTRACT

Objectives: There are many studies that evaluate the role of surgery in the treatment of complications of pediatric acute sinusitis; however there are few studies, if any that report the incidence of surgery following recovery from acute complicated sinusitis. The goal of this study was to report the incidence and indications for surgical intervention after recovery from complications of pediatric acute sinusitis.
Methods: We reviewed the records of all children admitted to a tertiary care children's hospital between January 2005 and September 2010 with a diagnosis of sinusitis and an orbital or intracranial complication. Eighty-six patients met inclusion criteria. Charts were reviewed for type of complication, initial treatment (medical or surgical), type of procedure, secondary procedures, age, and comorbidities. Statistical analysis was completed using independent samples student *t*-tests and Mann–Whitney tests.
Results: A total of 86 patients with a mean age of 6.38 years (2 months to 18 years) were identified. Eighty patients had orbital complications while six presented with intracranial complications. Twenty-seven patients (31%) underwent sinus surgery during the acute phase of their illness whereas 59 patients (69%) were treated medically. After hospitalization and recovery for acute complicated sinusitis, surgery was performed on nine patients (mean age 4.86 years) within 1 month to 2 years post hospitalization. Of the nine patients who required secondary surgery following resolution of the initial complicated sinusitis, four patients were following initial surgical intervention and five patients had initially resolved their complication with medical therapy alone. Indications for subsequent surgery included failure of medical therapy for persistent rhinosinusitis (8 patients) and second complication (1 patient).
Conclusions: This study suggests that following resolution of complicated pediatric rhinosinusitis, very few patients may need further surgical intervention. Subsequent intervention is best guided by clinical judgment, symptoms during outpatient clinic visits, and failure of medical therapy.

1. Introduction

Rhinosinusitis is one of the most common diseases in the pediatric population, accounting for nearly a quarter of all pediatric antibiotic prescriptions [1]. Given the ease at which communicable disease spread in the pediatric population, children can experience up to six to eight upper respiratory infections (URIs) per year. Up to 5% of these URIs can be complicated by acute sinusitis [2]. Most patients with acute sinusitis will recover; however it is estimated that 5–10% will go on to develop an orbital and/or intracranial complications [3,4]. Orbital complications are more common than intracranial complications and are typically due to spread from ethmoid sinusitis. These complications can be classified using the criteria devised by Chandler et al. [1,5,6]. Briefly, class I is 'preseptal cellulitis', class II is 'orbital cellulitis', class III is 'subperiosteal abscess', class IV is 'orbital abscess', and class V is 'cavernous sinus thrombosis' [5]. This classification system does not represent a disease spectrum with one stage progressing to the next but rather a description of increasing severity of orbital complications. Intracranial complications include meningitis, epidural abscess, subdural empyema, or cerebral abscess [1,7].

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Management of these complications can be either medical, surgical, or a combination of both. In regard to subperiosteal abscess, several groups note that in certain groups of patients, subperiosteal abscesses (SPA) can be managed medically. This typically includes younger patients, with medial, small to moderate sized abscesses, and minimal proptosis [1,8,9]. Intracranial complications are generally considered a surgical disease, and require a combination of intravenous antibiotics and surgical drainage. However, small intracranial abscesses and meningitis without any intracranial fluid collections can be managed medically [7,10].

Although there is literature exploring the prevalence and treatment options for sinusitis complications, there is little evidence on the prevalence of sinus disease following recovery from complicated sinusitis and the incidence of subsequent or secondary surgery. The purpose of this study is to present the incidence and indications for surgical intervention after initial recovery from complications of acute sinusitis.

2. Methods

A retrospective chart review was conducted following IRB approval at the Children's Hospital of Wisconsin (CHW) from January 2005 to September 2010 looking for children diagnosed with orbital and/or intracranial complications of acute sinusitis. A CHW database search was created for all hospitalizations containing the International Classification of Diseases-9 (ICD-9) code of 'sinusitis' (461.0, 461.1, 461.2, 461.3, 461.8, 461.9, 473.0, 473.1, 473.2, 473.8, and 473.9) and 'disorders of the orbit' (376.00, 373.13, 376.01, 376.02, 376.03) or 'intracranial abscess' (324.0) or 'phlebitis and thrombophlebitis of intracranial venous sinuses' (325) or 'meningitis' (320).

Initial search resulted in 112 patients. Twenty-six patients had incomplete charts or incorrect ICD-9 codes and were excluded resulting in a total of 86 patients available for analysis. The following information was collected: age at diagnosis, comorbidities, type of complication, surgical intervention during initial hospitalization (if applicable), type and time of surgical intervention following resolution of acute complicated sinusitis (secondary surgery), and length of follow-up. One patient was removed from the analysis of the secondary surgery group since this patient presented 6 years after initial hospitalization for a second complication. This complication was likely independent of the initial complication and therefore considered an outlier.

Statistical analysis was completed using independent samples *t*-test to compare mean ages between the surgical and non-surgical group. Mann–Whitney tests were used to compare median ages of those that required secondary surgery to those that only required primary surgery or medical therapy.

3. Results

A total of 86 patients met inclusion criteria for this study. Twenty-seven patients underwent surgical intervention during the acute phase of their illness while fifty-nine patients were treated medically (Table 1). The mean age for the surgical treatment group was 8.96 years whereas the mean age for the medical therapy group was 5.20 years, $p < .0005$. Nine patients required secondary surgery following recovery from their initial complication of acute sinusitis within 2 years of initial hospitalization (mean 6.6 months). The mean length of follow-up for all patients was 7.6 months whereas the mean length of follow-up of patients requiring secondary surgery was 11.5 months.

Table 1
Medical versus surgical therapy.

Category	*N*	Average age (years)	Median age (years)
All patients	86	6.38	5.51
Initial medical treatment	59	5.20	4.61
Initial surgical treatment	27	8.96	10.03
Those requiring secondary surgery[a]	9	4.86	4.69

[a] Four patients from initial surgical therapy group and five patients from medical therapy group.

Table 2
Types of complications.

Complication	*N*	Initial surgical treatment (27 patients)	Initial medical treatment (59 patients)
Preseptal cellulitis	18	2	16
Orbital cellulitis	31	6	25
Subperiosteal abscess	49	22	27
Orbital abscess	1	1	0
Cavernous sinus thrombosis	0	0	0
Intracranial abscess	4	4	0
Meningitis	6	2	4

Subperiosteal abscess was the most common complication observed in the initial surgical group (22 patients) while intracranial complications were found in 5 of the 27 patients (Table 2). One surgical patient was diagnosed with an intracranial abscess (subdural epyema) and meningitis. SPA was only observed in 46% of the medically treated patients. There was a higher proportion of preseptal cellulitis (16/59) and orbital cellulitis (25/59) in the medical therapy group compared to the surgical therapy group (Table 2). There were no differences in comorbidities between the surgical and medical therapy groups.

Of the 86 patients admitted for complicated sinusitis, secondary surgery was performed on nine patients (Table 3). The average age at presentation of those that required a secondary surgery was 4.86 years and the median age was 4.68 years. Of the nine patients requiring secondary surgery, four patients initially had surgery and five had medical therapy alone. Patients that required secondary surgery (9 patients, median age 4.68 years) tended to be younger than those patients that only required an initial surgical intervention (23 patients, median age 10.38 years, $p = .02$). There was no significant difference in median age when comparing the medical therapy group (54 patients, median age 4.92 years) to those that underwent secondary surgery, $p = .82$. Indications for secondary surgery included failure of medical therapy for persistent rhinosinusitis and second complication.

4. Discussion

Pediatric rhinosinusitis is primarily a medically treated disease. Surgery is indicated in chronic rhinosinusitis refractory to medical therapy and certain complications of acute sinusitis [2,11]. There is an abundance of literature exploring the incidence and indications for surgery in pediatric sinus disease in both acute and chronic settings, however there is a paucity of information in regards to outcomes of patients after recovery from acute pediatric complicated sinusitis. Specifically there is a lack of information regarding incidence and indications for subsequent surgery.

Mortimore et al. conducted a five-year review looking at management of acute complicated sinusitis [12]. Their series consisted of 87 patients admitted with acute pansinusitis, of which 63 patients were diagnosed with one or more complications. Fifteen patients recovered with medical therapy alone while forty-eight patients required surgical intervention during the initial hospitalization. Only two patients (2/63) in their cohort required surgery (frontoethmoidectomy for recurrent acute sinusitis) following their initial hospitalization. All patients were followed

Table 3
Intervention after recovery from acute complicated rhinosinusitis.

Patient	Initial complication	Initial treatment	Secondary surgery	Indication
1	SPA, orbital cellulitis	AE, MA, orbitotomy	MA, revision MA, revision AE	Persistent CRS symptoms
2	Orbital cellulitis, meningitis	AE, MA, orbitotomy, frontal sinus trephination	Maxillary and frontal sinus irrigations	Persistent CRS symptoms
3	SPA	Orbitotomy, DCR	AE, endoscopic frontal sinusotomy	Persistent CRS symptoms
4	SPA, epidural abscess	AE, MA, orbitotomy, craniotomy	Adenoidectomy	Persistent CRS symptoms
5	SPA, preseptal cellulitis	Antibiotics	Maxillary sinus irrigations	Persistent CRS symptoms
6	SPA	Antibiotics	TE, MA	Second complication (SPA)
7	Orbital cellulitis	Antibiotics	Adenoidectomy	Persistent CRS symptoms
8	Orbital cellulitis	Antibiotics	Adenoidectomy	Persistent CRS symptoms
9	Preseptal cellulitis	Antibiotics	Adenoidectomy	Persistent CRS symptoms

AE, anterior ethmoidectomy; TE, total ethmoidectomy; MA, maxillary antrostomy; DCR, dacrocystorhinostomy; SPA, subperiosteal abscess; CRS, chronic rhinosinusitis.

up two weeks after discharge; however follow-up thereafter was variable up to two years. Although this study included a mixed population with a mean age greater than 20 years, it suggests that patients can be managed conservatively following resolution of acute complicated sinusitis.

In our case series, patients who were medically managed tended to be younger than those managed surgically (mean 5.20 years versus 8.96 years, $p < .0005$). This finding is in agreement with management of subperiosteal abscesses. In a review by Garcia and Harris, intravenous antibiotics and observation was initiated in patients younger than age nine with small to moderate sized medial SPAs. In their series, 93% of patients who met their criteria for expectant management responded to medical therapy [9].

Of the eighty-six patients included in this series, four patients from the surgical group (14.8%) and five patients from the medical therapy group (8.5%) went on to undergo subsequent surgery within two years of initial presentation. Using the Fisher exact test, there was no significant difference ($p = .45$) in the rate of secondary surgery between the two groups. In addition, patients who required initial surgical therapy were followed for nearly twice the length of patients requiring initial medical therapy (mean 11.2 months versus 6 months respectively). Therefore, given that there is not a significant difference in rate of secondary surgery between the two groups, we suggest that physicians consider following all patients for up to one year after recovery from complications of acute sinusitis. However, the overall rate of secondary surgery was only 10%, suggesting a low likelihood of a need to operate following resolution of acute complicated sinusitis.

One limitation of this study is its retrospective nature. Without prospectively cataloging the data, some patients had incomplete charts and follow-up times were relatively short. In addition, many patients transferred to the institution did not have initial imaging available. Complete charts with actual imaging would have facilitated calculation of Lund–Mackay scores as a surrogate marker for disease severity [13]. This might have been helpful in testing the potential association between Lund–Mackay score during initial hospitalization and need for subsequent surgery.

5. Conclusion

In our series of eighty-six patients, nine patients required at least one surgery following resolution of acute complicated sinusitis. A majority of these patients presented within one year of their initial hospitalization and required secondary surgery for persistent rhinosinusitis. Consequently, otolaryngologists should consider following patients with a complication of acute sinusitis for up to one year. However, the incidence of surgical intervention following resolution of acute complicated rhinosinusitis was quite low and subsequent intervention is best guided by clinical judgment.

Conflict of interest

There are no conflicts of interest to report.

Acknowledgements

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The Therapeutic Dilemma of Cochlear Nerve Deficiency: Cochlear or Brainstem Implantation?

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Abstract

Objective. To compare the outcomes between 2 age-matched cohorts of children with cochlear nerve deficiency: those receiving auditory brainstem implants (group A) or cochlear implants (group B).

Study Design. Retrospective cohort study.

Setting. Tertiary referral center.

Subjects and Methods. Subjects were selected from a pool of 537 children fitted with cochlear implants (n = 443) or auditory brainstem implants (n = 94) over the past 14 years. Performance, examined with the Category of Auditory Performance scale, and complications were compared with a mean follow-up of 5 years.

Results. All children had bilateral profound sensorineural hearing loss and cochlear nerve deficiency. Magnetic resonance imaging documented an absent cochlear nerve (n = 12) and a small cochlear nerve (n = 8) in group A and an absent cochlear nerve (n = 11) and a small cochlear nerve (n = 9) in group B (P = 1.000). Children with cochlear implants had Category of Auditory Performance scores spanning from 0 to 3 levels of performance, and all required manual communication mode and visual supplementation. Children with auditory brainstem implants had Category of Auditory Performance scores spanning from 2 to 7, and most patients demonstrated behavioral responses irrespective of inner ear malformations and an absent cochlear nerve or small cochlear nerve ($P < .001$).

Conclusions. In children with cochlear nerve deficiency, patients fitted with cochlear implants did not develop speech understanding and production. Those fitted with auditory brainstem implants had the opportunity to develop open-set speech perception, acquiring verbal language competence using oral communication exclusively and participating in mainstream education. The overall complication rate of auditory brainstem implants was not greater than that of cochlear implants.

Keywords

cochlear implant, cochlear nerve deficiency, auditory brainstem implant

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Hearing restoration in children with cochlear nerve deficiency (CND) is a therapeutic challenge, with conflicting reports describing children who, despite cochlear nerve hypoplasia or aplasia on magnetic resonance imaging (MRI), show auditory responses to different procedures, including simple amplification,[1,2] cochlear implants (CIs),[3-6] and auditory brainstem implants (ABIs).[7-11] An evident caveat of most of these studies is the very small number of subjects in any given subgroup comparison.

Clearly, children with CND are a special population and generally perform more poorly than average pediatric CI recipients, but exceptions have been described. This raises medical and ethical matters of selecting the device and intervention that might prove most beneficial. However, the current literature at present indicates unequivocally that CIs and not ABIs are the first-line treatment for these children, even in the absence of any scientific evidence that CIs outperform ABIs in this cohort of children. So, in many centers, CIs continue to be offered to patients with CND, surmising that some cochlear nerve fibers are present but not visible due to MRI limitations or because they occur within the facial or vestibular nerve.[12,13]

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Supported by studies showing better outcomes in children with CND when fitted with ABIs compared with children with CIs,[14,15] ABI recently has been proposed as the first-line treatment in children with CND. This proposal has generated the therapeutic dilemma of selecting CI or ABI as the best treatment option to be offered to children with CND.

To clarify these issues, we reviewed our population of children fitted with ABIs (n = 94) and CIs (n = 443) over the past 14 years and extracted 2 age-matched groups of children diagnosed with CND and fitted with a CI or an ABI who were younger than 3 years and operated on by the same surgeon (V.C.). The aim of the investigation was to determine whether differences exist in the trajectories of auditory development of the 2 procedures to justify the option of ABI as a first-line treatment in children with CND.

Materials and Methods

The Verona University Ethics Board approved the study, and all families gave their informed consent.

From 1998 to 2013, we fitted 443 children with CIs and 94 with ABIs following the outcome of a personal preimplantation audiological assessment described in detail elsewhere.[16] The expected outcome, possible risks, and prevalence of the complications of CI and ABI surgery were discussed with the parents and their consent obtained. Consideration was given to the surgical indication of the referring doctor, but the final decision on the surgical procedure was adopted at the discretion of the family in agreement with the proposal of the surgeon. So far, 32 children have traveled internationally to have hearing restored with a bionic device, but the high or low socioeconomic status of the family has never interfered with the surgeon's selection of the procedure.

From the 2 groups of children fitted with CIs or ABIs, we were able to retrieve the clinical charts of 54 children who met the following criteria: bilateral profound hearing loss from congenital deafness with CND, absent or small cochlear nerves, cochlear and internal auditory canal (IAC) malformations, no prior hearing experience (including hearing aid use), no previous meningitis and no coexisting hindbrain anomalies, unilateral CI and ABI implantation,[3] and all operated on during the same period (2004-2009) before 3 years of age. From this pool of 54 children, 14 were excluded from the study (see **Figure 1** for details of exclusion criteria). Approximately 50% of these initial 54 children had other nonauditory disabilities.

So finally, from a total of 537 children fitted with CIs (n = 443) or ABIs (n = 94) over the past 14 years, only 2 groups of 20 children, matched for age and fitted with ABIs or CIs, fulfilled the selection criteria. Both groups were followed for up to 8 years to compare outcome measures.

The retrosigmoid and posterior tympanotomy approaches were used for the ABIs and CIs, respectively.[7,14-16] Electrically evoked auditory brainstem recordings (EABRs) were performed preoperatively, intraoperatively at the end of surgery, and during follow-up in all children. All children in each group had unilateral CIs (17 Cochlear devices, Sydney, Australia, and 3 Med-El devices, Innsbruck, Austria) or ABIs (18 Cochlear and 2 Med-El devices) fitted.

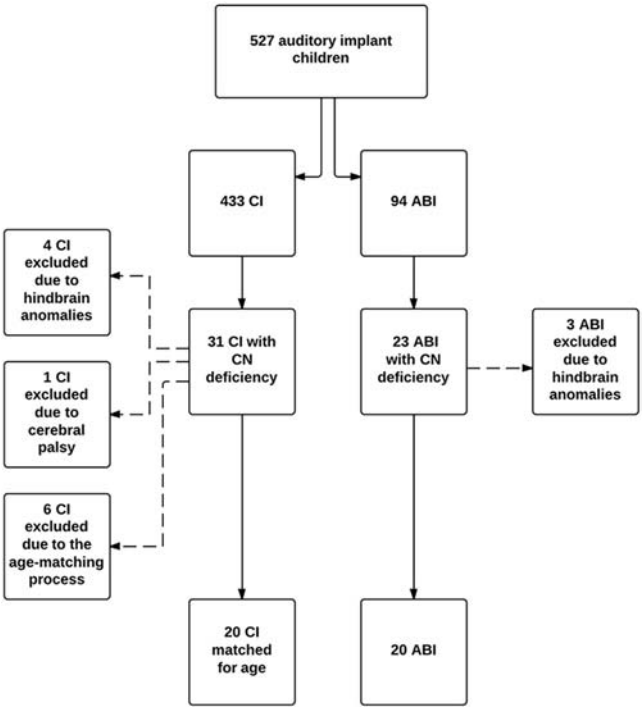

Figure 1. Flowchart for patient selection for inclusion in the auditory brainstem implant (ABI) and cochlear implant (CI) groups.

The algorithm for the rehabilitation of children fitted with CIs and ABIs included conditioned play audiometry, practiced at the beginning of every fitting session either with standardized instrumental sounds or with speech sounds (Six Ling's Sound Test) as a routine.

The evaluation of auditory perceptual ability was assessed with the Category of Auditory Performance (CAP) test[17,18] as previously illustrated.[15]

Statistical analysis included the *t* test, Wilcoxon Mann-Whitney test, Fisher exact test, and linear regression analysis, as appropriate.

Results

Demographic, clinical, and follow-up data are detailed in **Table 1**. All children completed the 24-month follow-up, while 16 subjects in each group were still enrolled in the study at 36 months.

Four children in group A (ABI) had associated cognitive deficits (among these subjects, 3 also had mild motor disabilities), 1 had behavioral impairment (attention-deficit hyperactivity disorder), 1 child was visually impaired, and 2 children were diagnosed with a polymalformative syndrome (Down and Moebius syndromes). Four children in group B (CI) also had associated cognitive deficits (1 also had mild motor disabilities), 1 child was visually impaired, and 3 children had other syndromes (Down, Shprintzen, and Moebius syndromes). There were 11 and 10 right ears and 9 and 10 left ears, respectively, in groups A and B ($P = 1.000$).

Table 1. Demographic Data for the 2 Study Populations.[a]

	Group A (ABI)	Group B (CI)	*P* Value
No. of patients	20	20	
Age at implantation, mean ± SD, y	1.4 ± 0.5	1.3 ± 0.4	.489[b]
Sex, male/female	13/7	11/9	.748[c]
Side, right/left	11/9	10/10	1.000[c]
Follow-up, median (interquartile range), y	6.9 (3.2-8)	4.7 (3.1-8)	.666[a]
Cochlear nerve deficiency, absent/small	12/8	11/9	1.000[b]
Auditory neuropathy spectrum disorders (normal cochleae)	5	4	1.000[b]
Associated cochlear malformations (subjects)	15	16	1.000[b]
Associated disabilities (subjects)	8	8	1.000[b]

Abbreviations: ABI, auditory brainstem implant; CI, cochlear implant.
[a]Values are presented as numbers unless otherwise indicated.
[b]*t* Test/Wilcoxon Mann-Whitney test as appropriate.
[c]Fisher exact test.

The EABR recordings performed intraoperatively demonstrated no auditory response in CI recipients and at least an auditory response on 8 to 11 (Cochlear) and 4 to 6 (Med-El) electrodes in children fitted with an ABI.

Imaging

Magnetic resonance imaging documented an absent cochlear nerve (ACN) and a small cochlear nerve (SCN) in 12 and 8 and in 11 and 9 children, respectively, in groups A and B ($P = 1.000$). Interestingly, among children with ACN, an open auditory nerve canal (ANC) was found in 5 and 4 children in groups A and B, respectively. The facial nerve (FN) had an aberrant course in 4 and 5 children in groups A and B, respectively.

Measurements of the IAC and ANC diameters were evaluated with high-resolution computed tomography (CT) scans for each child in both groups. The IAC was atretic in 4 and 3 children in groups A and B, respectively ($P = 1.000$). The diameter of the IAC was reduced (ie, less than 3 mm) in 12 and 13 children in groups A and B, respectively. The ANC diameter measurements showed abnormalities in children in both groups. A severe stenosis with an ANC diameter of less than 1.0 mm (0.31 ± 0.43 mm) was observed in 13 children in group A and 11 in group B. A moderate stenosis with a diameter of less than 1.8 mm was observed in 3 children in group A and 4 in group B (1.53 ± 0.25 mm). In the remaining children, the ANC was normal but empty on MRI. Because of the difficulty in obtaining clear auditory nerve (AN) diameter measurements, it was not possible to compute the correlation between the diameter of the AN and FN.

Cochlear abnormalities of different degrees were present in both groups: moderate in 6 and 5 children and severe in 9 and 11 children in groups A and B, respectively. Interestingly, cochlear morphology was normal on CT and MRI in 5 children in group A and 4 in group B, but the ANC was of abnormally reduced size in both groups. Severe vestibular malformations were associated with severe or extreme abnormalities of the cochlea in both groups. No child in the present 2 cohorts showed evidence of cochlear ossification.

Auditory Perceptual Abilities

The CAPs obtained before implantation scored 0 in all children in both groups. Both groups were tested with the CAP procedure at each visit after device activation, every 3 months for the first 24 months. After 24 months of device use, CAP scores showed significantly poorer outcomes in group B (0.7 ± 0.5) compared with group A (2.4 ± 1.3) ($P < .001$).

After the 24-month test, 5 children in group B were obtaining no benefit from the CI. After full discussion and informed consent from the parents, these children had the CI removed and an ipsilateral ABI fitted; these children dropped out of the present study. In the remaining children, CAP measurements were collected approximately every 6 months up to 8 years. At the 48-month follow-up, 1 child in group A could not be tested because the family went back to their original country and 4 more children in group B obtaining no benefit from the CI had the CI explanted and an ipsilateral ABI fitted. These children also dropped out of the study. At the 60- and 72-month follow-up, the number of ABI children remained the same, but the number of CI children dropped to 6 because 3 more children had the CI removed and had an ABI fitted ipsilaterally. **Figure 2** shows a scatterplot of the CAP scores of groups A and B as a function of ABI and CI experience. The CAP scores were higher in group A at all follow-ups of behavioral testing. After 2 years of device use, CAP scores continued to improve in group A, whereas group B reached a plateau at an approximate score of 2 within 4 years and did not improve significantly even after 8 years of CI experience (6.1 ± 1.0 vs 2 ± 0.8, $P < .0001$), with the exception of 2 patients, who were at least able to respond to speech sounds, without any identification skill, and to recognize very simple environmental sounds, such as continuous vs interrupted stimuli (**Figure 3**).

Nearly all ABI children demonstrated behavioral responses irrespective of inner ear and IAC morphology.

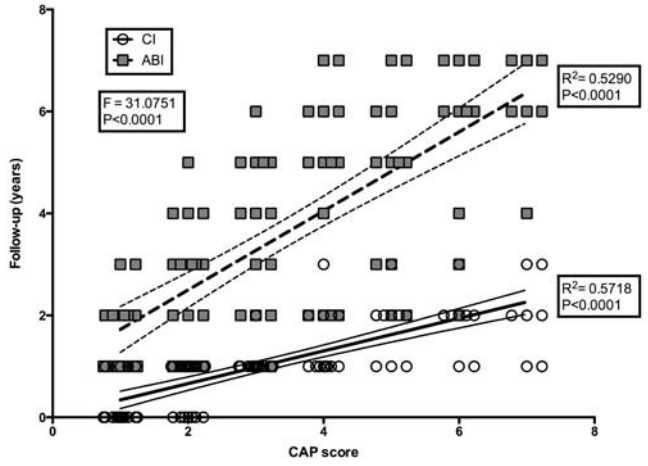

Figure 2. Category of Auditory Performance (CAP) developmental trajectory in children with cochlear nerve deficiency: auditory brainstem implant (ABI) vs cochlear implant (CI). The trend lines for the ABI and CI groups are represented by the dashed and solid lines, respectively.

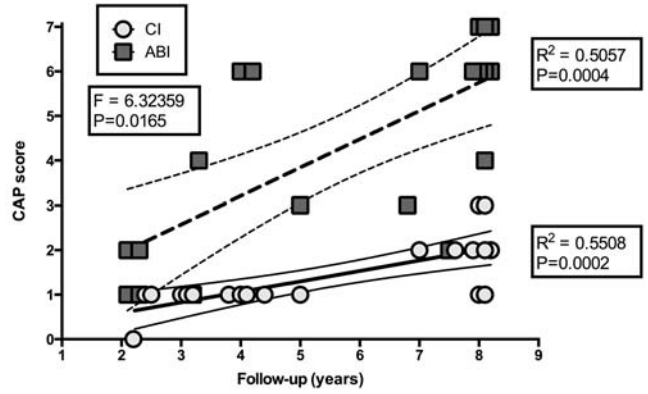

Figure 3. Category of Auditory Performance (CAP) scores and trend lines of 40 children with cochlear nerve deficiency fitted with an auditory brainstem implant (ABI) or a cochlear implant (CI) at the last follow-up.

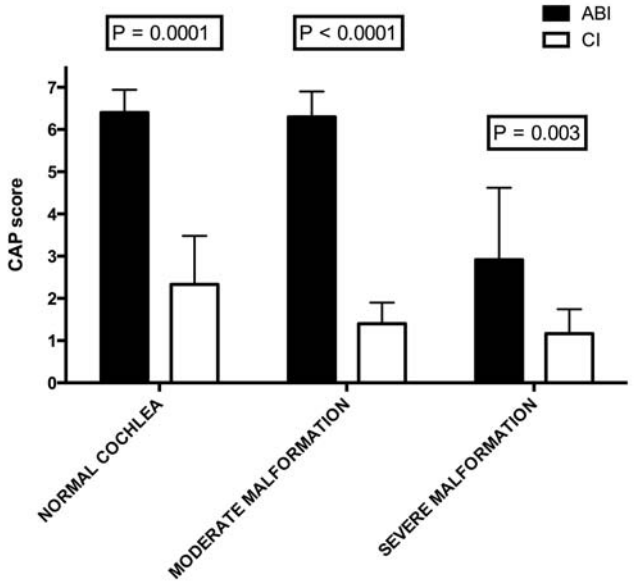

Figure 4. Last Category of Auditory Performance (CAP) scores of children with cochlear nerve deficiency fitted with an auditory brainstem implant (ABI) or a cochlear implant (CI) grouped by degree of cochlear malformation.

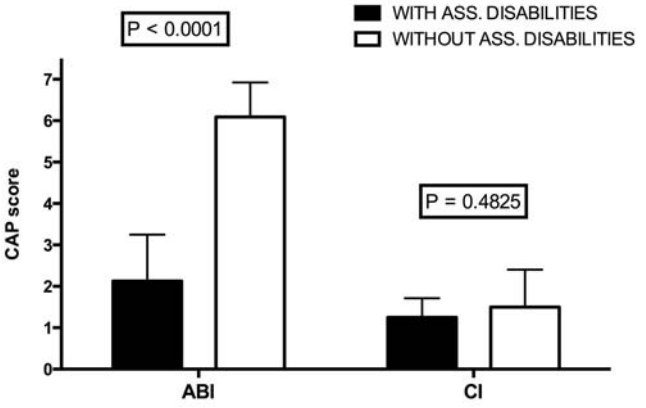

Figure 5. Last Category of Auditory Performance (CAP) scores in children with cochlear nerve deficiency fitted with an auditory brainstem implant (ABI) or a cochlear implant (CI) with or without associated disabilities.

The benefit from CI was limited to auditory awareness with behavioral responses induced at very high levels of charge units, often associated with nonauditory stimulation such as facial nerve stimulation and disequilibrium, so much so that in 5 patients, all electrodes had to be inactivated and the children explanted and fitted with ABIs.

The children with normal cochleae and either ACNs or SCNs fitted with ABIs demonstrated a significantly earlier and better perceptual outcome on the CAP test than did children with cochlear abnormalities; all children with normal cochleae had a CAP score of more than 5 at the last follow-up after ABI fitting (6.4 ± 0.5 vs 2.3 ± 1.2; $P <$ .0001) (**Figure 4**). No children with normal cochleae presented associated disabilities.

The ABI children without associated disabilities showed better auditory performance than children with associated disabilities at all follow-up intervals (6.1 ± 0.8 vs 2.1 ± 1.1; $P <$ .0001, at the last follow-up). Conversely, the CI children without associated disabilities demonstrated a small but not significant difference in performance at all follow-up intervals (1.5 ± 0.9 vs 1.4 ±0.4; P = .483, at the last follow-up) compared with children with disabilities (**Figure 5**).

Safety

No major anesthesiological or surgical complications such as cardiac arrest, facial palsy, or flap breakdown were observed in any child.

Among minor anesthesiological complications, 2 children aged 13 and 24 months in the ABI group experienced

transitory bronchospasm and hypotension, both of which resolved with medical treatment. Blood pressure range during surgery was not statistically significantly different in the 2 study groups ($P = .552$). No perioperative surgical complications were encountered in any children. Blood loss was recorded as less than 30 mL in all patients. There were 3 minor postoperative complications: 2 cases of wound seroma (1 in each group) and 1 case of wound infection in group B; all were treated conservatively. Children in groups A and B were discharged, respectively, after an average of 6.3 ± 2.1 and 2.6 ± 1.8 days ($P < .001$). Delayed wound healing (10 days after surgery) was observed in 1 child in group A and in 2 subjects in group B. Within 2 years of implantation, postoperative otitis media was observed in the same ear as the CI in 3 children. All were treated medically with no further complications. No complications related to ABI or CI activation or long-term use were evident in any subject, apart from those children who experienced facial nerve stimulation and had some CI electrodes deactivated.

Discussion

Earlier studies involving behavioral outcome measures in children with CND fitted with CIs have reported very poor results, leading to decisions not to provide a CI to these children.[19-22] However, more recent studies indicate that limited speech detection and discrimination and, very occasionally, higher levels of auditory performance may be observed in these children.[23-27] The recent innovative proposal of offering ABIs as first-line treatment in children with CND, corroborated by significantly better outcome compared with children fitted with CIs,[3,7-11,14-16] complicated the decision with regard to the best treatment option for children with CND and generated a pivotal therapeutic dilemma.

Clearly, if some reasonably good outcomes are achieved with CIs, it is difficult to decide in favor of an ABI as the initial treatment in these patients, considering the potentially serious risks of this intracranial procedure. These reservations, supported by the inability of preoperative MRI and EABRs to provide unambiguous information with regard to the status of the cochlear nerve, have suggested cautiously that children with CND should first undergo a trial with CIs to verify the benefit of the procedure and, only after confirming the inefficacy of the CI, could ABI possibly be considered.

A recent study[15] described a cohort of 21 children with a clinical diagnosis of CND fitted with CIs. Among these children 13 presented ACNs and 8 SCNs, respectively. As a result of failure of progression of auditory ability in all these children, the CIs were explanted and ABIs fitted ipsilaterally. At surgery, the so-called SCN was demonstrated in all cases to be the nervus intermedius. This very important observation confirmed that the determination of the individual nerves in ears with stenotic IAC is limited by the degree of spatial separation of the nerves.[12,13] In this cohort of children, the opportunity to develop open-set speech perception and acquire speech was obtained only after fitting an ABI.

The time course for the development of auditory perception in profoundly deaf children with CND following CI or ABI may extend over many years, and long-term investigations are needed to determine whether the 2 devices differ significantly in the trajectories of auditory development to justify the option of the ABI as a first-line treatment in these children. To provide a contribution to this theme and unravel the dilemma of the best treatment for children with CND, the present retrospective study was performed. To our knowledge, no such studies exist in the literature.

The outcome of the present investigation indicates that CAP scores were significantly poorer in the CI group compared with the ABI group: most children in the ABI group experienced a gradual increase in performance over time, whereas children in the CI group achieved some initial improvement in behavioral test scores without any further improvement even after long-term implant experience. Within the first year of activation, the entire ABI group obtained awareness of environmental sounds, and 45% responded to speech sounds. At the second year of follow-up, 50% of these young patients were able to recognize environmental sounds and 20% discriminated speech sounds, while in the third year of ABI use, 31.3% of group A were in open-set speech perception. Eight of 11 subjects who reached the fifth year of ABI fitting were able to understand simple commands with no lip reading, and 3 were capable of sustaining a telephone conversation with a familiar speaker. After 8 years of follow-up, 12 children from the CI cohort in the present study were explanted and fitted with ABIs, obtaining a partial recovery.

A comparison of the complications associated with ABI and CI surgery confirms that, even though the potential complications of a retrosigmoid craniotomy are clearly greater than those of the transmastoid approach of CI surgery, in practice, both major and minor complication rates are comparable in the hands of well-trained surgical teams.[27]

Further consideration should be given to the cost-benefit ratio and psychological involvement of the family of a child diagnosed with profound hearing loss and CND at the age of 3 to 4 months who is fitted first with a hearing aid for 6 to 12 months and then with a CI for a further 1 to 3 years and finally, only after all these inconveniences, receives the suggestion to have their child fitted with an ABI.

As a result of this study, we advocate EABR preoperative evaluation in CI and ABI candidates and intraoperative evaluation and programming with threshold determination in children with CND fitted with CIs and ABIs. Similarly, periodic EABRs should be performed to objectively assess CI or ABI device ''efficacy'' in these children and stratify candidates into those expected or not expected to achieve open-set speech perception.

The CI children who achieve poor speech perception results after 2 years of CI use and who have an abnormal EABR may receive limited benefit from their CI, and such candidates may profit from the ABI. The long-term outcome

study of the present article shows that children with CND and ABI do outperform those treated with CI.

We have learned that fitting a CI in a subject with CND, cochlear and IAC malformations, and no RW-EABRs may be a waste of time and expense. At the same time, a child fitted with CI showing no postoperative EABRs and no auditory progress for more than 2 years should not wait any further and should be fitted with a contralateral ABI.

Cochlear nerve deficiency is a relatively common cause of profound sensorineural hearing loss that challenges the decision-making process with regard to whether to proceed with a CI or an ABI.

In the present cohort of children with CND, those fitted with CIs did not develop speech understanding and production. Those fitted with ABIs frequently developed open-set speech perception, with some acquiring verbal language competence using oral communication and participating in mainstream education. Furthermore, since the overall complication rate of ABIs was not greater than that of CIs, consideration should be given to the use of ABI technology as the first surgical prosthesis of choice in this patient population.

Author Contributions

Liliana Colletti, conception and design of the study, acquisition of data, analysis and interpretation of data, drafting and revising the article, final approval; **Giacomo Colletti**, conception and design of the study, analysis and interpretation of data, drafting and revising the article, final approval; **Marco Mandalà**, conception and design of the study, acquisition of data, analysis and interpretation of data, drafting and revising the article, final approval; **Vittorio Colletti**, conception and design of the study, acquisition of data, analysis and interpretation of data, drafting and revising the article, final approval.

Disclosures

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Is "No Response" on Diagnostic Auditory Brainstem Response Testing an Indication for Cochlear Implantation in Children?

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Objectives: To compare the results of a "no response" (NR) result on auditory brainstem response (ABR) testing with those of behavioral pure-tone audiometry and ultimate clinical tracking to cochlear implantation (CI).

Design: Retrospective review of pediatric patients who underwent multifrequency ABR testing in a 5 year span. Total of 1143 pediatric patients underwent ABR testing during the study period and 105 (9.2%) were identified with bilateral NR based on absent responses to both click and tone burst stimuli. For the children with NR, various clinical parameters were evaluated as these children progressed through the CI evaluation process. Children were grouped based on whether they underwent ABRs for diagnostic or for confirmatory purposes.

Results: Of the 105 children who met inclusion criteria, 94 had sufficient follow-up to be included in this analysis. Ninety-one (96.8%) of 94 children with bilateral NR ABRs were ultimately recommended for and received a CI. Three (3.2%) children were not recommended for implantation based on the presence of multiple comorbidities rather than auditory factors. None of the children (0%) had enough usable residual hearing to preclude CI. For those who had diagnostic ABRs, the average time at ABR testing was 5.4 months (SD 6.2, range 1–36) and the average time from ABR to CI was 10.78 months (SD 5.0, range 3–38).

Conclusions: CI should tentatively be recommended for children with a bilateral NR result with multifrequency ABR, assuming confirmatory results with behavioral audiometric testing. Amplification trials, counseling, and auditory-based intervention therapy should commence but not delay surgical intervention, as it does not appear to change the eventual clinical course. Children not appropriate for this "fast-tracking" to implantation might include those with significant comorbidities, auditory neuropathy spectrum disorder, and unreliable or poorly correlated results on behavioral audiometric testing.

Key words: Auditory brainstem response, Cochlear implant, Cochlear implant candidacy, Hearing loss.

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INTRODUCTION

Auditory brainstem response (ABR) testing is widely accepted for identification and diagnosis of hearing loss in the pediatric population. For patients who are unable to participate in behavioral audiometry because of age or medical comorbidities, frequency-specific tone burst ABR is useful for estimating the pure-tone audiogram so that early intervention can be implemented. There is extensive literature supporting a strong correlation between estimated ABR and behavioral pure-tone thresholds (Stapells 2000). However, *correlation* does not necessarily imply that the test is *predictive*. In fact, there remains a great deal of variation regarding the accuracy of ABR as a predictor of actual behavioral thresholds. Factors that contribute to this variation include stimulus characteristics and recording parameters as well as developmental age and degree of hearing loss (Sininger 2006). In one study, the inherent degree of uncertainty in estimating pure-tone thresholds from ABR thresholds with a 95% confidence levels was ±15dB HL (Stapells 2000). So the range of pure-tone thresholds estimated from ABR thresholds can be quite large with individuals in the upper limits of the range possibly amenable to amplification (Marttila & Karikoski 2006). Furthermore, ABR estimates are generally less accurate in the lower frequencies and in those with severe to profound hearing loss (Gorga et al. 2006). ABR tends to overestimate the degree of hearing loss in individuals with severe to profound impairments (Marttila & Karikoski 2006; Sininger 2006). Thus, even in the setting of a "no response" (NR) result on ABR testing, definitive conclusions about usable residual hearing cannot be made.

In the current management paradigm, children with congenital hearing loss and a NR result on ABR testing are initially fitted with hearing aids based on threshold estimates predicted by the ABR with the use of a prescriptive formula for estimating gain and output. Reliable behavioral audiometric testing is then used to confirm pure-tone thresholds more precisely between 6 and 8 months of age and hearing aid adjustments are made as needed. For those children who do not make appropriate progress in communication skills development, despite good compliance with well-fit amplification and auditory-based intervention, a cochlear implant (CI) is recommended. When uncomplicated, this process should result in cochlear implantation by the end of the first year of life. This paradigm is consistent with the goals and recommendations of the Joint Committee on Infant Hearing (Reference Note 1).

Unfortunately, a variety of factors can and often do cause considerable delays in access to a CI (Table 1). From an auditory perspective, even in the setting of a bilateral NR result on ABR testing, behavioral audiometric testing often reveals that the degree of residual hearing might support meaningful progress with proper fit and use of amplification. In these cases, the hearing aid trial may be extended with the hope of greater progress in lieu of exposing the child to unnecessary surgery and potential compromise of residual hearing. Moreover, for families that are noncompliant with the early stages of the hearing aid trial, a period of prolonged counseling and observation is often recommended to improve acceptance of the commitment needed for success. In some cases, other medical diagnoses, including

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TABLE 1. Factors that can delay cochlear implantation

Auditory
Delay in diagnosis
Significant residual hearing
Fluctuating hearing
Unreliable or conflicting test results
Under-fit amplification
Speech development
Good progress despite profound hearing loss
Medical
Anatomic uncertainty (cochlear nerve deficiency severe inner ear malformations, etc.)
Multiple comorbidities (prematurity, CP, autism, etc.)
Auditory neuropathy spectrum disorder
Parental issues
Poor follow-up
Poor compliance with amplification trial
Socioeconomic barriers
Parental education/understanding

serious maladies as well as issues such as persistent otitis media can result in delays. Inefficient programmatic designs requiring multiple transitions of care between physicians, audiologists who provide hearing aids, speech and auditory verbal therapists, as well as audiologists who work with cochlear implants may result in further delays.

This study aimed to better characterize the clinical course of children with a bilateral NR result on diagnostic ABR (dABR) as managed with the paradigm described above. We compared the clinical time course and outcomes of children with NR result on ABR testing who went on to obtain a CI and those who did not. We also demonstrated the time course to CI in this distinct group of patients, identifying any systematic and/or incidental delays. We believe that if all children with a NR ABR can be shown to consistently progress to a CI, then the NR ABR could potentially be considered as one of the early indications for CI. With such knowledge at hand, we can anticipate the needs of such a child who is expected to progress to a future CI and therefore mitigate many of the aforementioned delays.

MATERIALS AND METHODS

The institutional review board at the study institution approved the study. A retrospective review of all pediatric patients (<18 years of age) who underwent ABR testing at the study institution between July 1, 2006, and June 30, 2011, was undertaken to identify those with a binaural NR result. All testing was performed and analyzed by experienced pediatric audiologists. Patients were tested either in natural sleep conditions in the clinic or under sedation/general anesthesia in an operating room, imaging center, or a sedation suite. All ABRs were included in the review, regardless of location (operating room or clinic) or condition (sedation or natural sleep). ABR testing was recorded with the Biologic Navigator Pro system (Natus Medical Inc., San Carlos, CA). The ABR protocol includes at a minimum of two main stimulus types: a 100 μsec click and a "single-cycle" 250 Hz tone burst. Responses to tone bursts at frequencies of 500, 1000, 2000, and 4000 Hz were tested when possible. Because of time constraints, not all frequencies could be completed for all patients. The single-cycle 250 Hz tone burst is shaped by a Blackman window with 2-msec rise/fall times and no plateau. A 2-channel recording is undertaken (Fz – A1 or A2, referenced to Fpz) using a bandwidth of 100 to 3000 Hz (clicks) or 30 to 3000 Hz (250 Hz tone bursts) and a time window of 20 msec. The physiologic ABR threshold is taken as the lowest stimulus level at which a wave V response can be visually detected in the response. A NR result was defined as no definable response waveforms at the maximum outputs of the equipment (90 dB nHL) for clicks and at least a 250 Hz tone burst. Those with response morphologies consistent with Auditory Neuropathy Spectrum Disorder (ANSD) were excluded from the study. Diagnosis of ANSD is made based on an absent or grossly abnormal ABR and the presence of a cochlear microphonic using single-polarity stimulation and/or presence of otoacoustic emissions. The cochlear microphonic is distinguished from neural responses if the response inverts with polarity inversion and latency remains constant with changing stimulus level. Stimulus artifact is also ruled out by disconnecting the sound tube during recording.

Only children with bilateral NR results were included in the study. For these children, demographic and medical data were extracted from the electronic medical record to include date of birth, newborn hearing screening (NBHS) results, age of diagnosis, comorbidities, and radiographic imaging results. Behavioral audiometric measures were also collected for those children with testing performed at the study institution, by experienced pediatric audiologists, using standard visual reinforcement audiometry techniques. This testing was attempted on all patients starting between 6 and 8 months of age unless severe medical comorbidities precluded testing. Children were tested at regular intervals of 3–4 weeks until reliable data were collected. Children without reliable test results, those with only behavioral observation results, those unable to complete testing, and those with only tests performed outside the study institution were excluded.

All children were fit with hearing aids at the study institution using desired sensation level prescriptive targets. Probe microphone measures were used to quantify the real-ear-to-coupler-difference (RECD) for verification of speech audibility and maximum output (Bagatto et al. 2005). When the RECD could not be measured because of limited cooperation or subject noise, an age-related average RECD estimated the acoustic characteristics of the child's occluded ear. Progress in communication and audition skills during amplification trial was assessed by a speech language pathologist and compared with age-matched hearing peers. Referral to the CI program was based on the amount of residual hearing and/or progress with amplification while being enrolled in an active, diagnostic auditory-based intervention program. This referral process from the diagnostic/hearing aid audiologists to the CI program is a highly integrated one that is enhanced by an electronic, real-time management system as well as a weekly, multidisciplinary meeting in an effort to expedite transitions. The time course of clinical progression and final hearing assistive device strategy was documented.

Data were entered in a Microsoft Excel Spreadsheet (Redmond, Washington, USA) and outcomes summarized. In an effort to accurately understand the time course of clinical progression between ABR testing, behavioral audiometric testing, and CI surgery, two distinct categories of patients emerged and were analyzed separately. ABRs were considered as dABR if the ABR was performed before any behavioral testing. In

some cases, older children were referred to our institution after behavioral testing and/or ABR testing had already been performed. If any behavioral data had been obtained before ABR testing regardless of testing method, the ABR was considered confirmatory (cABR). Often, cABR was performed just before CI surgery to also rule out ANSD. Patients ultimately receiving bilateral CIs were noted, but analysis included only time course up to the date of the first CI.

RESULTS

A total of 1142 pediatric patients underwent ABR testing in the 5-year period and 105 (9.2%) met the above criteria for inclusion in the study. A summary of hearing loss etiologies and significant comorbidities can be found in Table 2.

Of the 105 children identified in the review, 11 (10.5%) were lost to follow-up at the time of data collection and/or did not have reliable behavioral audiometry results. Ninety-four ($n = 94$) children with NR ABRs had adequate data to report with appropriate follow-up. Of the 94 patients, 80 (85.1%) failed the NBHS in at least one ear, 8 (8.5%) passed, and 6 (6.4%) did not have newborn screening data because of birth outside of the United States or adoption history. As a tertiary care medical center, many children were referred after some degree of workup or diagnosis elsewhere before initial evaluation at our institution. The mean age at presentation to our institution was 16.9 months (SD 25.3, range 1–137). The mean age at the time of ABR testing for all included patients was 19.3 months (SD 26.9, range 1–140). The mean age at dABR was 5.40 months (SD 6.2, range 1–36) as compared to 35.79 months (SD 28.4, range 4–131) for cABR.

Although all 94 patients had an NR response on ABR testing at the maximum stimulus level for the frequency tested, the actual corresponding thresholds documented on behavioral testing showed a wide range of results. Figure 1 compiles the corresponding behavioral thresholds for all tested ears (175 total ears), although not all frequencies were able to be tested on both ears for all subjects. Behavioral responses at 250 Hz demonstrated a particularly broad range varying from 40 dB HL to no measurable responses. The range at higher frequencies showed somewhat less variability. Of the four children with thresholds 65 dB HL or better at 250 and 500 Hz, one had progressive hearing loss and the remainder failed to make progress with amplification. All had a history of prematurity with three requiring mechanical ventilation in the neonatal intensive care unit. The majority of patients (>50%) with a NR ABR had no demonstrable evidence of residual hearing on behavioral testing at any of the frequencies tested.

The various clinical outcomes are graphically depicted in Figure 2. Of the 94 children, 91 (96.8%) ultimately received at least one CI and 49 (52.1%) received bilateral CIs. Importantly, no child (0%) demonstrated auditory thresholds on behavioral testing or sufficient progress in speech and language development with amplification to contraindicate implantation. Of the 3 (3.2%) children who did not receive a CI, this result was secondary to significant and pervasive comorbidities.

For the 91 patients who ultimately went on to receive a CI, the progression through the CI evaluation process varied greatly. Two distinct patterns of progression emerged from this group based on the purpose of the initial ABR. ABRs were considered as dABR if the study was performed before any behavioral testing. If the ABR was performed with the purpose of verifying prior behavioral testing data, then it was considered as cABR. Table 3 summarizes the range, average, and SD of ages at ABR testing, behavioral testing, and CI surgery, as well as the amount of time elapsed between each of the above measures. The overall mean age at time of ABR

TABLE 2. Etiology of hearing loss and comorbidities in patients with a "no response" auditory brainstem response

Etiology	*N* (%)
Unknown	57 (54.3)
Connexin 26	9 (8.6)
Cytomegalovirus infection	11 (10.5)
Waardenburg syndrome	7 (6.7)
CHARGE syndrome	5 (4.8)
Meningitis	3 (2.9)
Other congenital syndrome	5 (4.8)
Inner ear malformations	29 (27.6)
Cochleo-vestibular dysplasia	18 (17.1)
Enlarged vestibular aqueduct	3 (2.9)
Cochlear nerve deficiency or hypoplasia	8 (7.6)
Medical co-morbidities	
Prematurity	20 (19.0)
Hyperbilirubinemia	11 (10.5)
Neonatal intensive care unit stay	17 (16.1)
Seizure disorder	9 (8.6)
Developmental delay	23 (21.9)
Cerebral palsy	7 (6.7)
Family history of hearing loss	17 (16.1)

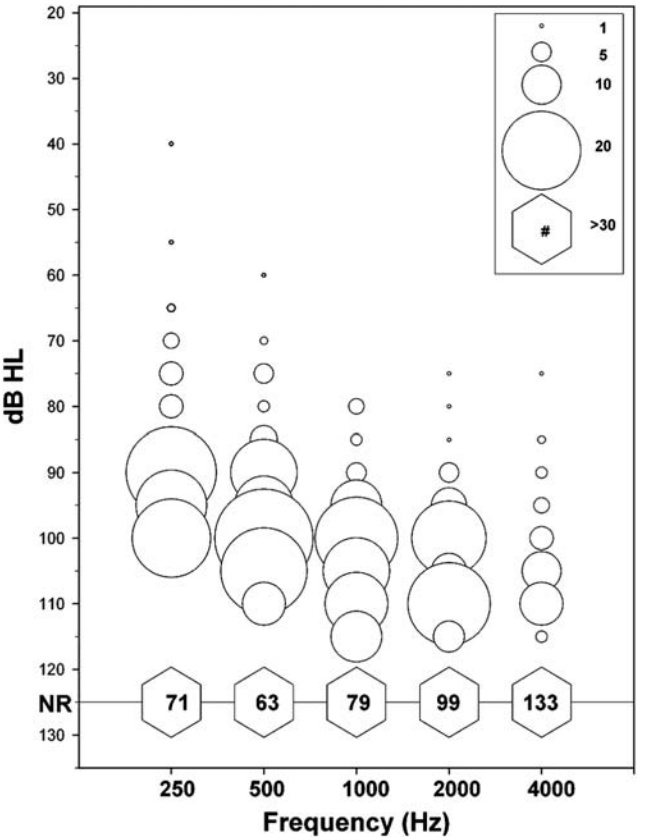

Fig. 1. Residual hearing as confirmed by behavioral audiometry for patients with no response on auditory brainstem response.

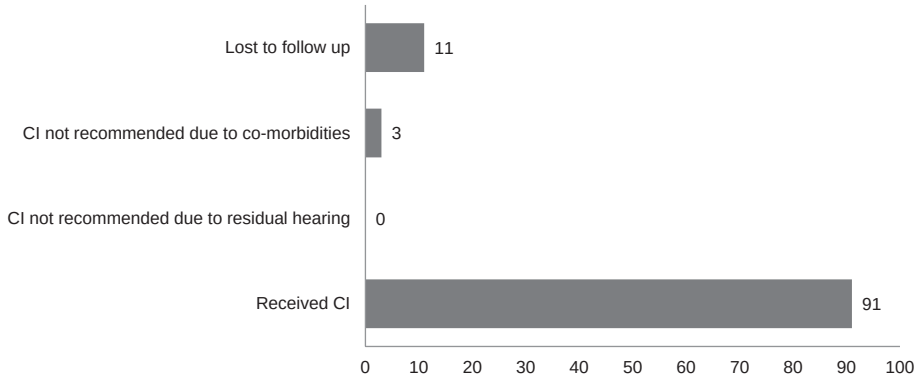

Fig. 2. Clinical outcomes of all included patients.

TABLE 3. Age at ABR diagnosis and timing to behavioral audiometry testing and CI surgery

		Age (Months) at Testing/Intervention			Time (Months) Between Testing/Interventions		
	N (%)	ABR	Behavioral Testing	CI Surgery	ABR to Behavioral Testing	Behavioral Testing to CI Surgery	ABR to CI Surgery
Diagnostic ABR (dABR)	53 (58.2)	1–36 **5.40** (6.2)	6–36 **10.04** (5.0)	8–41 **15.98** (6.5)	0–13 **4.71** (2.7)	1–28 **5.87** (3.8)	3–38 **10.78** (5.0)
Confirmatory ABR (cABR)	38 (41.8)	4–131 **35.79** (28.4)	5–131* **34.58** (27.9)	6–136 **40.32** (28.2)	Variable† **N/A**	1–18 **5.20** (3.7)	0–22 **4.49** (4.9)
Overall	91	1–131 **18.09** (24.1)	5–131 **20.29** (22.0)	6–136 **26.14** (22.3)	Variable† **N/A**	1–28 **5.59** (3.8)	0–38 **8.15** (5.8)

*For each category, range as well as **average** and (SD) are shown.*
**First reliable audiometric data closest to date of NR ABR.*
†Audiometric data may have been obtained before or after ABR.
ABR, auditory brainsem response; CI, cochlear implantation.

testing was 18.09 months (SD 24.1, range 1–131). The overall mean age at the time of CI surgery was 26.14 months (SD 22.3, range 6–136). Since referrals to the CI team are based on behavioral audiometry, not surprisingly the time from behavioral testing to CI surgery for both the dABR and cABR groups is similar, 5.87 versus 5.20 months, respectively. The time from ABR to CI surgery is lowered for the cABR group since many of the ABRs were performed on the day of surgery to rule out ANSD and confirm behavioral audiometric test results.

To further characterize how the CI evaluation process is affected by the age at ABR testing, only the data from the children with dABRs were considered for the statistical analysis. Figure 3 shows the relationship between the various time intervals between interventions and age of ABR for the dABR group. The correlation coefficient (r) was graphically demonstrated for each relationship. Although children progressed through the CI evaluation process at varying rates, those who presented at later ages progressed to CI faster than younger patients. As depicted in the bottom graph of Figure 3, there is a statistically significant negative correlation between age at ABR testing and time to CI surgery ($r = -0.335$, $p = 0.014$). This is, of course, is confounded by the fact that older children are able to perform behavioral testing sooner than younger children as seen in the top graph of Figure 3, which shows a clear negative correlation between time of ABR testing and time to behavioral testing ($r = -0.593$, $p = <0.001$). Once confirmatory behavioral testing is obtained and referral to the CI team is made, the amount of time until CI surgery remains fairly constant regardless of age at initial ABR. The middle graph of Figure 3 shows no significant correlation between age at ABR testing and time from behavioral testing to CI surgery ($p = 0.713$), with average time interval of 5.87 months (SD 3.8). This suggests that delays in progressing to CI in a timely fashion likely arise during the time between dABR testing and reliable behavioral testing when referral to the CI team is made.

Only 15 (34.0%) children had more than 1-year duration between the dABR and CI surgery. Reasons for the long elapsed time within this group included delays in behavioral testing because of middle ear pathology ($n = 7$), need for other medical interventions ($n = 4$), lost to follow-up or scheduling conflicts ($n = 7$), and/or parental choice ($n = 1$). Appropriate progress with amplification ($n = 0$) and too much residual hearing ($n = 0$) did not account for delays in this group of children.

DISCUSSION

Universal NBHS has greatly improved early identification of children with hearing loss. dABR testing allows clinicians to estimate auditory thresholds for the purposes of fitting amplification at a much earlier age than behavioral testing. Despite the advances in early diagnosis, many congenitally deaf children do not receive hearing aids or CIs until 2 years of age or older. The benefits of early intervention in the form of amplification and CI have been described in numerous studies.

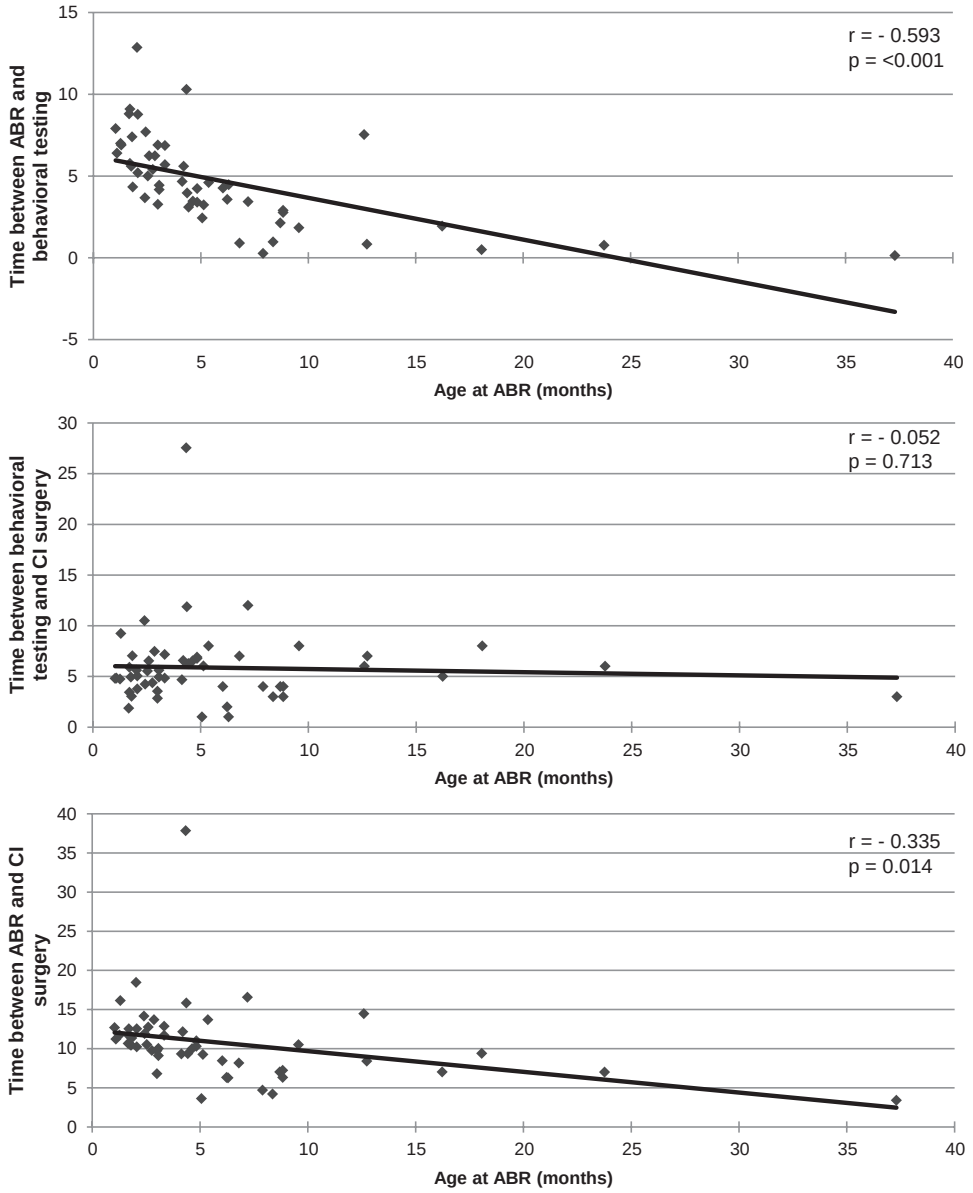

Fig. 3. Time course between auditory brainstem response, behavioral testing, and cochlear implantation surgery (in months) versus age at auditory brainstem response testing. A color version is available online.

Children implanted before 2 years of age develop speech and language at rates that can far exceed those of older implanted children (Colletti et al. 2005; Dettman et al. 2007; Niparko et al. 2010). Children implanted before 1 year of age can show spoken language abilities nearly on par with normal-hearing peers (Niparko et al. 2010). These studies and others clearly show the paramount importance of early diagnosis and intervention in the developmental outcome of children with hearing loss (Colletti 2009).

Results of this study suggest that a bilateral NR ABR is a strong indicator of progression to CI since every child who had a NR result on ABR testing during the 5-year observation period at this institution ultimately received a CI. This is compelling information for clinicians charged with counseling therapeutic intervention for children with a NR ABR. Historically, in our program, referral for a CI evaluation was made at the time of confirmation of severe to profound hearing loss with behavioral audiometry, in the present study, on average 6 months from the time of dABR. Thus, referral age for CI for the youngest children was on average 10 months of age. While this seems early enough, the outliers in the present study certainly experienced a number of delays. Similar to previous studies, significant delays related to the CI process include poor patient cooperation, developmental or cognitive delays, and middle ear issues requiring surgical intervention (Lester et al. 2011). Logistical issues such as inefficient transitions between care providers, poor compliance, and lost to follow-up during times of diagnostic uncertainty further compound the problem. The high probability of the NR ABR at indicating progression to CI could be used to create an increased level of clarity for families and clinicians during this complex and often emotional decision-making period. The anticipation of the likely clinical course of events can possibly obviate some of the typical yet detrimental delays. The relationship between the NR ABR and

clinical decision-making could be used to help guide families towards an accelerated track to CI.

Based on the results of the present study, we have instituted a number of new programmatic changes to reduce the age at implantation among children with NR dABRs. First, we have become more proactive in the management of otitis media, considering early tympanostomy tube placement rather than watchful waiting among children with middle ear effusion present at the time of dABR. More importantly, CI surgery can be discussed with many families at the time of NR dABR or shortly thereafter. While this may be as early at 2–3 months of age, it allows families to begin setting expectations and allows clinicians to plan their diagnostic testing and therapeutic interventions accordingly. While we remain flexible in our ability to change the plan based on unexpected progress with amplification or other extenuating circumstances, this proactive planning aligns the family and team expectations.

The rationale behind confirming ABR results with behavioral testing is to identify children who have greater degrees of residual hearing than those predicted by the ABR. Presumably, some of these children could benefit from amplification, thereby obviating the need for a CI. The results of this study did identify children with NR ABRs who have significant residual hearing on behavioral testing. Some children had low frequency thresholds as good as 40–60 dB HL at 250 and 500 Hz, respectively. However, all of these children ultimately went on to receive a CI because of poor progress with their hearing aids or progressive loss of residual hearing. Previous studies have suggested that hearing aid trials do not significantly change clinical outcome after implantation but can substantially delay fitting of CI (Govaerts et al. 2002; Colletti et al. 2005). Based on the results of the present study and others, further consideration must be given to the value of the hearing aid trial amongst children with NR ABRs. It does not suggest that there is no benefit to fitting amplification in infants in a timely and appropriate manner. Stimulation of the auditory system, even when it does not afford normal development of spoken language, promotes the development of communication skills. Therefore, all infants with NR ABRs should still be fitted with hearing aids as early as possible and usage should be encouraged throughout the CI process. The length of the hearing aid trial, however, should not be extended beyond the time it takes to resolve other considerations for successful cochlear implantation. These may include the acquisition of medical information, other medical treatments, and appropriate counseling and habilitative planning.

Eleven patients in the study were lost to follow-up and did not have corresponding behavioral audiometric data. It is possible but unlikely that these patients did not return for follow-up because there was significant residual hearing that obviated further CI evaluation. The severity of the hearing impairment and the importance of proper follow-up must be stressed at the time of the NR ABR so as to ensure continued hearing evaluation and not delay appropriate intervention.

In conclusion, bilateral NR ABRs using multifrequency stimuli are highly predictive of progression to CI. This information can be used to counsel families and align services toward the goal of implantation at or before 1 year of age. Watchful waiting of middle ear effusions, long hearing aid trials in anticipation of appropriate speech and language development, and unclear messaging regarding parental expectations should be avoided in the setting of a NR ABR. Importantly, great care should be taken to insure that ABR testing protocols are of the highest quality in an effort to utilize this information appropriately.

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Clinical Indications for Canal Wall-down Mastoidectomy in a Pediatric Population

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Abstract

Objective. To establish clinically derived indications for performing canal wall-up or canal wall-down surgery when treating children with cholesteatoma.

Study Design. Case series with chart review.

Setting. Tertiary care academic pediatric otolaryngology practice.

Subjects and Methods. Retrospective review of 420 children who underwent 700 procedures for cholesteatoma between 1996 and 2010.

Results. The canal wall was preserved in 89.5% of cases. Common reasons for removing the canal wall were to provide access to the disease, extensive erosion of key structures, and the desire to avoid further surgery. The mean pure-tone average (PTA) for the canal wall-up group was 30 dB, whereas the canal wall-down group had a mean PTA of 45 dB. A matched-pairs analysis demonstrated that the better performance of the canal wall-up group was independent of preoperative hearing levels. Furthermore, although the presence of the stapes did influence hearing results, the canal wall-up procedure yielded better results even when the condition of the stapes was taken into account. The number needed to treat with canal wall-up to prevent 1 case of hearing loss (ie, mean threshold $>$30 dB) would be around 6. The need for revision surgery was higher in the canal wall-up group (51%) compared with the canal wall-down group (21%).

Conclusion. In the setting of adequate follow-up and open access to surgical resources, most children with cholesteatoma can be managed with an intact canal wall technique. The authors believe that the better audiometric outcomes and easier postoperative care outweigh the need for revision surgery in this group.

Keywords

pediatric, cholesteatoma, surgery, modified radical mastoidectomy, canal wall

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The goals of cholesteatoma surgery are to eradicate disease, establish a dry ear, and restore or preserve serviceable hearing.[1] The means by which surgeons achieve these goals have varied historically and are more controversial in children than in adults. Those who advocate a canal wall-up (CWU) technique cite a maintenance-free ear, fewer activity restrictions, easier hearing aid fitting, and a more natural appearance as the advantages of this technique.[2,3] Proponents of the canal wall-down (CWD) technique maintain that its lower rate of recidivism and reduction in the total number of surgeries outweigh the advantages of the CWU technique.[4] Although as a whole, CWU procedures tend to result in better hearing,[5,6] some have concluded that middle ear factors such as condition of the mucosa and stapes superstructure are more important to hearing outcomes than the presence of the canal wall.[1,2,7,8] The recent development of hybrid and reconstruction techniques has been advocated to provide the intraoperative advantages of the CWD technique (ie, exposure) while maintaining the postoperative advantages of the CWU technique.[9,10] In the setting of relatively easy access to medical care, a uniform CWD approach is rarely adopted.

The CWU approach has often been advocated for children, especially because of their generally poor tolerance of mastoid cavity cleaning. Little has been published on the circumstances in which a CWD approach may be more appropriate for children. We review our surgical experience and clinical outcomes from a large series of pediatric cholesteatomas to determine the clinical indications for taking the canal wall down in children.

Methods

The Hospital for Sick Children Research Ethics Board approved this study. A retrospective review of all cases of cholesteatoma treated at The Hospital for Sick Children

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between 1996 and 2010 was conducted. A database was constructed to record appropriate patient information as well as relevant surgical details. This database was initiated retrospectively, with more recent patients added prospectively.

The extent of cholesteatoma was graded according to the Mills classification system.[11] Using this system, cholesteatomas are given points in 3 categories: stage (S), ossicular erosion (O), and complication (C) (outlined in **Figure 1**). For those cases where the canal wall was taken down, the operative reports were reviewed to discern the reasons for performing the CWD technique.

Pre- and postoperative air conduction hearing threshold was assessed from averaged pure-tone audiometry (PTA) at 500 Hz, 1 kHz, 2 kHz, and 4 kHz. Audiometric analysis was performed according to the guidelines of the American Academy of Otolaryngology—Head and Neck Surgery.[12] All statistical analysis was performed using appropriate parametric or nonparametric methods with significance defined as $P < .05$.

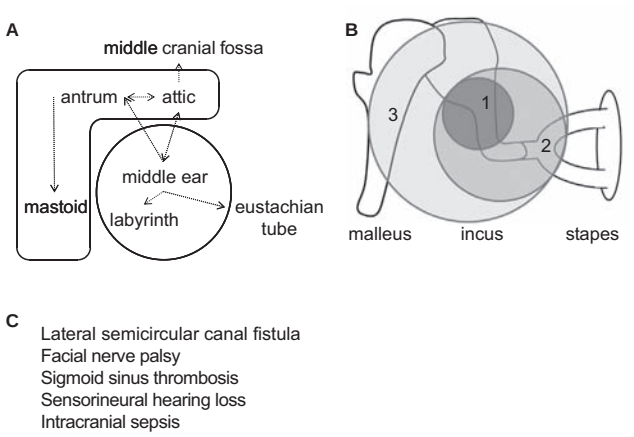

Figure 1. The Mills classification system for cholesteatoma (adapted from Saleh and Mills[11]). (A) Stage (S) score is calculated by adding 1 point for each labeled subsite involved with cholesteatoma. Arrows indicate routes of extension. (B) Ossicular erosion (O) score is calculated by adding 1 point for each ossicle eroded by cholesteatoma as indicated. (C) Complication (C) score is calculated by adding 1 point for each of the listed complications encountered.

Results

We reviewed 420 patients (435 total ears, 222 left) who underwent 700 procedures related to cholesteatoma. Two hundred eight patients had 1 procedure, and 26 patients were referred after having had a prior CWD procedure. Males were twice as abundant as females (289 vs 131), which is consistent with established incidence rates of cholesteatoma in children.[13] The age range was from 1 to 18 years of age. Congenital cholesteatoma was discovered incidentally in two 1-year-old children, one with pre–cochlear implant imaging and the other at tympanostomy tube placement during cleft palate surgery. The mean age at surgery was 10.8 years. There was no significant difference in the median ages of those patients who had CWU and CWD procedures (10.4 and 9.4 years, respectively, $P > .5$, Mann-Whitney test). Our average follow-up was 4.45 years.

There were 542 procedures in which cholesteatoma was present and the canal wall had not been taken down in prior surgery. The canal wall was preserved in 485 of these procedures, yielding an 89.5% rate of canal preservation. There were 57 CWD procedures in 56 patients, and thus 14.2% of patients ultimately received a CWD procedure. Of the 57 CWD procedures, the decision to remove the wall was made at the first surgery in 38 cases (9.7% of 390 first looks), on a second look in 13 cases (6.7% of 193 second looks), and on a third look in 6 cases (10.3% of 58 third looks). The median Mills stage score (S score) for cholesteatoma in CWU cases was 2 compared with 4 for CWD cases ($P < .001$, Mann-Whitney test); however, an S score of 4 has low predictive value for needing a CWD procedure (**Table 1**). The ossicular scores (O scores) were not significantly different (median, 1 for CWU and 2 for CWD, $P > .05$). In the 485 CWU cases, 24 cholesteatomas had a complication score (C score) of 1, whereas 13 of the 57 CWD cases had a C score of 1 ($P < .001$, Yates-corrected χ^2). Lateral canal fistula is often cited as an indication for CWD. However, we were able to remove the matrix from the membranous labyrinth in 9 instances with CWU without causing sensorineural hearing, although 2 individuals had profound sensorineural loss in the affected ear preoperatively.

As cholesteatoma extent by Mills score did not predict when a CWD procedure would be needed, we examined other factors that influenced this decision (**Table 2**). The most common reason for deciding to perform a CWD procedure was to improve poor access to the cholesteatoma, which was generally the result of an under-pneumatized mastoid coupled with an anterior sigmoid sinus and low tegmen.

We examined the rates of recidivism and the need for second surgeries in the CWU and CWD groups (**Table 3**). Of the 57 CWD procedures in our series, follow-up of at least 1 year was available for 53 and of at least 6 months for 55. In the CWU group, there were 352 first-look procedures. Three hundred twenty-one cases had 1-year follow-up, and 346 had a 6-month follow-up. Of these, 180 (51.1%) received a second look. Of the 159 second looks followed for at least 1 year, 52 (32.7%) received a third look. Of the 38 third looks followed for at least 1 year, 3 (7.9%) received a fourth look. The decision to defer a second look was based on clinical appearance and confidence of complete extirpation of disease at the first surgery. Magnetic resonance imaging (MRI) was not routinely used to monitor for disease recurrence.

Hearing outcomes were available for 320 patients: 255 CWU and 65 CWD or revision CWD procedures (mean and median follow-up time 355 and 214 days, respectively; range, 39-1656 days). The mean and median PTA for CWD procedures were 46 dB and 51 dB, respectively, compared with 30 dB for CWU procedures ($P < .001$, Mann-Whitney test). Of CWU patients, 53.7% had a final PTA less than 30 dB—the same was true of 18.5% of CWD individuals ($P < .001$, χ^2 test). This equates to a number needed to treat of 5

Table 1. Stratification of Canal Wall-up (CWU) and Canal Wall-down (CWD) Procedures with Respect to Mills Stage (S) Score

S Score	CWU, No.	CWD, No.
≥4	93	39
≤3	392	18
Sensitivity, Specificity, and Predictive Value of Mills S Score ≥4 in Determining the Need for CWD		
	% Total (No.Total No.)	
Sensitivity	68.4 (39/[39 + 18])	
Specificity	80.8 (392/[392 + 93])	
Positive predictive value	29.5 (39/[39 + 93])	
Negative predictive value	95.6 (392/[392 + 18])	

Table 2. Factors Contributing to the Decision to Perform a Canal Wall-down (CWD) Procedure

Factor Contributing to CWD	No.[a]	%
Poor mastoid pneumatization, low tegmen, anterior sigmoid	27	42.9
Extensive disease resulting in erosion of the ossicular heads or the need for extensive atticotomy	23	36.5
Erosion of the posterior canal wall	13	20.6
Desire to avoid further surgery	8	12.7
Cleft palate or other reason for pervasive eustachian tube dysfunction	6	9.5
Rapid recurrence and aggressive disease	6	9.5
Poor follow-up	4	6.3
Complication from cholesteatoma	4	6.4
No reason given	5	7.9

[a]More than 1 reason was often given for each procedure, yielding more reasons in this table than total procedures. Total of 63 CWD procedures (57 with initial surgery at our institution and 6 revisions from an outside institution).

(ie, the number of cases in which a canal wall would have to be preserved to give 1 additional case of normal hearing). The best results were obtained in a CWU procedure with an intact stapes, whereas a CWD procedure with an absent stapes generally provided the least favorable hearing results (**Table 4**).

Results comparing preoperative and postoperative hearing of the CWU and CWD groups are shown in **Figure 2**. Postoperative hearing results for all individuals in our series correlated well with preoperative hearing ($R = 0.56$ overall, $R = 0.52$ CWU, $R = 0.68$ CWD, $P < .001$ for all) (**Figure 3**), as shown previously.[14] The CWD group had worse preoperative hearing than the CWU group, which might thus confound the comparison of postoperative hearing results between the CWU and CWD groups. To control for this preoperative hearing difference, we performed a matched-pair analysis between the CWD group and selected CWU patients matched for preoperative hearing, status of the ossicular chain, and extent of cholesteatoma. Matching was blinded to postoperative hearing thresholds, and there was no difference in preoperative hearing between the 2 subsets of patients ($P = .54$, Wilcoxon matched-pairs signed-rank test), indicating that our pairing algorithm was satisfactory. After matching, CWU patients had better postoperative hearing (median, 38 dB vs 51 dB, $P = .004$) and greater hearing improvement (median, 7 dB vs 0 dB, $P = .004$) than the CWD group (**Figure 2C**). Of the matched pairs, 11 of 36 (31%) patients had socially serviceable hearing (PTA <30 dB) after CWU surgery compared with 5 of 36 (14%) after CWD surgery (not significant; Fisher exact test). Power analysis of these matched-pair data indicates that a sample size of 246 would be required to achieve significance with this proportion (power = 0.9; $\alpha = 0.05$), and if so substantiated, the number needed to treat would then be 6 cases of canal wall preservation for 1 additional case of normal hearing. Again, a significant difference in postoperative hearing ($P = .02$) and hearing improvement ($P = .03$) was seen between the CWU and CWD groups when the stapes was eroded; however, in the case of an intact stapes, results did not reach statistical significance ($P = .1$ for postoperative hearing and $P = .1$ for hearing improvement).

Discussion

Our study of 420 children with cholesteatoma has allowed us to complete a detailed analysis of the factors that influenced our decision to perform CWU or CWD pediatric tympanomastoid surgery. We prefer a CWU approach to pediatric cholesteatoma and were able to preserve the canal wall in 89.5% of cases in which cholesteatoma was present. This approach is widely practiced in children, particularly

Table 3. Rates of and Reasons for Revision Surgery in the Canal Wall-down (CWD) and Canal Wall-up (CWU) Groups

	No.	% Total (No./Total No.)	% Stage (No./Total No.)
CWD procedures	57		
Required revision	12	21.1 (12/57)	
Reason for revision			
Recurrent cholesteatoma	4		
Pearl	4		
Web	2		
Fluid accumulation	1		
Dysosteosclerosis	1		
CWU procedures			
First looks	352		
Second looks	180	51.1 (180/352)	
Recidivism	106	30.1 (106/352)	58.9 (106/180)
No cholesteatoma	74		
Third looks	52	14.8 (52/352)	28.9 (52/180)
Recidivism	25	13.9 (25/180)	48 (25/52)
No cholesteatoma	27		
Fourth looks	3		
No cholesteatoma	3		

Table 4. Hearing Results of Canal Wall-up (CWU) and Canal Wall-down (CWD) Procedures

	Mean PTA, dB	% with PTA <30 dB
CWU	30.7	53.7
CWD	45.4	18.5
CWU with stapes	25.8[a]	68.1
CWU without stapes	36.7[a]	36.8
CWD with stapes	40.5[b]	23.8
CWD without stapes	47.7[b]	15.9

Abbreviation: PTA, pure-tone audiometry.
[a]Comparison of these groups demonstrates a statistically significant difference ($P < .001$).
[b]Comparison of these groups demonstrates a statistically significant difference ($P < .05$).

because of their greater difficulty with management of the open mastoid cavity (with respect to aural toilet and swimming) and the hope that middle ear function may improve with age to yield a healthy, stable ear.[1,15] We did not find a significant difference in age between children who received a CWU or CWD procedure; however, older children generally tolerate cleaning of mastoid cavities better than young children, so we favor a CWU approach in younger children. If a CWD procedure is required when the child is older, the decision can be made with the patient's input and understanding that ongoing office debridement would likely be required.

The main disadvantages of the CWU technique are a higher rate of recidivism and need for a second surgery. However, it is important to note that recidivism and revision surgery are not unique to the CWU approach. Approximately one-fifth of CWD cases require revision, and a review of the literature presented by Dodson et al[1] demonstrates an overall rate of residual and recurrent disease of 22% in CWD procedures. Revisions of CWD surgery are often minor, permeatal procedures, and only 4 of 12 cases had frank recurrence requiring complete revision. In young children, minor revisions and even cleaning can require general anesthetic. We feel the financial and emotional costs of second-look CWU surgery are offset somewhat by avoidance of unpleasant cavity management. Intraoperative use of laser and endoscopes to reduce residual disease rates, as well as the use of MRI as a radiologic "second look," has the potential to reduce the need for second-look surgery. Use of laser and endoscopy has increased over the study period. This, coupled with the increase in surgeons' experience, may have contributed to a slight increase in the proportion of CWU cases with time, but we are unable to separate and control for these factors in our analysis.

The CWD approach does lead to lower rates of recidivism and revision and thus remains indicated in those who

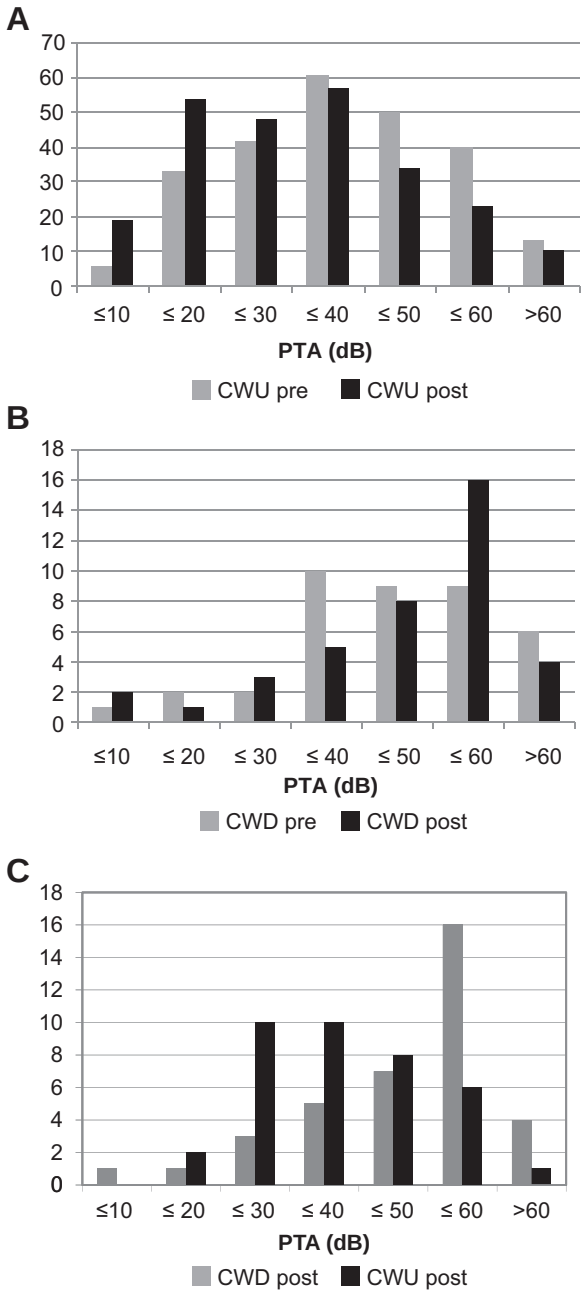

Figure 2. Bin analysis of preoperative and postoperative hearing levels. Histograms demonstrate the absolute number of patients with pure-tone audiometry (PTA; dB) in the indicated range. Bin analysis of preoperative and postoperative hearing results for (A) CWU and (B) CWD groups are shown. The postoperative hearing bin results for the CWD cases and the matched CWU cases used in the matched-pair analysis are shown in (C).

desire to avoid additional surgery and in those who have poor follow-up. We also performed the CWD approach when the child's medical comorbidities put them at a high anesthetic risk. Although the situation did not arise in our series, the lower rates of recurrence and revision surgery are also the reasons that a CWD procedure is often advocated in the case of cholesteatoma in an only-hearing ear.

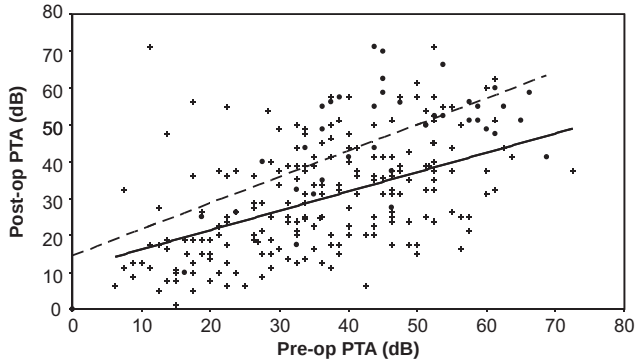

Figure 3. Postoperative hearing is correlated with preoperative hearing. Postoperative hearing is graphed with respect to preoperative hearing for the canal wall-up (CWU; +) and canal wall-down (CWD; •) groups. Trend lines for the CWU (solid) and CWD (dashed) data sets are shown. PTA, pure-tone audiometry.

Our hearing results are better after the CWU procedure, even when controlling for disease severity. This is true regarding either the mean pure-tone average or the number of patients with socially serviceable hearing (PTA $\leq$30 dB hearing level [HL]). Other studies have shown conflicting results on whether CWU provides better hearing outcome.[2,6-8,16] The conclusion that has been drawn from these studies is that other factors such as the condition of the middle ear mucosa or stapes superstructure have a greater influence on hearing outcome than the presence of the canal wall. Our results support the conclusion that the absence of the stapes significantly worsens hearing results in both the CWU and CWD cases; however, our stratified results demonstrated that the condition of the stapes alone did not account for the differences seen in the hearing results.

Our results support the notion that preoperative hearing remains an important predictor of postoperative hearing.[14] Even given equal preoperative hearing, however, the CWU group still shows better postoperative hearing and greater improvement in hearing than the CWD group. This effect did not reach significance when the stapes was intact, possibly because of the small number of individuals in the CWD group who had an intact stapes. It is likely that with a larger sample of matched pairs, the difference would reach significance given the observed trend. Furthermore, it is important to remember that this holds true only for a subset of patients in whom the preoperative hearing was relatively poor. In individuals with good preoperative hearing, we would particularly recommend a CWU procedure when possible to maximize the chances of obtaining a good postoperative hearing result. Similarly, in the presence of an intact ossicular chain, a CWU approach is indicated to preserve the ossicular chain and optimize postoperative hearing thresholds.

The primary aim of our article was to determine the clinical indications for performing a CWD procedure within the context of a health care system and clinical preference that support CWU procedures. Understanding this context is important—in our catchment area, health care is universally

funded, which supports unimpeded access to operating rooms and expertise. The fulcrum upon which many surgical decisions are made is resource availability, and a greater predominance of CWD surgery may be appropriate in other health care systems.[17] On occasion, the decision to perform a CWD procedure is made preoperatively based on patient factors (such as desire to avoid further surgery or anesthetic risk), but usually, the decision to take the canal wall down is made intraoperatively. An important point therefore is the complete communication of this possibility with the family at the time of obtaining consent.

The most common reason for performing a CWD procedure was to provide access to the cholesteatoma for complete removal. A low tegmen tympani or anteriorly extending sigmoid sinus restricts access to the attic and posterior mesotympanum. Removing the canal wall in these cases may be the best way to exenterate disease. In many cases, the cavity created by externalizing an under-pneumatized mastoid leads to an ideally small and maintenance-free cavity. A low-lying tegmen in itself is not necessarily a reason to remove the canal wall. We have been able to avoid taking the canal wall down in many cases where a low tegmen was present by performing an atticotomy to access the cholesteatoma and then using cartilage or bone pate to reconstruct the defect, as reported by others.[18,19] Endoscopic surgery also facilitates removal of cholesteatoma behind anatomical obstructions and is helpful in preserving the canal wall or ossicular chains for disease in the posterior mesotympanum and medial epitympanum.[20,21]

Destruction of the ossicular heads, or their removal to adequately access the cholesteatoma, or the presence of a large atticotomy leads to a high likelihood of recurrence if the canal wall is left intact and the scutum is not adequately reconstructed. Accordingly, extensive disease of this sort is frequently treated with a CWD procedure and cited as a contributing factor in approximately half of CWD cases. Extensive disease in and of itself is not necessarily an indication to remove the canal wall. Even disease extending to the sinus tympani is not necessarily best treated with a CWD approach as removing the canal wall provides only modest additional visualization and access to this space. We commonly use endoscopes, occasionally with the retrofacial approach, to address sinus tympani disease. Insofar as it might represent aggressive disease, extensive disease may serve as an indication for removing the canal wall. This assessment should be made on an individual basis: extensive disease found on the first surgery might be treated differently from extensive disease found on a second look 6 months after an initial surgery.

We graded the cholesteatomas in our series using the classification system described by Saleh and Mills.[11] Although there was a significant difference between the S score of the cholesteatomas that were treated with CWD and CWU approaches, the S score in and of itself is not an accurate predictor of who will need the CWD approach. This reinforces our assertion that disease extent alone should not dictate the approach.

A component of the Mills grading system, the complication or C score, was significantly higher in individuals who required a CWD approach. Although a lateral canal fistula is often cited as an indication to perform a CWD approach, we were often able to remove the matrix from the membranous labyrinth, preserving the canal wall. Accordingly, we feel that a horizontal canal fistula does not necessarily mandate a CWD approach, and the protection, caloric and otherwise, that an intact canal wall provides might be beneficial in these cases.[22,23]

Conclusions

In a setting of adequate follow-up and excellent access to operative resources, we have been able to treat the vast majority of cases of cholesteatoma in our practice with a CWU procedure. In our series, hearing results are better with the CWU procedure, even when the status of the stapes is taken into account. We feel that the better hearing results and easier postoperative care justify the higher rate of recurrence and the increased need for revision surgery. Multiple patient-related factors such as the need to avoid further surgery or recalcitrant eustachian tube dysfunction, anatomic factors such as a low tegmen or anterior sigmoid, disease characteristics such as aggressive disease and erosion of key structures (eg, posterior canal wall), and surgeons' preference and experience ultimately influence the decision to take the canal wall down. A patient-centered approach demands that the decision is based on careful consideration of these factors for each individual, rather than a strict protocol.

Author Contributions

Alexander J. Osborn, study design, data analysis, manuscript preparation, final approval of manuscript; **Blake C. Papsin**, study design, data acquisition, manuscript preparation, final approval of manuscript; **Adrian L. James**, study design, data acquisition, manuscript preparation, final approval of manuscript.

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Clinical Practice Guideline: Tympanostomy Tubes in Children

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Abstract

Objective. Insertion of tympanostomy tubes is the most common ambulatory surgery performed on children in the United States. Tympanostomy tubes are most often inserted because of persistent middle ear fluid, frequent ear infections, or ear infections that persist after antibiotic therapy. Despite the frequency of tympanostomy tube insertion, there are currently no clinical practice guidelines in the United States that address specific indications for surgery. This guideline is intended for any clinician involved in managing children, aged 6 months to 12 years, with tympanostomy tubes or being considered for tympanostomy tubes in any care setting, as an intervention for otitis media of any type.

Purpose. The primary purpose of this clinical practice guideline is to provide clinicians with evidence-based recommendations on patient selection and surgical indications for and management of tympanostomy tubes in children. The development group broadly discussed indications for tube placement, perioperative management, care of children with indwelling tubes, and outcomes of tympanostomy tube surgery. Given the lack of current published guidance on surgical indications, the group focused on situations in which tube insertion would be optional, recommended, or not recommended. Additional emphasis was placed on opportunities for quality improvement, particularly regarding shared decision making and care of children with existing tubes.

Action Statements. The development group made a *strong recommendation* that clinicians should prescribe topical antibiotic eardrops only, without oral antibiotics, for children with uncomplicated acute tympanostomy tube otorrhea. The panel made *recommendations* that (1) clinicians should not perform tympanostomy tube insertion in children with a single episode of otitis media with effusion (OME) of less than 3 months' duration; (2) clinicians should obtain an age-appropriate hearing test if OME persists for 3 months or longer (chronic OME) or prior to surgery when a child becomes a candidate for tympanostomy tube insertion; (3) clinicians should offer bilateral tympanostomy tube insertion to children with bilateral OME for 3 months or longer (chronic OME) and documented hearing difficulties; (4) clinicians should reevaluate, at 3- to 6-month intervals, children with chronic OME who did not receive tympanostomy tubes until the effusion is no longer present, significant hearing loss is detected, or structural abnormalities of the tympanic membrane or middle ear are suspected; (5) clinicians should not perform tympanostomy tube insertion in children with recurrent acute otitis media (AOM) who do not have middle ear effusion in either ear at the time of assessment for tube candidacy; (6) clinicians should offer bilateral tympanostomy tube insertion to children with recurrent AOM who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy; (7) clinicians should determine if a child with recurrent AOM or with OME of any duration is at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors; (8) in the perioperative period, clinicians should educate caregivers of children with tympanostomy tubes regarding the expected duration of tube function, recommended follow-up schedule, and detection of complications; (9) clinicians should not encourage routine, prophylactic water precautions (use of earplugs, headbands; avoidance of swimming or water sports) for children with tympanostomy tubes.

The development group provided the following *options*: (1) clinicians may perform tympanostomy tube insertion in children with unilateral or bilateral OME for 3 months or longer (chronic OME) and symptoms that are likely attributable to OME including, but not limited to, vestibular problems, poor school performance, behavioral problems, ear discomfort, or reduced quality of life and (2) clinicians may perform tympanostomy tube insertion in at-risk children with unilateral or bilateral OME that is unlikely to resolve quickly as reflected by a type B (flat) tympanogram or persistence of effusion for 3 months or longer (chronic OME).

Keywords

otitis media, tympanostomy tubes, grommets, otorrhea, middle ear effusion, pediatric otolaryngology, developmental delay disorders

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Introduction

Insertion of tympanostomy tubes is the most common ambulatory surgery performed on children in the United States. The tympanostomy tube, which is approximately 1/20th of an inch in width, is placed in the child's eardrum (tympanic membrane) to ventilate the middle ear space (**Figures 1 and 2**). Each year, 667,000 children younger than 15 years receive tympanostomy tubes, accounting for more than 20% of all ambulatory surgery in this group.[1] By the age of 3 years, nearly 1 of every 15 children (6.8%) will have tympanostomy tubes, increasing by more than 2-fold with day care attendance.[2]

Tympanostomy tubes are most often inserted because of persistent middle ear fluid, frequent ear infections, or ear infections that persist after antibiotic therapy. All of these conditions are encompassed by the term *otitis media* (middle ear inflammation), which is second in frequency only to acute upper respiratory infection (URI) as the most common illness diagnosed in children by health care professionals.[4] Children younger than 7 years are at increased risk of otitis media because of their immature immune systems and poor function of the eustachian tube, a slender connection between the middle ear and back of the nose that normally ventilates the middle ear space and equalizes pressure with the external environment.[5]

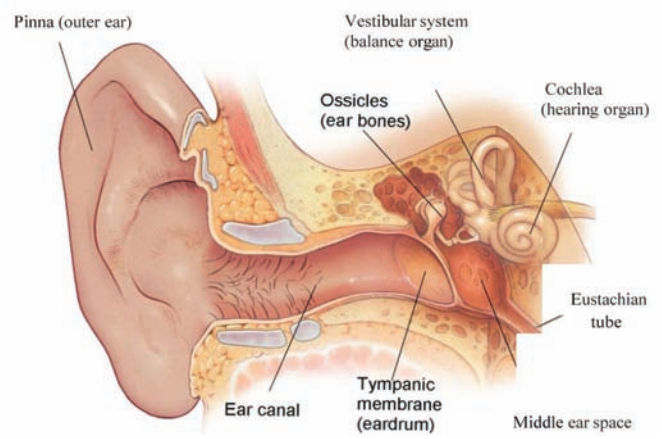

Figure 1. Relationship of the outer ear (pinna and ear canal), middle ear (ossicles and tympanic membrane), and inner ear (cochlea vestibular system). Tubes are inserted into the tympanic membrane (eardrum). Reproduced with permission.[3]

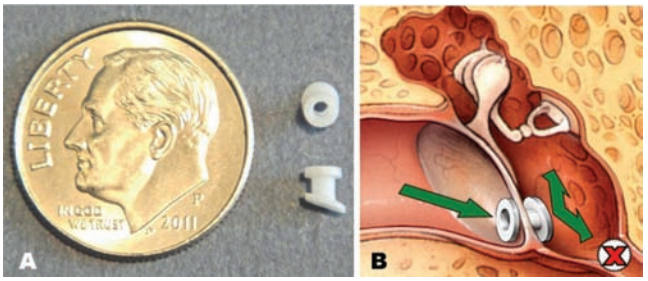

Figure 2. (A) Size of tympanostomy tube compared to a dime. (B) Tympanostomy tubes are also called "ventilation tubes" because the opening allows air to enter the middle ear directly from the ear canal (arrows), which bypasses the child's poorly functioning eustachian tube (X). Reproduced with permission.[3]

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Table 1. Abbreviations and definitions of common terms.

Term	Definition
Myringotomy	A surgical procedure in which an incision is made in the tympanic membrane for the purpose of draining fluid or providing short-term ventilation
Tympanostomy tube insertion	Surgical placement of a tube through a myringotomy incision for purposes of temporary middle ear ventilation. Tympanostomy tubes generally last several months to several years, depending on tube design and placement location in the tympanic membrane. Synonyms include *ventilation tubes, pressure equalization tubes, grommets* (United Kingdom), and *bilateral myringotomy and tubes*
Otitis media with effusion (OME)	The presence of fluid in the middle ear without signs or symptoms of acute ear infection (AOM)
Chronic OME	OME persisting for 3 months or longer from the date of onset (if known) or from the date of diagnosis (if onset unknown)
Hearing assessment	A means of gathering information about a child's hearing status, which may include caregiver report, audiologic assessment by an audiologist, or hearing testing by a physician or allied health professional using screening or standard equipment, which may be automated or manual. Does not include the use of noisemakers or other nonstandardized methods
Acute otitis media (AOM)	The rapid onset of signs and symptoms of inflammation of the middle ear
Persistent AOM	Persistence of symptoms or signs of AOM during antimicrobial therapy (treatment failure) and/or relapse of AOM within 1 month of completing antibiotic therapy. When 2 episodes of otitis media occur within 1 month, it may be difficult to distinguish recurrence of AOM (ie, a new episode) from persistent otitis media (ie, relapse)
Recurrent AOM	Three or more well-documented and separate AOM episodes in the past 6 months or at least 4 well-documented and separate AOM episodes in the past 12 months with at least 1 in the past 6 months[9]
Middle ear effusion (MEE)	Fluid in the middle ear from any cause but most often from OME and during, or after, an episode of AOM
Conductive hearing loss (CHL)	Hearing loss, from abnormal or impaired sound transmission to the inner ear, which is often associated with effusion in the middle ear
Sensorineural hearing loss (SNHL)	Hearing loss that results from abnormal transmission of sound from the sensory cells of the inner ear to the brain
Tympanostomy tube otorrhea (TTO)	Discharge from the middle ear through the tube, usually caused by AOM or external contamination of the middle ear from water entry (swimming, bathing, or hair washing)
Retraction pocket	A collapsed area of the tympanic membrane into the middle ear or attic with a sharp demarcation from the remainder of the tympanic membrane
Tympanogram[10]	An objective measure of how easily the tympanic membrane vibrates and at what pressure it does so most easily (pressure-compliance function). If the middle ear is filled with fluid (eg, OME), vibration is impaired and the line will be flat; if the middle ear is filled with air but at a higher or lower pressure than the surrounding atmosphere, the peak on the graph will be shifted in position based on the pressure (to the left if negative, to the right if positive)

Despite the frequency of tympanostomy tube insertion, there are currently no clinical practice guidelines in the United States that address specific indications for surgery. When children require surgery for otitis media with effusion (OME; **Table 1**), insertion of tympanostomy tubes is the preferred initial procedure, with candidacy dependent primarily on hearing status, associated symptoms, and the child's developmental risk.[6] Placement of tympanostomy tubes significantly improves hearing, reduces effusion prevalence,[7] may reduce the incidence of recurrent acute otitis media (AOM), and provides a mechanism for drainage and administration of topical antibiotic therapy for persistent AOM (**Table 1**). In addition, research indicates that tympanostomy tubes also can improve disease-specific quality of life (QOL) for children with chronic OME, recurrent AOM, or both (**Table 1**).[8]

Risks and potential adverse events of tympanostomy tube insertion are related to general anesthesia usually required for the procedure and the effect of the tympanostomy tube on the tympanic membrane and middle ear.[11] Tympanostomy tube sequelae are common but generally transient (otorrhea) or do not affect function (tympanosclerosis, focal atrophy, or shallow retraction pocket). Tympanic membrane perforations, which may require repair, are seen in about 2% of children after placement of short-term tympanostomy tubes.[11]

When making clinical decisions, the risks of tube insertion must be balanced against the risks of prolonged or recurrent otitis media, which include suppurative complications, damage to the tympanic membrane, adverse effects of antibiotics, and potential developmental sequelae of hearing loss. Additional information on the potential benefits and risks of tympanostomy tubes is detailed in the Health Care Burden section of this guideline, and recommendations for clinical care are provided in the section titled Guideline Key Action Statements.

Table 2. Risk factors for developmental difficulties.[a]

Permanent hearing loss independent of otitis media with effusion
Suspected or confirmed speech and language delay or disorder
Autism-spectrum disorder and other pervasive developmental disorders
Syndromes (eg, Down) or craniofacial disorders that include cognitive, speech, or language delays
Blindness or uncorrectable visual impairment
Cleft palate, with or without associated syndrome
Developmental delay

[a]Sensory, physical, cognitive, or behavioral factors that place children who have otitis media with effusion at increased risk for developmental difficulties (delay or disorder).[6]

The frequency of tympanostomy tube insertion combined with variations in accepted indications for surgery create a pressing need for evidence-based guidelines to aid clinicians in identifying the best surgical candidates and optimizing subsequent care.

Purpose

The primary purpose of this clinical practice guideline is to provide clinicians with evidence-based recommendations on patient selection and surgical indications for and management of tympanostomy tubes in children. A clinical practice guideline is defined, as suggested by the Institute of Medicine, as "statements that include recommendations intended to optimize patient care that are informed by systematic review of the evidence and an assessment of the benefits and harms of alternative care options."[12]

This guideline is intended for any clinician involved in managing children, aged 6 months to 12 years, with tympanostomy tubes or children being considered for tympanostomy tubes in any care setting as an intervention for otitis media of any type. The target audience includes specialists, primary care clinicians, and allied health professionals, as represented by this multidisciplinary guideline development group (see the Methods section).

Children younger than 6 months are excluded from this guideline because evidence is extremely limited (they have also been excluded from nearly all randomized trials of tube efficacy), and their treatment requires individualized decision making based on specific clinical circumstances. This guideline also does not pertain to children diagnosed as having retraction-type ear disease (atelectasis or adhesive otitis media), complications of AOM, or barotrauma nor to children prescribed medications instilled into the middle ear for conditions such as sudden idiopathic sensorineural hearing loss or Meniere's disease. Children older than 12 years are excluded because they have not been included in any randomized trials of tube efficacy.[7]

Although children considered at risk for developmental delays or disorders (**Table 2**) are often excluded for ethical reasons from clinical research involving tympanostomy tubes, the guideline development group decided to include them in the scope because these patients may derive enhanced benefit from tympanostomy tubes.[13] This decision was based on clinical experience of the guideline development group and a recommendation from a multidisciplinary guideline on OME that "clinicians should distinguish the child with OME who is at risk for speech, language, or learning problems from other children with OME, and should more promptly evaluate hearing, speech, language, and need for intervention," including tympanostomy tubes.[6]

In planning the content of the guideline, the development group broadly discussed indications for tube placement, perioperative management, care of children with indwelling tubes, and outcomes of tympanostomy tube surgery (**Table 3**). Given the lack of current published guidance on surgical indications, despite a substantial evidence base of randomized trials and systematic reviews on which to base such guidance, the group decided early in the development process to identify situations for which tube insertion would be optional, recommended, or not recommended. Additional emphasis was placed on opportunities for quality improvement, particularly regarding shared decision making and care of children with existing tubes. Last, knowledge gaps were identified to guide future research.

Health Care Burden

Tympanostomy tube insertion is the primary surgical intervention for otitis media, which is a worldwide pediatric health problem. Most children have experienced at least 1 AOM episode by age 3 years, and by age 6 years, nearly 40% have experienced 3 or more infections.[14] At any given time, approximately 20% of young school-aged children have middle ear effusion (MEE), with nearly all school-aged children having at least 1 episode during their childhood.[14]

The financial impact of otitis media on health care is enormous. Otitis media–related Medicaid expenditures in the United States were $555 million for the 12.5 million covered children younger than 14 years in 1992.[15] Concurrently, national expenditures for treatment and disability associated with otitis media exceeded $4 billion. Direct costs associated with childhood otitis media include office visits, diagnostic tests, medical treatment, and surgical procedures. Indirect costs for AOM are substantial, estimated at 61% to 83% of the total expense,[16] and include child school absence, caregiver absence from work or school, and canceled family activities because of child illness.

With nearly 670,000 tympanostomy tube insertions annually in children in the United States[1] and an average cost of $2700 per procedure,[17] the contribution to health care costs is approximately $1.8 billion. This does not include additional costs related to follow-up care (which continues until after the tube extrudes), treatment of otorrhea, and management of any other sequelae or complications. A cost analysis based on chart review from one managed care organization showed that tympanostomy tube insertion is cost-effective for otitis media in children,[17] but no large-scale studies or formal cost-effectiveness analyses are available to assess the generalizability of this claim.

Table 3. Topics and issues considered in tympanostomy tube guideline development.[a]

Indications for Tube Placement	Perioperative Management	Care of Children with Tubes	Outcomes
Otitis media with effusion	Baseline hearing assessment	Early extrusion of tubes	Quality of life (child and caregiver)
Recurrent acute otitis media	Optimal conditions for general anesthesia (impact of upper respiratory infections)	Dry ear (water) precautions	School performance, attendance
Persistent acute otitis media	Assessment for surgery	Tube otorrhea	Long-term sequelae (perforation, retraction pocket, hearing loss)
Hearing loss caused by middle ear effusion	Assessment of anesthetic complications including laryngospasm, hypoxemia, bronchospasm	Tube granuloma or granulation tissue	Vestibular function
Unacceptable antibiotic burden for treating acute otitis media	Need for intravenous access during surgery	Obstructed tube lumen	Hearing levels and outcomes during life of tube and after tube extrusion
Situations in which tube insertion would be recommended	Need to sterilize ear canal prior to tube placement	Postoperative hearing assessment	Physical suffering (pain, sleep disturbance)
Situations in which tube insertion would be an option	Tube duration: short-term, intermediate, long-term	Frequency of follow-up for indwelling tubes	Speech and language development
Situations in which tube insertion would not be recommended	Tube composition	Setting for follow-up; which clinician is responsible or best suited	Listening in complex environments
	Tube location in the tympanic membrane	Frequency of hearing assessment (postoperative and for surveillance)	Prevalence of middle ear effusion
	Need to irrigate middle ear with saline		Need for additional tube surgery
	Use of perioperative topical otic preparations		Need for oral antibiotics
	Adenoidectomy as an alternative or adjunct to tubes		Incidence of acute otitis media
	Pain management after surgery		Incidence of otorrhea
	Alternatives to general anesthesia		Chronic suppurative otitis media
	Recovery room issues: emergent delirium, nausea/vomiting, parental/caregiver anxiety		Retained tube
	Learning curve for tube surgery		Medialized tube

[a]This list was created by the guideline development group to refine content and prioritize action statements; not all items listed were ultimately included or discussed in the guideline.

Benefits of Tympanostomy Tubes

Tympanostomy tube insertion is associated with short-term QOL improvements.[18] Otitis media can affect QOL for the child and caregiver. In one study of children with chronic OME or recurrent AOM, 88% of caregivers were worried or concerned about their child's ear infections or middle ear fluid at least some of the time, with 42% spending most or all of their time preoccupied with their child's condition.[19] Physical suffering was a problem for 85% of children, emotional distress for 76%, and activity limitations for 57%. Another investigation of children with otitis media noted that 31% of caregivers had to cancel family activities, 29% reported lack of sleep, and 12% missed work or school.[20]

The efficacy of tympanostomy tubes in managing chronic OME, recurrent AOM, or both has been studied in randomized controlled trials (RCTs) and systematic reviews. For children with chronic OME, tube insertion reduces the prevalence of MEE by 32% in the first year and improves average hearing levels (HLs) by 5 to 12 dB.[7,13] Although RCTs have, in general, not found a significant impact of tympanostomy tube insertion on speech, language, or cognitive outcomes,[7,13,18] the trials typically included only healthy children without developmental delays at entry. A nonrandomized study, however, did show improved caregiver perception of speech and language after tympanostomy tube placement, especially for children with developmental delays.[21]

The efficacy of tympanostomy tubes for preventing recurrent AOM is unclear, with systematic reviews reporting insufficient evidence,[18] small short-term benefits,[22,23] or moderate benefits of similar magnitude to antibiotic prophylaxis.[24] Part of this debate relates to inclusion criteria for RCTs in the reviews, some of which excluded children with chronic OME between AOM episodes and others that did not. When limited

to trials with AOM that clears between episodes (without chronic OME), the effect is no longer significant. Specific recommendations for tympanostomy tube insertion in children with recurrent AOM are discussed later in this guideline.

No studies have evaluated the effects of tympanostomy tubes for managing severe or persistent AOM because of difficulties enrolling these children in RCTs. Increasing problems with bacterial resistance,[25] however, have created a role for tympanostomy tube placement to allow drainage of infected secretions, obtain middle ear fluid for culture, and provide a direct route for delivering antibiotic eardrops to the middle ear. Similarly, when children with tympanostomy tubes continue to experience AOM episodes, they can usually be managed with topical antibiotic drops,[18] avoiding the adverse effects of systemic therapy.

Risks and Adverse Events Associated with Tympanostomy Tubes

Potential benefits of tubes must be balanced against the associated risks, including general anesthesia and direct tube-related sequelae. The incidence of anesthesia-related death for children undergoing diverse surgical procedures (including tympanostomy tube insertion) ranges from 1 in 10,000 to 1 in 45,000 anesthetics delivered.[26] In the perioperative period, children are more prone to laryngospasm and bronchospasm than adults are, which may increase the risk of anesthetic complications.

The most common sequela of tympanostomy tubes is otorrhea (TTO), seen in approximately 16% of children within 4 weeks of surgery and 26% of children at any time the tympanostomy tube remains in place.[11] Most tympanostomy tubes used in the United States remain in place for 12 to 14 months, during which approximately 7% of children experience recurrent TTO. Other complications include blockage of the tympanostomy tube lumen in 7% of intubated ears, granulation tissue in 4%, premature extrusion of the tympanostomy tube in 4%, and tympanostomy tube displacement into the middle ear in 0.5%.[11]

Longer-term sequelae of tympanostomy tube placement include visible changes in the appearance of the tympanic membrane. Myringosclerosis consists of white patches in the ear drum from deposits of calcium and can be seen while the tube is in place or after extrusion. Myringosclerosis is more common in intubated ears than in controls,[7,11,18] is usually confined to the drum, and very rarely causes clinically significant hearing issues. Tympanic membrane atrophy, atelectasis, and retraction pockets are all more commonly observed in children with otitis media who are treated with tympanostomy tubes than in those who are not.[27] These tympanic membrane changes, with the exception of tympanosclerosis, appear to resolve over time in many children and rarely require medical or surgical treatment. Persistent perforation of the tympanic membrane is seen in 1% to 6% of ears after tympanostomy tubes are placed.[18] When perforations persist, surgical closure may be required.

The long-term impact of tympanostomy tubes on hearing acuity has been studied. Children in a longitudinal otitis media study had their hearing measured at 6 years of age.[28] Children who had tympanostomy tubes in the past had a 1- to 2-dB worsening in hearing thresholds compared with those who did not have tympanostomy tubes. This hearing worsening is trivial, and it should be noted that the mean HLs in these children with or without a history of tubes was 4.3- to 6.2-dB HL, which is well within the range of normal hearing. Another study of children aged 8 to 16 years who had participated in an RCT of tympanostomy tubes versus medical treatment for otitis media 6 to 10 years prior found hearing thresholds 2.1 to 8.1 dB poorer in those children who had a history of tympanostomy tubes. The greatest hearing deficits were seen when testing low-frequency tones.[29]

In summary, tympanostomy tubes do produce visible changes in the appearance of the tympanic membrane and may cause measurable long-term hearing loss. These outcomes do not appear to be clinically important or require intervention in the overwhelming majority of patients. The post–tympanostomy tube sequela most likely to require intervention is persistent perforation, with 80% to 90% success rates for surgical closure with a single outpatient procedure.[30]

Some investigators have questioned the appropriateness of tympanostomy tube surgery based on audits and chart review.[31,32] Most criticism has centered on surgery in children with OME of less than 3 months' duration, determined by extrapolation of findings at discrete office visits. Additional criticism concerns the appropriateness of tympanostomy tubes for recurrent AOM. The frequency of tube surgery, associated health care burden, and concerns over the appropriateness of surgery create a clear need for evidence-based surgical indications and management strategies regarding tympanostomy tube placement.

Generalizability of Evidence Regarding Risks and Benefits

Most high-quality evidence on tympanostomy tube efficacy and adverse events comes from published studies that have been conducted using otherwise healthy children without comorbid illnesses, syndromes, or disorders. Therefore, we have included several recommendations in the guideline related to managing children with coexisting conditions that may put them at added risk for speech, language, or developmental sequelae of otitis media. These recommendations must therefore be interpreted with the caveat that they may involve extrapolations from studies performed in otherwise healthy children.

Methods

This guideline was developed using an explicit and transparent a priori protocol for creating actionable statements based on supporting evidence and the associated balance of benefit and harm.[33] Members of the panel included a pediatric and adult otolaryngologist, otologist/neurotologist, anesthesiologist, audiologist, family physician, behavioral pediatrician, pediatrician, speech/language pathologist, advanced nurse practitioner, physician assistant, resident physician, and consumer advocates.

Literature Search

An information specialist with the Cochrane ENT Disorders Group conducted 2 literature searches using a validated filter strategy. The initial literature search identified clinical practice guidelines, systematic reviews, and meta-analyses related to tympanostomy tubes in children published between 2005 and February 2012. The search was performed in multiple databases including the National Guidelines Clearinghouse (www.guideline.gov), The Cochrane Library, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine Database, Agency for Healthcare Research and Quality, EMBASE, PubMed, Guidelines International Network, Health Services/Technology Assessment Tools, CMA Infobase, NHS Evidence ENT and Audiology, National Library of Guidelines, National Institute of Clinical Excellence, Scottish Intercollegiate Guidelines Network, New Zealand Guidelines Group, Australian National Health and Medical Research Council, and the TRIP database. The search yielded 10 guidelines and 19 systematic reviews or meta-analyses. After removing duplicates, articles not obviously related to tympanostomy tubes, those not indicating or explicitly stating a systematic review methodology, and non–English language articles, 4 guidelines and 15 systematic reviews or meta-analyses remained.

A second literature search identified RCTs published between 1980 and March 2012. The following databases were used: MEDLINE, EMBASE, CINAHL, and CENTRAL. The search identified 171 RCTs. After removing duplicates, non–English language articles, and animal model studies, 113 articles remained.

The following parameters were used to define the search questions:

1. Population: Children
2. Intervention: Tympanostomy tube insertion, including indications for tube placement, preoperative care, and postoperative care
3. Comparison: Any techniques
4. Outcome: Any
5. Setting: Inpatient, outpatient

Final results of both literature searches were distributed to panel members, including electronic full-text versions, if available, of each article. This material was supplemented, as needed, with targeted searches to address specific needs identified in writing the guideline through July 2012.

In a series of conference calls, the guideline development group defined the scope and objectives of the proposed guideline. During the 12 months devoted to guideline development ending in September 2012, 2 in-person meetings were held during which electronic decision support (BRIDGE-Wiz) software was used to facilitate the creation of actionable recommendations and action statement profiles.[34] Internal electronic review and feedback for each guideline draft was used to ensure accuracy of content and consistency with standardized criteria for creating clinical practice guidelines.[35]

After completing the action statement profile, the group rated their level of confidence in the aggregate evidence underpinning the recommendation as "high," "medium," or "low" based on the quantity, consistency, precision, and generalizability of the evidence. Any differences of opinion among guideline development group members concerning any aspect of the action statement, accompanying profile, or amplifying text were also documented with a rating of "none," "minor," or "major," with an explanation of any differences that occurred.

American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF) staff used the Guideline Implementability Appraisal and Extractor software to appraise adherence of the draft guideline to methodological standards, ensure clarity of recommendations, and predict potential obstacles to implementation.[36] Guideline panel members received summary appraisals in September 2012 and modified an advanced draft of the guideline based on the appraisal.

The final guideline draft underwent extensive external peer review. Comments were compiled and reviewed by the panel's chair; a modified version of the guideline was distributed and approved by the guideline development panel. Recommendations contained in the guideline are based on the best available data published through September 2012. Where data were lacking, a combination of clinical experience and expert consensus was used. A scheduled review process will occur at 5 years from publication, or sooner if new compelling evidence warrants earlier consideration.

Classification of Evidence-Based Statements

Guidelines are intended to produce optimal health outcomes for patients, to minimize harms, and to reduce inappropriate variations in clinical care. The evidence-based approach to guideline development requires the evidence supporting a policy be identified, appraised, and summarized and that an explicit link between evidence and statements be defined. Evidence-based statements reflect both the quality of evidence and the balance of benefit and harm that is anticipated when the statement is followed. The definitions for evidence-based statements are listed in **Tables 4** and **5**.[37]

Guidelines are not intended to supersede professional judgment but rather may be viewed as a relative constraint on individual clinician discretion in a particular clinical circumstance. Less frequent variation in practice is expected for a "strong recommendation" than might be expected with a "recommendation." "Options" offer the most opportunity for practice variability.[37] Clinicians should always act and decide in a way that they believe will best serve their patients' interests and needs, regardless of guideline recommendations. They must also operate within their scope of practice and according to their training. Guidelines represent the best judgment of a team of experienced clinicians and methodologists addressing the scientific evidence for a particular topic.

Making recommendations about health practices involves value judgments on the desirability of various outcomes associated with management options. Values applied by the guideline panel sought to minimize harm and diminish unnecessary

Table 4. Guideline definitions for evidence-based statements.

Statement	Definition	Implication
Strong recommendation	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B).[a] In some clearly identified circumstances, strong recommendations may be made based on lesser evidence 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 means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation) but the quality of evidence is not as strong (Grade B or C).[a] In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and be sensitive to patient preferences.
Option	An option means that either the quality of evidence that exists is suspect (Grade D)[a] or that well-done studies (Grade A, B, or C)[a] show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation	No recommendation means there is both a lack of pertinent evidence (Grade D)[a] and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

[a]See **Table 5** for definition of evidence grades.

Table 5. Levels for grades of evidence.[a]

Grade	Treatment and Harm	Diagnosis
A	Well-designed randomized controlled trials performed on a population similar to the guideline's target population	Systematic review of cross-sectional studies with consistently applied reference standard and blinding
B	Randomized controlled trials; overwhelmingly consistent evidence from observational studies	Individual cross-sectional studies with consistently applied reference standard and blinding
C	Observational studies (case control and cohort design)	Nonconsecutive studies, case-control studies, or studies with poor, nonindependent, or inconsistently applied reference standards
D	Mechanism-based reasoning or case reports	
X	Exceptional situations in which validating studies cannot be performed and there is a clear preponderance of benefit over harm	

[a]American Academy of Pediatrics classification scheme[37] updated for consistency with current level of evidence definitions.[38]

and inappropriate therapy. A major goal of the panel was to be transparent and explicit about how values were applied and to document the process.

Financial Disclosure and Conflicts of Interest

The cost of developing this guideline, including travel expenses of all panel members, was covered in full by the AAO-HNSF. Potential conflicts of interest for all panel members in the past 2 years were compiled and distributed before the first conference call. After review and discussion of these disclosures,[39] the panel concluded that individuals with potential conflicts could remain on the panel if they (1) reminded the panel of potential conflicts before any related discussion, (2) recused themselves from a related discussion if asked by the panel, and (3) agreed not to discuss any aspect of the guideline with industry before publication. Lastly, panelists were reminded that conflicts of interest extend beyond financial relationships and may include personal experiences, how a participant earns a living, and the participant's previously established "stake" in an issue.[40]

Guideline Key Action Statements

Each evidence-based statement is organized in a similar fashion: **an evidence-based key action statement in bold**, followed by the *strength of the recommendation in italic*. Each

Table 6. Summary of guideline action statements.

Statement	Action	Strength
1. OME of short duration	Clinicians should *not* perform tympanostomy tube insertion in children with a single episode of OME of less than 3 months' duration.	Recommendation (against)
2. Hearing testing	Clinicians should obtain an age-appropriate hearing test if OME persists for 3 months or longer (chronic OME) OR prior to surgery when a child becomes a candidate for tympanostomy tube insertion.	Recommendation
3. Chronic bilateral OME with hearing difficulty	Clinicians should offer bilateral tympanostomy tube insertion to children with bilateral OME for 3 months or longer (chronic OME) AND documented hearing difficulties.	Recommendation
4. Chronic OME with symptoms	Clinicians may perform tympanostomy tube insertion in children with unilateral or bilateral OME for 3 months or longer (chronic OME) AND symptoms that are likely attributable to OME that include, but are not limited to, vestibular problems, poor school performance, behavioral problems, ear discomfort, or reduced quality of life.	Option
5. Surveillance of chronic OME	Clinicians should reevaluate, at 3- to 6-month intervals, children with chronic OME who did not receive tympanostomy tubes, until the effusion is no longer present, significant hearing loss is detected, or structural abnormalities of the tympanic membrane or middle ear are suspected.	Recommendation
6. Recurrent AOM without MEE	Clinicians should *not* perform tympanostomy tube insertion in children with recurrent AOM who do not have middle ear effusion in either ear at the time of assessment for tube candidacy.	Recommendation (against)
7. Recurrent AOM with MEE	Clinicians should offer bilateral tympanostomy tube insertion to children with recurrent AOM who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy.	Recommendation
8. At-risk children	Clinicians should determine if a child with recurrent AOM or with OME of any duration is at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors (see **Table 2**).	Recommendation
9. Tympanostomy tubes in at-risk children	Clinicians may perform tympanostomy tube insertion in at-risk children with unilateral or bilateral OME that is unlikely to resolve quickly as reflected by a type B (flat) tympanogram or persistence of effusion for 3 months or longer (chronic OME).	Option
10. Perioperative education	In the perioperative period, clinicians should educate caregivers of children with tympanostomy tubes regarding the expected duration of tube function, recommended follow-up schedule, and detection of complications.	Recommendation
11. Acute tympanostomy tube otorrhea	Clinicians should prescribe topical antibiotic eardrops only, without oral antibiotics, for children with uncomplicated acute TTO.	Strong recommendation
12. Water precautions	Clinicians should *not* encourage routine, prophylactic water precautions (use of earplugs, headbands; avoidance of swimming or water sports) for children with tympanostomy tubes.	Recommendation (against)

Abbreviations: AOM, acute otitis media; MEE, middle ear effusion; OME, otitis media with effusion.

key action statement is followed by an "action statement profile" of aggregate evidence quality, level of confidence in the evidence, benefit-harm assessment, and statement of costs. In addition, there is an explicit statement of any value judgments, the role of patient (caregiver) preferences, clarification of any intentional vagueness by the panel, exceptions to the statement, any differences of opinion, and a repeat statement of the strength of the recommendation. Several paragraphs subsequently discuss the evidence base supporting the statement. An overview of each evidence-based statement in this guideline can be found in **Table 6**.

The role of patient preference in making decisions deserves further clarification. For some statements, for which the evidence base demonstrates clear benefit, although the role of patient preference for a range of treatments may not be relevant, clinicians should provide patients with clear and comprehensible information on the benefits of facilitating patient understanding and shared decision making, which leads to better patient adherence and outcomes. In cases in which evidence is weak or benefits are unclear, the practice of shared decision making, again where the management decision is made by a collaborative effort between the clinician and an informed patient, is extremely useful. Factors related to patient preference include (but are not limited to) absolute benefits (numbers needed to treat), adverse effects (number needed to harm), cost of drugs or procedures, and frequency and duration of treatment.

STATEMENT 1. OME OF SHORT DURATION: Clinicians should *not* perform tympanostomy tube

insertion in children with a single episode of OME of less than 3 months' duration, from the date of onset (if known) or from the date of diagnosis (if onset is unknown). *Recommendation against based on systematic review of observational studies of natural history and an absence of any randomized controlled trials on efficacy of tubes for children with OME less than 2 to 3 months' duration and a preponderance of benefit over harm.*

Action Statement Profile

- Aggregate evidence quality: Grade C, based on a systematic review of observational studies and control groups in RCTs on the natural history of OME and an absence of any RCTs on efficacy of tympanostomy tubes for children with OME less than 2 months' duration
- Level of confidence in evidence: High
- Benefits: Avoidance of unnecessary surgery and its risks, avoidance of surgery in children for whom the benefits of tympanostomy tubes have not been studied and are uncertain, avoidance of surgery in children with a condition that has reasonable likelihood of spontaneous resolution, cost savings
- Risks, harms, costs: Delayed intervention in children who do not recover spontaneously and/or in children who develop recurrent episodes of MEE
- Benefit-harm assessment: Preponderance of benefit
- Value judgments: Exclusion of children with OME of less than 2 months' duration from all published RCTs of tube efficacy was considered compelling evidence to question the value of surgery in this population, especially considering the known risks of tympanostomy tube surgery
- Intentional vagueness: None
- Role of patient (caregiver) preferences: Limited, because of good evidence that otherwise healthy children with OME of short duration do not benefit from tympanostomy tube insertion
- Exceptions: At-risk children (**Table 2**); see Statements 6 and 7 for explicit information on at-risk children
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to avoid unnecessary surgery in children with OME of short duration that is likely to resolve spontaneously because of favorable natural history. When a clinician first diagnoses OME in a child, the cause of the effusion is often unknown. Otitis media with effusion is often self-limited when caused by a URI or when it follows a recent episode of AOM. An observation period of 3 months will distinguish OME that is usually self-limited from OME that may have been present for months prior to diagnosis and is unlikely to resolve spontaneously.

Otitis media with effusion is commonly seen in association with a viral URI or may be either a prelude to, or sequela of, AOM.[41] The latter circumstance is common, with a 70% prevalence rate of OME at 2 weeks, 40% at 1 month, 20% at 2 months, and 10% at 3 months.[42] Otitis media with effusion is also seen in conjunction with acute nasopharyngitis, without prior middle ear disease; there are no data about spontaneous resolution in this case, but, overall, the natural history of OME shows rates of spontaneous resolution or improvement ranging from 28% to 52% within three[43] or four months[44] of diagnosis.

Most studies of tympanostomy tube efficacy required documented bilateral OME for at least 3 months before entry into the study,[45-48] and one group of investigators enrolled children with at least 2 months of bilateral OME.[49,50] Because of these restrictions, there are no data to support tympanostomy tube insertion in children with OME of brief duration (less than 2 to 3 months), and no conclusions regarding potential risks versus benefits can be drawn in this group. In addition, since spontaneous resolution of brief OME is common, observation until the OME has been documented for at least 3 months can avoid unnecessary surgery.[43] Children with chronic OME despite observation would be candidates for tympanostomy tubes, as described later in this clinical practice guideline.

Children with OME who are at risk for developmental delays or disorders, as defined in **Table 2**, are excluded from this recommendation. While no studies specifically addressing tympanostomy tube insertion in at-risk children with OME of shorter duration exist, these children have other factors making OME with attendant hearing loss a significantly greater added risk to their speech and language development[7] and should therefore be managed on an individual basis when OME is diagnosed (see Statements 6 and 7).

STATEMENT 2. HEARING TESTING: Clinicians should obtain an age-appropriate hearing test if OME persists for 3 months or longer OR prior to surgery when a child becomes a candidate for tympanostomy tube insertion. *Recommendation based on observational and cross-sectional studies with a preponderance of benefit over harm.*

Action Statement Profile

- Aggregate evidence quality: Grade C, based on observational and cross-sectional studies assessing the prevalence of conductive hearing loss with OME
- Level of confidence in evidence: High
- Benefits: Documentation of hearing status, improved decision making regarding the need for surgery in chronic OME, establishment of baseline hearing prior to surgery, detection of coexisting sensorineural hearing loss
- Risks, harms, costs: Cost of the audiologic assessment
- Benefit-harm assessment: Preponderance of benefit
- Value judgments: None
- Intentional vagueness: The words *age-appropriate audiologic testing* are used to recognize that the specific methods will vary with the age of the child, but a full discussion of the specifics of testing is beyond the scope of this guideline

- Role of patient (caregiver) preferences: Some, caregivers may decline testing
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to promote hearing testing as an important factor in decision making when OME becomes chronic or when a child becomes a candidate for tympanostomy tube insertion (see Statements 4, 6, and 9). Chronic unilateral or bilateral OME is unlikely to resolve promptly and may lead to poor school performance and behavioral problems.[43,51] Therefore, knowledge of the child's hearing status is an important part of management and should prompt the clinician to ask questions about the child's daily functioning to identify any issues or concerns, which may be attributable to OME, that might otherwise have been overlooked (Statement 4).

The degree of hearing impairment is based primarily on the accurate measurement of hearing thresholds and secondarily by parent/caregiver and school (teacher) reports describing the perceived hearing ability of the child. The American Academy of Pediatrics[52] identified several key points relevant to hearing assessment in children, which, although not related exclusively to OME, are worthy of summary here:

- Any parental/caregiver concern about hearing loss should be taken seriously and requires an objective hearing screening of the patient.
- All providers of pediatric health care should be proficient with pneumatic otoscopy and tympanometry; however, neither of these methods assess hearing.
- Developmental abnormalities, level of functioning, and behavioral problems may preclude accurate results on routine audiologic screening and testing. In this situation, referral to an otolaryngologist and pediatric audiologist should be made.
- The results of abnormal audiologic screening should be explained carefully to parents/caregivers, and the child's medical record should be flagged to facilitate tracking and follow-up.
- Any abnormal objective screening result requires audiology referral and definitive testing.

When tympanostomy tube insertion is planned, an age-appropriate preoperative hearing test is recommended to establish appropriate expectations for the change in hearing anticipated after surgery and can also alert the clinician and family to a previously undiagnosed permanent (sensorineural) hearing loss if present. Normal hearing requires sound from the environment to efficiently reach the inner ear. Otitis media with effusion impairs sound transmission by reducing the mobility of the tympanic membrane and ossicles, thereby reflecting acoustic energy back into the ear canal instead of allowing it to pass freely to the cochlea.[53] Hearing is measured (**Figure 3**) in

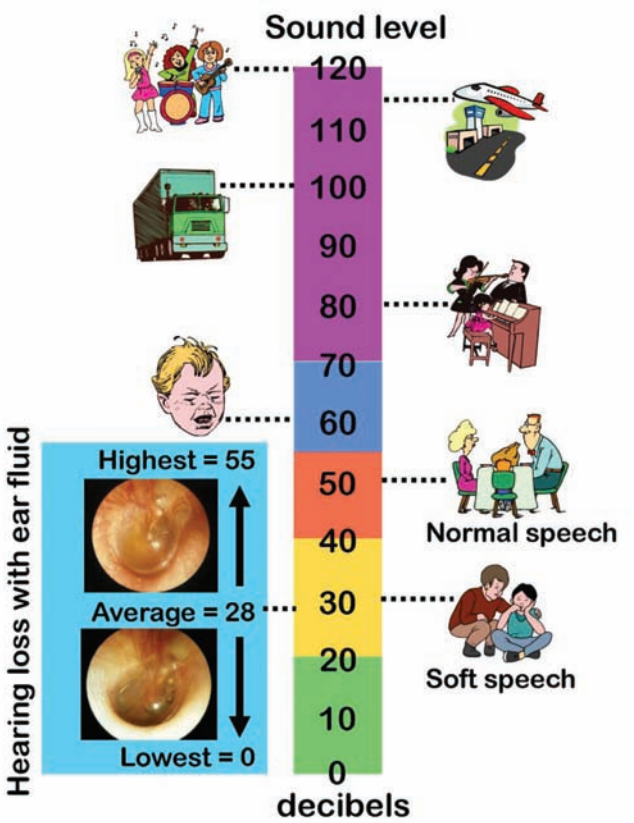


Figure 3. An average hearing level between 0 and 20 dB (hearing level) is normal (green), 21 to 40 dB is a mild hearing loss (yellow), 41 to 55 dB is a moderate loss (red), 56 to 70 dB is a moderately-severe loss, and 71 dB or higher is a severe or profound loss (purple). A child with average hearing loss from middle ear effusion in both ears (28 dB) would barely hear soft speech, with some children barely aware of normal speech or a baby crying. Reproduced with permission.[3]

decibels (dB), with a mean response greater than 20 dB HL indicating some degree of hearing loss for children.[54] The impact of OME on hearing ranges from no hearing loss up to a moderate hearing loss (0 to 55 dB HL).[55] The average hearing loss associated with OME in children is 28 dB HL, while a lesser proportion (approximately 20%) exceed 35 dB HL.[55,56]

When considering the impact of OME on a child's hearing, clinicians should appreciate that HLs, as measured in decibels, are a logarithmic scale of intensity: for every 3-dB increase, there is a doubling in sound intensity levels. Therefore, even small reductions in hearing thresholds can have a significant impact on sound intensity and the child's ability to understand speech. For example, a child with OME and an average HL of 28 dB would experience nearly an 8-fold decrease in sound intensity compared with a child with normal hearing thresholds of 20 dB.

The preferred method of hearing assessment is age-appropriate audiologic testing, through conventional audiometry or comprehensive audiologic assessment.[6,52] Children aged 4 years or older are suitable for conventional audiometry, in which the child raises his or her hand when a stimulus is

heard. This can be done in the primary care setting using a fail criterion of >20 dB HL at 1 or more frequencies (500, 1000, 2000, 4000 Hz) in either ear.

Comprehensive audiologic evaluation by an audiologist is recommended for children aged 6 months to 4 years and for any child who fails conventional audiometry in a primary care setting.[52] This assessment includes evaluating air-conduction and bone-conduction thresholds for pure tones, speech detection or speech recognition thresholds, and measuring speech understanding if possible.[7] Visual response audiometry is typically used to assess hearing in children aged 6 months to 2.5 years. It is performed by an audiologist, during which the child learns to associate speech or frequency-specific stimuli with a reinforcer, such as a lighted toy or video clips. Children aged 2.5 to 4 years are assessed using play audiometry, by having the child perform a task (eg, placing a peg in a pegboard or dropping a block in a box) in response to a stimulus tone. Ear-specific audiologic testing is recommended whenever possible using insert earphones to detect unilateral or asymmetrical hearing loss.

Although not the focus of this section, the importance of postoperative hearing testing in children who receive tympanostomy tubes deserves some emphasis. The consensus of the guideline development group was that any child with a hearing loss detected prior to tympanostomy tube insertion should have postoperative testing to confirm resolution of hearing loss. A hearing loss that was initially attributed to OME but persists after tube placement requires additional assessment to determine the cause of the loss and whether it is conductive, sensorineural, or mixed.

STATEMENT 3. CHRONIC BILATERAL OME WITH HEARING DIFFICULTY: Clinicians should offer tympanostomy bilateral tube insertion to children with bilateral OME for 3 months or longer AND documented hearing difficulties. *Recommendation based on randomized controlled trials and observational studies, with a preponderance of benefit over harm.*

Action Statement Profile

- Aggregate evidence quality: Grade B, based on well-designed RCTs showing reduced MEE prevalence and improved hearing after tympanostomy tube insertion; observational studies documenting improved QOL; and extrapolation of research and basic science principles for optimizing auditory access
- Level of confidence in the evidence: High
- Benefits: Reduced prevalence of MEE, improved hearing, improved child and caregiver QOL, optimization of auditory access for speech and language acquisition, elimination of a potential barrier to focusing and attention in a learning environment
- Risks, harms, costs: Risk of anesthesia, sequelae of the indwelling tympanostomy tubes (eg, otorrhea, granulation tissue, obstruction), complications after tube extrusion (myringosclerosis, retraction pocket, persistent perforation), failure of or premature tympanostomy tube extrusion,, tympanostomy tube medialization, procedural anxiety and discomfort, and direct procedural costs
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: Assumption that optimizing auditory access would improve speech and language outcomes, despite inconclusive evidence regarding the impact of MEE on speech and language development
- Intentional vagueness: The term *hearing difficulty* is used instead of *hearing loss* to emphasize that a functional assessment of how a child uses hearing and engages in their environment is important, regardless of what specific threshold is used to define hearing loss based on audiologic criteria
- Role of patient (caregiver) preferences: Substantial role for shared decision making regarding the decision to proceed with, or to decline, tympanostomy tube insertion
- Exceptions: None
- Policy level: Recommendation
- Difference of opinion: Minor differences regarding the role of caregiver report as a surrogate for audiologic assessment and whether the action taken by the clinician should be to "recommend" tubes (minority opinion) versus to "offer" tubes (majority opinion)

Supporting Text

The purpose of this statement is to identify children with chronic OME and associated hearing difficulties who should be offered tympanostomy tubes as part of management. Although the preceding statement (Statement 2) is also concerned with the impact of OME on hearing, the focus of this statement is on surgical candidacy and not diagnosis of hearing loss. In contrast, the preceding statement on hearing testing applies to OME regardless of laterality and is concerned more with gathering information to assist in management, not with the immediate use of that information in surgical decision making.

Once OME has persisted in both ears for 3 months or longer, the chance of spontaneous resolution is low: approximately 20% within 3 months, 25% after 6 months, and only 30% after 1 year of additional observation.[43] Therefore, most children diagnosed with chronic, bilateral OME will fail to improve in a timely fashion, even with prolonged observation. This low probability of resolution creates a need to assess the impact of persistent effusion on a child's quality of life and functional health status, particularly with regard to hearing status.

When OME becomes chronic, the child's HLs have traditionally been a major determinant factor in deciding whether to proceed with tympanostomy tube insertion.[6,57] Whereas earlier clinical practice guidelines had *recommended* tympanostomy tube insertion for children with chronic bilateral OME and hearing loss,[57] more recent guidelines[58] advise that such children be *considered for* surgical intervention. This

Table 7. Validated questions for assessing hearing difficulty by caregiver report.[a]

Question	Responses	Pass	Fail
How would you describe your child's hearing?	Normal, slightly below normal, poor, very poor	Normal	Slightly below normal, poor, or very poor
Has he/she misheard words when not looking at you?	No, rarely, often, always	No or rarely	Often or always
Has he/she had difficulty hearing when with a group of people (ie, not one-to-one)?	No, rarely, often, always	No or rarely	Often or always

[a]A hearing difficulty is present when there is a fail response for 2 or more questions.

change was based on randomized trials showing that many otherwise healthy children with mild hearing loss from OME do not necessarily benefit from more prompt tympanostomy tube insertion.[48,59-61] Our guideline development group agreed that children with chronic, bilateral OME and hearing loss should be *offered* tympanostomy tube surgery, with the final surgical decision based on shared decision making between the clinician and the child's caregiver.

A clinician fulfills the obligation of "offering" tympanostomy tube insertion to a child with bilateral OME and hearing loss by documenting in the medical record discussion of the following:

- Poor natural history of chronic, bilateral OME, which will likely persist in most children even after 1 year of observation
- Benefits and risk of tympanostomy tube insertion, as defined earlier in the Health Care Burden section of this guideline
- Alternatives to tympanostomy tube insertion are largely limited to surveillance (Statement 5), because medical therapy (antibiotics, antihistamines, decongestants, systemic steroids, and topical nasal steroids) is ineffective and not recommended[6,58]
- The final decision reached by the clinician and caregiver regarding further management: proceed with tympanostomy tube insertion, surveillance at 3- to 6-month intervals (Statement 5), or further evaluation and testing (audiologist, otolaryngologist, or both)

The preferred method for documenting hearing difficulty for children with chronic OME is age-appropriate audiologic testing,[6] as described in Statement 2. When conventional audiometry or comprehensive audiologic assessment produces inconclusive results or is not obtainable because of access or availability problems, one method of assessing hearing difficulties in children at least 3 years of age is by asking the 3 questions in **Table 7**. These questions are from the reported hearing difficulty (RHD) domain of the OM8-30 survey, which was developed for a large, randomized trial of tympanostomy tube efficacy for chronic OME.[47,62] Although caregiver surveys of child hearing, in general, are often inaccurate,[63,64] the questions in **Table 7** have demonstrated psychometric validity for children ages 3 to 9 years with chronic, bilateral OME.[65] The clinical relevance of these questions in children with OME is supported by the strong correlation of RHD responses with the Health Utilities Index, a widely used generic scoring system for calculating quality-adjusted life years.[66]

Clinicians can rapidly assess for hearing difficulty by asking the questions in **Table 7** and assigning a "pass" or "fail" outcome to each with the criteria specified. A hearing difficulty is likely when 2 or more failed responses are recorded. This cut point is based on a secondary analysis conducted specifically to support development of this guideline (Mark Haggard, unpublished data, June 19, 2012), using data from the original randomized trial in which the survey was used.[47] When applied to this cohort of children with chronic OME and documented hearing loss, 79% would fail 2 or more questions and be considered by caregiver report to have a hearing difficulty.

Children who have hearing difficulty based on the questions in **Table 7** should ideally have confirmation with audiologic testing. Conversely, pass responses to the questions in **Table 7** do not rule out the possibility of an underlying hearing loss. For example, there is evidence that caregivers tend to underestimate the impact of OME on child hearing, which may become apparent only after seeing how their child functions after the tympanostomy tubes have been placed.[67]

The primary benefits of tympanostomy tube placement are reduced prevalence of MEE resulting in improved hearing, improved patient and caregiver QOL,[13,18] and possible improved language acquisition through better hearing across the speech frequencies, binaural processing, and sound localization.[18,68,69] Systematic reviews of RCTs consistently describe improved hearing in the first 6 to 9 months[13,18] following tube placement as well as improved children's QOL the initial 2 to 9 months following tube surgery.[18]

Caregivers of children who meet the criteria for tympanostomy tube placement as described above should be informed of the potential risks of surgery. Risks of tympanostomy tube placement have been outlined under the section Health Care Burden. Tympanostomy tube otorrhea (TTO) occurs in up to 26% of children and is the most common complication of tympanostomy tube surgery.[11] In considering the benefits and harms of this procedure, the panel deemed that the benefits of improved hearing, speech and language development, and QOL outweigh the potential risks.

STATEMENT 4. CHRONIC OME WITH SYMPTOMS: Clinicians may perform tympanostomy tube insertion in children with unilateral or bilateral OME for 3 months or longer (chronic OME) AND symptoms that are likely attributable to OME that include, but are not limited to, balance (vestibular) problems, poor school performance, behavioral problems, ear discomfort, or reduced quality of life. *Option based on randomized controlled trials and before-and-after studies with a balance between benefit and harm.*

Action Statement Profile

- Aggregate evidence quality: Grade C, based on before-and-after studies on vestibular function and QOL, RCTs on reduced MEE after tubes for chronic OME, and observational studies regarding the impact of MEE on children as related, but not limited to, school performance, behavioral issues, and speech delay
- Level of confidence in evidence: High for vestibular problems and QOL; medium for poor school performance, behavioral problems, and ear discomfort, because of study limitations and the multifactorial nature of these issues
- Benefits: Reduced prevalence of MEE, possible relief of symptoms attributed to chronic OME, elimination of MEE as a confounding factor from efforts to understand the reason or cause of a vestibular problem, poor school performance, behavioral problem, or ear discomfort
- Risks, harms, costs: None related to offering surgery, but if performed, tympanostomy tube insertion includes risks from anesthesia, sequelae of the indwelling tympanostomy tubes (otorrhea, granulation tissue, obstruction), complications after tube extrusion (myringosclerosis, retraction pocket, persistent perforation), premature tympanostomy tube extrusion, retained tympanostomy tube, tympanostomy tube medialization, procedural anxiety and discomfort, and direct procedural costs
- Benefit-harm assessment: Equilibrium
- Value judgments: Chronic MEE has been associated with problems other than hearing loss; intervening when MEE is identified can reduce symptoms. The group's confidence in the evidence of a child benefitting from intervention was insufficient to conclude a preponderance of benefit over harm and instead found at equilibrium
- Intentional vagueness: The words *likely attributable* are used to reflect the understanding that the symptoms listed may have multifactorial causes, of which OME may be only one factor, and resolution of OME may not necessarily resolve the problem
- Role of patient (caregiver) preferences: Substantial role for shared decision making regarding the decision to proceed with, or to decline, tympanostomy tube insertion
- Exceptions: None
- Policy level: Option
- Differences of opinion: None.

Supporting Text

The purpose of this statement is to facilitate intervention for children with chronic OME and associated symptoms that are likely attributable to OME, when the child does not meet criteria for intervention in the preceding action statement (eg, bilateral OME with documented hearing difficulty). This is consistent with current guidelines from the United Kingdom that state "exceptionally, healthcare professionals should consider surgical intervention in children with chronic bilateral OME with a hearing loss less than 25–30 dB HL where the impact of the hearing loss on a child's developmental, social or educational status is judged to be significant."[58] In contrast, the guideline development group for this document also considered chronic unilateral OME as a surgical indication if they also presented with symptoms likely attributable to OME.

OME has a direct and reversible impact on the vestibular system.[69-73] Children with chronic OME have significantly poorer vestibular function and gross motor proficiency when compared with non-OME controls. Moreover, these deficiencies tend to resolve promptly following tympanostomy tube insertion, although 1 case-control study did not show vestibular benefits with rotational chair testing.[74] In aggregate, however, evidence suggests tympanostomy tube insertion is a reasonable option for children with chronic OME who have unexplained clumsiness, balance problems, or delayed motor development. Since most parents/caregivers do not appreciate the potential relation of these symptoms with OME, clinicians must often ask specific and targeted questions about clumsiness, balance (eg, frequent falls), or motor development (eg, delays in walking) to elucidate symptoms.

Certain behavioral problems occur disproportionately with OME, including distractibility, withdrawal, frustration, and aggressiveness.[75] In a large cohort study, for example, OME severity from age 5 to 9 years correlated with a lower intelligence quotient to age 13 years and with hyperactive and inattentive behavior until age 15 years.[76] The largest effects were observed for defects in reading ability between 11 and 18 years. An RCT of children treated with tympanostomy tubes for chronic OME had fewer documented behavioral problems compared with nonsurgical controls.[46] Children with OME have also been found to have more attention disorders and anxiety/depression-related disorders when compared with children without OME.[77]

Two prospective cohort studies evaluated QOL outcomes among children undergoing tympanostomy tube placement for otitis media using a disease-specific QOL measure, the OM-6 survey.[8,67] Rosenfeld and colleagues[8] found physical symptoms, caregiver concerns, emotional distress, hearing loss, and speech impairment significantly improved after tympanostomy tube placement. Timmerman and colleagues[67] also noted improved QOL among children after tympanostomy tube placement and concluded further that caregivers tend to underestimate their child's degree of baseline hearing impairment; when asked to reassess their preoperative rating of their

child's hearing after having seen the difference after surgery, most parents/caregivers increased their perception of initial hearing difficulty. Rovers and colleagues[61] did not find improved QOL outcomes after tympanostomy tube insertion for asymptomatic infants aged 1 to 2 years with chronic OME identified by screening; however, they used a generic QOL measure with unknown sensitivity to change for otitis media that may have missed clinically important disease-specific changes.

Children with OME may be at risk for poor school performance because of hearing loss, problems with behavior or attention, and difficulties understanding speech in noisy classroom settings. Recurrent or chronic otitis media is associated with emotional symptoms and hyperactive behavior in young school children, resulting in poorer attention skills and few social interactions.[78] Chronic OME has been correlated with delayed answering, limited vocabulary, and difficulties in speech and reading.[79] There are no randomized trials assessing the impact of tympanostomy tube insertion on these children, but such trials are unlikely to be performed because of ethical concerns. One observational study, however, showed that caregivers perceived improved school performance in children after tympanostomy tube insertion.[21]

The guideline development group concluded that the potential benefits of tympanostomy tubes for children with unilateral or bilateral OME with associated symptoms were partially offset by the costs and potential adverse outcomes related to the procedure. The decision to proceed with tympanostomy tube placement should be based on realistic expectations by the parent or caregiver about how a reduced prevalence of MEE after tympanostomy tube insertion might affect the child's QOL and functional health status.

STATEMENT 5. SURVEILLANCE OF CHRONIC OME: Clinicians should reevaluate, at 3- to 6-month intervals, children with chronic OME who do not receive tympanostomy tubes, until the effusion is no longer present, significant hearing loss is detected, or structural abnormalities of the tympanic membrane or middle ear are suspected. *Recommendation based on observational studies, with a preponderance of benefit over harm.*

Action Statement Profile

- Aggregate evidence quality: Grade C, based on observational studies
- Level of confidence in evidence: High
- Benefits: Detection of structural changes in the tympanic membrane that may require intervention, detection of new hearing difficulties or symptoms that would lead to reassessing the need for tympanostomy tube insertion, discussion of strategies for optimizing the listening-learning environment for children with OME, as well as ongoing counseling and education of parents/caregiver
- Risks, harms, costs: Cost of examination(s)
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: Although it is uncommon, untreated OME can cause progressive changes in the tympanic membrane that require surgical intervention. There was an implicit assumption that surveillance and early detection/intervention could prevent complications and would also provide opportunities for ongoing education and counseling of caregivers
- Intentional vagueness: The surveillance interval is broadly defined at 3 to 6 months to accommodate provider and patient preference; "significant" hearing loss is broadly defined as one that is noticed by the caregiver, reported by the child, or interferes in school performance or quality of life
- Role of patient (caregiver) preferences: Opportunity for shared decision making regarding the surveillance interval
- Exceptions: None
- Policy level: Recommendation
- Difference of opinion: None

Supporting Text

The purpose of this statement is to avoid the sequelae of chronic OME and to identify children who develop signs or symptoms that would prompt intervention. Although the natural history of most OME is favorable, resolution rates decrease the longer the effusion is present, and relapse is common.[43]

Children with chronic OME may develop structural changes of the tympanic membrane, hearing loss, and speech and language delay. Reevaluation at 3- to 6-month intervals facilitates ongoing counseling and education with the parents/caregiver to avoid such sequelae and should include otologic examination, with audiologic assessment as needed. Children with chronic OME are at risk for structural changes of the tympanic membrane because the effusion contains mucin, leukotrienes, prostaglandins, cytokines, and arachidonic acid metabolites that invoke a local inflammatory response.[80,81] Reactive changes may occur in the adjacent tympanic membrane and mucosal lining. Underventilation of the middle ear, which is common in young children, produces a negative pressure that over time may predispose to focal retraction pockets, generalized atelectasis of the tympanic membrane, and cholesteatoma.

Careful examination of the tympanic membrane can be performed using a handheld pneumatic otoscope to search for retraction pockets, ossicular erosion, and areas of atelectasis and atrophy. If there is any uncertainty that all structures are normal, further evaluation should be carried out using an otomicroscope. All children with these tympanic membrane conditions, regardless of OME duration, should have an audiologic evaluation. Conditions of the tympanic membrane that may benefit from tympanostomy tube insertion are posterosuperior retraction pockets, ossicular erosion, and adhesive atelectasis.[6] Ongoing surveillance is mandatory because the incidence of structural damage increases with effusion duration.

Hearing loss has been defined by conventional audiometry as a loss of >20 dB HL at 1 or more frequencies (500, 1000,

2000, 4000 Hz) and requires a comprehensive audiologic evaluation.[6] Any child with evidence of hearing impairment on screening or hearing testing should be referred for comprehensive audiologic evaluation, including thresholds and speech recognition, by a licensed audiologist in a soundproof booth. If a child with OME has HLs in the normal range (<20 dB HL), a repeat hearing test should be performed in 3 to 6 months if OME persists. Studies have shown mild sensorineural hearing loss to be associated with difficulties in speech, language, and academic performance in school, and persistent mild conductive hearing loss with OME may have similar impact.[6] With HLs >40 dB (moderate hearing loss), the child is at risk for problems with speech, language, and school performance,[6] and tympanostomy tube insertion should be recommended.

Randomized trials suggest that otherwise healthy children with persistent OME, who do not have any of the at risk criteria in **Table 2**, can be safely observed for 6 to 12 months without developmental sequelae or reduced overall QOL.[45,59-61] The impact of longer observation periods is unknown, so children for whom prolonged observation of OME is undertaken should have periodic assessment of speech, language, and QOL through targeted questions by the clinicians, validated disease-specific QOL surveys,[21] or formal language testing. Prior guidelines[8] recommend language testing for children with chronic OME and hearing loss (pure-tone average greater than 20 dB HL) on comprehensive audiologic evaluation.

Education of the child and parents/caregiver should begin at the first encounter and be an ongoing process. Clinicians should aim to create an understanding of the natural history of the disease as well as signs and symptoms of disease progression, in order to facilitate prompt medical attention and reduction in unnecessary antibiotic use. Communication between parents/caregivers and primary care providers should be encouraged, as should prompt referral to the otolaryngologist if otoscopy does not clearly demonstrate a normal tympanic membrane.

STATEMENT 6. RECURRENT AOM WITHOUT MEE: Clinicians should *not* perform tympanostomy tube insertion in children with recurrent acute otitis media who *do not* have MEE in either ear at the time of assessment for tube candidacy. *Recommendation against based on systematic reviews and randomized controlled trials with a preponderance of benefit over harm.*

Action Statement Profile

- Aggregate evidence quality: Grade A, based on a meta-analysis of RCTs, a systematic review of RCT control groups regarding the natural history of recurrent AOM, and other RCTs
- Level of confidence in evidence: High
- Benefits: Avoid unnecessary surgery and its risks, avoid surgery in children for whom RCTs have not demonstrated any benefit for reducing AOM incidence or in children with a condition that has reasonable likelihood of spontaneous resolution, cost savings
- Risks, harms, costs: Delay in intervention for children who eventually require tympanostomy tubes, need for systemic antibiotics among children who continue to have episodes of recurrent AOM
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: Implicit in this recommendation is the ability to reassess children who continue to have AOM despite observation and to perform tympanostomy tube insertion if MEE is present (Statement 7); risk of complications or poor outcomes from delayed tube insertion for children who continue to have recurrent AOM is minimal
- Intentional vagueness: The method of confirming the absence of MEE should be based on clinician experience and may include tympanometry, simple otoscopy, and/or pneumatic otoscopy
- Role of patient (caregiver) preferences: Limited, because of favorable natural history and good evidence that otherwise healthy children with recurrent AOM without MEE do not have a reduced incidence of AOM after tympanostomy tube insertion
- Exceptions: At-risk children (see **Table 2**), children with histories of severe or persistent AOM, immunosuppression; prior complication of otitis media (mastoiditis, meningitis, facial nerve paralysis); multiple antibiotic allergy or intolerance
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to help children and families avoid surgical intervention for recurrent AOM (as defined in **Table 1**) without MEE because the natural history is quite favorable and benefits of tympanostomy tubes for this clinical indication are uncertain.

The best evidence on the natural history of recurrent AOM without MEE comes from RCTs of antibiotic prophylaxis for recurrent AOM, all of which exclude children with OME or persistent MEE from participation. A systematic review of 15 such trials found highly favorable rates of improvement in the placebo groups: children with recurrent AOM entered these trials with a mean baseline rate of 5.5 or more annual episodes but averaged only 2.8 annual episodes while on placebo.[43] Furthermore, 41% had no additional episodes of AOM while on placebo for a median duration of 6 months, and 83% had only 2 or fewer episodes. Individual AOM episodes, if they did occur in these trials, were treated with a 7- to 10-day course of oral antibiotic.

Systematic reviews of tympanostomy tube insertion for recurrent AOM have shown either a transient benefit of questionable clinical significance,[22] no additional benefit compared with antibiotic use,[24] or no benefit at all.[18,23] In addition, an RCT that specifically excluded children with baseline MEE found no benefit of tympanostomy tube insertion for reducing the subsequent

incidence of AOM.[9] This trial, did, however, find that tubes decreased the mean percentage time with otitis media (of any type) over the next 2 years, but the absolute decrease was modest, about 8% or 30 days per year.[6] Conversely, an RCT published after the systematic reviews noted above found significant benefits of tympanostomy tubes for preventing recurrent AOM in children aged 10 months to 2 years. This study, however, included children with persistent MEE, and these effusions were aspirated during tympanostomy tube surgery.[82]

This guideline statement applies to children with recurrent AOM not found to have MEE at the time they are assessed for tympanostomy tube candidacy. When implemented in clinical practice, it is understood that some children will be referred by their primary care provider based on their evaluation finding an effusion is present, only to have that effusion resolve prior to the surgical consultation.

The absence of MEE at the time of assessment for tube candidacy, even if recently documented by another clinician, suggests favorable eustachian tube function and a good prognosis, based on evidence cited earlier in this section for the natural history of recurrent AOM without baseline effusion. Tympanostomy tube insertion is not recommended in this situation, but the child should be reassessed if he or she continues to have recurrent AOM episodes. Clinicians should note that the subsequent guideline statement (recurrent AOM with MEE) allows for tympanostomy tubes to be placed in these patients, should MEE be documented in subsequent clinical evaluations.

The risks of not performing tympanostomy tube placement lie mostly in exposure to additional courses of systemic antibiotics for the subset of children who continue to have recurrent episodes and in delay of eventual tympanostomy tube placement in those children who may go on to have persistent AOM or recurrent AOM with MEE. Children with recurrent AOM without MEE who are observed but later develop persistent MEE may be offered tympanostomy tubes as outlined in the subsequent guideline action statement.

The guideline development group concluded that tympanostomy tube insertion should not be performed in children having recurrent AOM without MEE given the high likelihood of spontaneous improvement, quantifiable risks, and lack of convincing evidence for benefit. This guideline statement, however, does not apply to children with complications of otitis media or multiple antibiotic allergies/intolerances, severe/chronic OME, or immunosuppression or children at risk for, or already experiencing, developmental delays as outlined in **Table 2**.

STATEMENT 7. RECURRENT AOM WITH MEE: Clinicians should offer bilateral tympanostomy tube insertion in children with recurrent AOM who have unilateral or bilateral MEE at the time of assessment for tube candidacy. *Recommendation based on randomized controlled trials with minimal limitations and a preponderance of benefit over harm.*

Action Statement Profile

- Aggregate evidence quality: Grade B, based on RCTs with minor limitations
- Level of confidence in evidence: Medium; some uncertainty regarding the magnitude of clinical benefit and importance, because of heterogeneity in the design and outcomes of clinical trials
- Benefits: Mean decrease of approximately 3 episodes of AOM per year, ability to treat future episodes of AOM with topical antibiotics instead of systemic antibiotics, reduced pain with future AOM episodes, improved hearing during AOM episodes
- Risks, harms, costs: Risks from anesthesia, sequelae of the indwelling tympanostomy tubes (otorrhea, granulation tissue, obstruction), complications after tube extrusion (myringosclerosis, retraction pocket, persistent perforation), premature tympanostomy tube extrusion, retained tympanostomy tube medialization, procedural anxiety and discomfort, and direct procedural costs
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: In addition to the benefits seen in RCTs, the presence of effusion at the time of assessment served as a marker of diagnostic accuracy for AOM
- Intentional vagueness: The method of confirming the presence of middle ear effusion should be based on clinician experience and may include tympanometry, simple otoscopy, and/or pneumatic otoscopy
- Role of patient (caregiver) preferences: Substantial role for shared decision making regarding the decision to proceed with, or to decline, tympanostomy tube insertion
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to offer tympanostomy tubes as a management option for children with a history of recurrent AOM (as defined in **Table 1**) who have MEE at the time of assessment for tube candidacy. In contrast to the previous action statement (recurrent otitis media *without* MEE), this statement requests that clinicians offer tympanostomy tubes to children who have an effusion present in 1 or both ears when evaluated for possible tube placement. This effusion serves as both a marker for diagnostic accuracy of AOM and an indicator of underlying eustachian tube dysfunction with decreased ability to clear middle ear fluid following an episode of AOM. Bilateral insertion of tympanostomy tubes is recommended even if only unilateral effusion is present because more than 70% of children have similar eustachian tube function on the right and left sides.[83]

The difficulty in accurately diagnosing AOM has been well documented, relating primarily to confirming the presence of MEE.[84] Symptoms of otalgia and fever are nonspecific for AOM, making them unreliable for primary diagnosis.[85,86] Clinicians often rely on simple otoscopy for diagnosis, but obstructing cerumen and poor lighting may compromise

visibility, and a child's crying can induce tympanic membrane erythema, leading to overdiagnosis.[87] Although pneumatic otoscopy can improve diagnostic certainty for MEE, it is not widely used, and may be unavailable, in the primary care setting.[87] Repeated overdiagnosis of AOM may lead to an unwarranted referral to an otolaryngologist for surgical intervention.

Middle ear effusion following an episode of AOM often takes time to resolve, with persistence of effusion in 70% of ears at 2 weeks, 40% at 1 month, 20% at 2 months, and 10% at 3 months.[42] The natural history of persistent MEE is favorable, but when middle ear fluid persists, it is thought to be an indicator of underlying eustachian tube dysfunction that may possibly predispose to future AOM recurrence. Moreover, persistent MEE in a child with recurrent AOM provides some reassurance regarding diagnostic certainty (at least for the most recent AOM episode), although it is not possible to distinguish chronic OME from MEE after AOM.

Tympanostomy tube insertion in children with recurrent AOM decreased the average number of AOM episodes by about 2.5 per child-year in 2 RCTs that did not exclude children with persistent effusion at the time of trial entry.[88,89] Another RCT of children younger than 2 years with recurrent AOM, including those with persistent MEE at trial entry but excluding children with histories of chronic OME, also found that tympanostomy tube insertion resulted in a significant, but modest, reduction in subsequent AOM episodes (0.55 per child-year).[82] Similarly, when children with OME lasting 2 months or longer receive tympanostomy tubes, there is a modest reduction in subsequent AOM episodes (0.20 to 0.72 per child-year).[49,50] In contrast, a trial of tympanostomy tubes in children with a history of recurrent AOM but without MEE found no reduction in subsequent AOM after insertion of tympanostomy tubes.[9]

Several systematic reviews have attempted to assess the efficacy of tympanostomy tubes for recurrent AOM, but there has been widespread disagreement regarding trial selection and inclusion criteria, with most reviews excluding studies that allowed children to have MEE or OME at baseline.[18,19,22-24] For this reason, we have focused on individual trial results, as summarized in the preceding paragraph. The issue of whether or not tubes benefit children with recurrent AOM who present without persistent effusion is discussed in the prior guideline action statement.

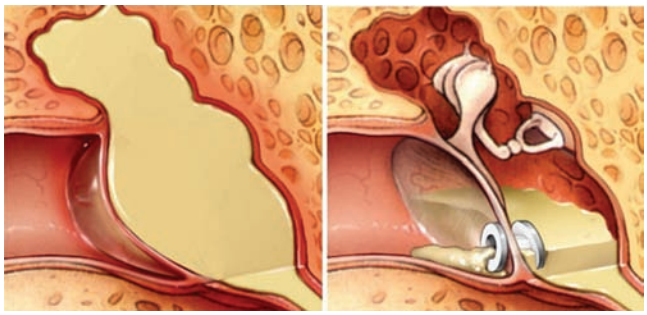


Figure 4. Acute otitis media without a tympanostomy tube (left) and with a tube (right). Without a tube, the tympanic membrane is bulging and inflamed, which causes pain and sometimes rupture. Reproduced with permission.[3]

Although the primary rationale for offering tympanostomy tubes to children with recurrent AOM and persistent MEE is to reduce the incidence of future infections, there are additional benefits including decreased pain, should AOM occur with tubes in place, as well as the ability to manage such infection with topical antibiotic eardrops (**Figure 4**; **Table 8**). Tympanostomy tubes can serve as a drug-delivery mechanism, allowing concentrated antibiotic eardrops to reach the middle ear space directly through the tube lumen. Eardrops alone are highly effective for AOM with tubes.[18] Please refer to Statement 10 later in this document for additional information on managing TTO.

Clinicians should offer tympanostomy tubes to children with recurrent AOM and MEE, but whether or not to proceed with surgery is largely dependent on shared decisions with the child's caregiver. The benefits of tympanostomy tube insertion are significant, but modest, and are offset by procedural and anesthetic risks, as discussed earlier. Children with more severe AOM episodes, multiple antibiotic allergies, or any of the comorbid conditions in **Table 2** may derive greater benefit from timely tympanostomy tube insertion. A period of surveillance (Statement 5), with reassessment at 3- to 6-month intervals, can be employed when there is any uncertainty

Table 8. Comparison of acute otitis media with and without a tympanostomy tube.[a]

Issue	AOM without a Tube	AOM with a Tube
Ear pain	Mild to severe	None, unless skin irritated or tube occluded
Drainage from the ear canal (otorrhea)	No, unless eardrum ruptures	Yes, unless tube obstructed
Duration of middle ear effusion after infection	Can last weeks or months	Usually resolves promptly
Needs oral antibiotics	Often	Rarely
Needs antibiotic eardrops	No benefit	Often
Risk of eardrum rupture	Yes	No, unless tube obstructed
Risk of suppurative complications	Rare	Exceedingly rare

Abbreviation: AOM, acute otitis media.
[a]Adapted.[3]

about the appropriateness of surgery, since improvements may occur from natural history, especially when chronic OME is not present.[9,82]

STATEMENT 8. AT RISK CHILDREN: Clinicians should determine if a child with recurrent AOM or with OME of any duration is at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors (see Table 2). *Recommendation based on observational studies with a preponderance of benefit over harm.*

Action Statement Profile

- Aggregate evidence quality: Grade C, based on observational studies
- Level of confidence in evidence: High for Down syndrome, cleft palate, and permanent hearing loss; medium for other risk factors
- Benefits: Facilitation of future decisions about tube candidacy, identification of children who might benefit from early intervention (including tympanostomy tubes), identification of children who might benefit from more active and accurate surveillance of middle ear status as well as those who require more prompt evaluation of hearing, speech, and language
- Risks, harms, costs: None
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: Despite the limited high-quality evidence about the impact of tubes on this population (nearly all RCTs exclude children who are at risk), the panel considered it important to use at-risk status as a factor in decision making about tube candidacy, building on recommendations made in the OME guideline.[6] The panel assumed that at-risk children would be less likely to tolerate OME or recurrent AOM than would the otherwise healthy child
- Intentional vagueness: None
- Role of patient (caregiver) preferences: None, since this recommendation deals only with acquiring information to assist in decision making
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to highlight the importance of identifying children with comorbid conditions that alter their susceptibility to AOM, OME, or potential developmental sequelae from MEE. This statement builds on multidisciplinary guidance first introduced in an OME clinical practice guideline in 2004 that recommended that "clinicians should distinguish the child with OME who is at risk for speech, language, or learning problems from other children with OME, and should more promptly evaluate hearing, speech, and the need for intervention."[6]

Children who are at risk for developmental difficulties (**Table 2**) would likely be adversely affected by the conductive hearing loss that accompanies OME, even though definitive studies are lacking.[6,90] Whereas a child with baseline normal hearing might tolerate a 15- to 20-dB hearing decrease from OME without problems, one with permanent hearing loss, independent of OME, would have substantial difficulty that could worsen existing speech and language delays.[91,92] In addition, the benefits of hearing aids in children with permanent hearing loss could be reduced by the presence of MEE.[91] Similarly, a child with blindness or uncorrectable visual impairment would be more susceptible to OME sequelae, including imbalance, sound localization, communication, delayed language development, and impaired ability to interact and communicate with others.[6]

Developmental, behavioral, and sensory disorders are not uncommon among children younger than 17 years in the United States.[93] These include children with primary language impairments and others with autism-spectrum disorders or syndromes that adversely affect cognitive and linguistic development. Hearing loss of any type (conductive, sensorineural, or mixed) may significantly worsen outcomes for affected children, making detection of OME and management of chronic effusion of utmost importance. Frequent MEE, caused by recurrent AOM or chronic OME (unilateral or bilateral), can degrade the auditory signal, causing difficulties with speech recognition, higher-order speech processing, speech perception in noise, and sound localization.[55] Last, children with developmental disabilities may lack the communication skills or sensory perception to reliably express pain or discomfort associated with AOM and would benefit from more active monitoring.

Children with Down syndrome have poor eustachian tube function associated with recurrent AOM and chronic OME. They also have a risk of mixed or sensorineural hearing loss as well as stenotic ear canals that can impede assessment of tympanic membrane and middle ear status.[94-98] Such risks may persist throughout childhood, requiring multiple tympanostomy tube placements if a surgical option is chosen. Hearing loss also can be difficult to document accurately in very young children with Down syndrome, except when evaluated by pediatric audiologists, often using eletrophysiologic (auditory brainstem response) tests. Hearing assessments are recommended for these children every 6 months starting at birth. Otolaryngologic evaluation is also recommended for recurrent AOM and OME, if middle ear status cannot be determined or if hearing loss is found.[99] Children with stenotic ear canals are best assessed using an otologic microscope every 3 to 6 months to remove cerumen and detect OME.[99]

Cleft palate is a common orofacial malformation, with a prevalence of 1 in 700 live births.[100] Otitis media with effusion occurs in nearly all infants and children with cleft palate[101,102] because of the limited ability of the eustachian tube to open actively, resulting from abnormal insertions of the tensor veli palatini and the levator veli palatini muscles.[103] Chronic OME in children with cleft palate is almost always associated with

some degree of conductive hearing loss.[103] Children with cleft palate should be managed by a multidisciplinary cleft palate team. Continued monitoring for OME and hearing loss should continue throughout childhood, including after palate repair, because of a continued high prevalence of effusion and hearing loss.[104]

Children with special health care needs (**Table 2**) require closer monitoring for OME and attendant hearing loss. Such close monitoring should begin once the child is identified as high risk. Eustachian tube dysfunction not only affects children with Down syndrome and cleft palate but is commonly associated with craniofacial syndromes or malformations involving the head and neck. By determining if a child with any degree of OME has any of the risk factors in **Table 2**, clinicians can better counsel families about the potential impact of otitis media on their child's development and on tympanostomy tubes as a management option (see Statement 9).

STATEMENT 9. TYMPANOSTOMY TUBES AND AT-RISK CHILDREN: Clinicians may perform tympanostomy tube insertion in at-risk children with unilateral or bilateral OME that is unlikely to resolve quickly as reflected by a type B (flat) tympanogram or persistence of effusion for 3 months or longer. *Option based on a systematic review and observational studies with a balance between benefit and harm.*

Action Statement Profile

- Aggregate evidence quality: Grade C based on a systematic review of cohort studies regarding natural history of type B tympanograms and observational studies examining the impact of MEE on at-risk children
- Level of confidence in evidence: Moderate to low, because of methodological concerns with the conduct, outcome reporting, and follow-up of available observational studies.
- Benefits: Improved hearing, resolution of MEE in at-risk children who would otherwise have a low probability of spontaneous resolution, mitigates a potential obstacle to child development
- Risks, harms, costs: Risk of anesthesia, sequelae of the indwelling tympanostomy tubes (otorrhea, granulation tissue, obstruction), complications after tube extrusion (myringosclerosis, retraction pocket, persistent perforation), failure of or premature tympanostomy tube extrusion, tympanostomy tube medialization, procedural anxiety and discomfort, and direct procedural costs
- Benefit-harm assessment: Equilibrium
- Value judgments: Despite the absence of controlled trials identifying benefits of tympanostomy tube placement in at-risk children (such children were excluded from the reviews cited), the panel agreed that tympanostomy tubes were a reasonable intervention for reducing the prevalence of MEE that would otherwise have a low likelihood of prompt spontaneous resolution. Untreated persistent MEE would place the child at high risk for hearing loss from suboptimal conduction of sound through the middle ear, which could interfere with subsequent speech and language progress
- Intentional vagueness: None
- Role of patient (caregiver) preferences: Substantial role for shared decision making with caregivers regarding whether or not to proceed with tympanostomy tube insertion
- Exclusions: None
- Policy level: Option
- Differences of opinion: None regarding the action statement; a minor difference of opinion about whether children with Down syndrome or cleft palate should be considered independently of children with speech and language delays/disorders

Supporting Text

The purpose of this statement is to facilitate prompt management of children with OME who have sensory, physical, cognitive, or behavioral factors that place them at increased risk for developmental delays or disorders (**Table 2**). In contrast to Statement 2 (chronic bilateral OME with hearing difficulties), this statement gives clinicians the option to perform tympanostomy tube insertion in at-risk children with OME that is unilateral or may not have apparent hearing difficulties but is unlikely to resolve promptly. Although the at-risk conditions listed in **Table 2** represent diverse disorders that are managed very differently, they are considered jointly in this guideline because all children with 1 or more of these conditions are likely to be more sensitive to an impact of chronic OME on development than would children who are not at risk.

Chronic OME and at-risk children. The rationale for offering tympanostomy tubes to at-risk children is to minimize the potential impact of chronic OME on child development by improving hearing quality and reducing effusion prevalence.[6] Children with OME typically have mild hearing loss (about 25-28 dB HL), with 20% of affected ears having levels exceeding 35 dB HL.[55] After tympanostomy tube insertion, HLs improve by a mean of 5 to 12 dB while the tubes are patent,[7,13,18] and the prevalence of MEE is reduced by 32% to 73%.[7,13,18]

Otitis media with effusion that is unilateral or not associated with hearing loss, however, may still affect an at-risk child because of degraded auditory input that reduces binaural processing and speech perception.[55] Other effects of chronic effusion include problems with speech recognition, higher-order speech processing, and speech perception in noise. For example, children with bilateral OME and normal hearing for the better ear have substantial difficulties recognizing words at soft listening levels and at normal levels with background noise, a problem that resolves after placement of tympanostomy tubes.[63]

When unilateral OME is present, the decision to perform unilateral or bilateral tympanostomy tube insertion should be

based on caregiver preference and the likelihood of persistent OME developing in the opposite ear. Unilateral tube insertion should be performed only when the caregiver understands the risk of subsequent OME in the contralateral ear and the potential need for a second tube insertion procedure should this occur. Bilateral tube insertion is preferred if the risk of future OME is high (eg, very young child, frequent AOM accompanying the OME) or the caregiver wishes to have the child undergo only a single surgical procedure.

At-risk children with syndromes or craniofacial anomalies often have eustachian tube dysfunction that predisposes to otitis media, chronic OME, and recurrent episodes of infection. The natural history of otitis media in this population is largely unknown but is likely worse than for an otherwise healthy child. Acute otitis media, especially if recurrent, can be difficult to manage in at-risk children because of a lack of obvious symptoms (eg, high tolerance to pain seen in some children with autistic spectrum disorders), inability to communicate about pain (eg, autistic spectrum disorders, speech and language disorders), poor cooperation with examination (eg, with aggressive or self-injurious behavior), narrow external ear canals (eg, Down syndrome), or difficulty taking oral antibiotics (eg, multiple medication allergies, medication refusal).

Predictors of OME persistence. Otitis media with effusion is unlikely to resolve quickly when present for 3 months or longer, regardless of tympanogram type. When children with OME for 3 months are observed in randomized trials, spontaneous resolution occurs in only 19% of ears after an additional 3 months, 25% at 6 months, and 31% at 12 months.[43] This is in stark contrast to OME persisting after a documented episode of AOM, which has about 75% to 90% resolution after 3 months.[42,43] Persistence of OME for 3 months or longer can be documented by review of medical records, review of prior audiometry or tympanometry results, or by the caregiver reporting when a clinician first diagnosed the effusion and whether it was present at subsequent evaluations.

Otitis media with effusion with a type B (flat) tympanogram is also unlikely to resolve quickly, regardless of prior effusion duration, based on cohort studies of otherwise healthy young children.[43] Preschool children with OME on tympanometric screening (type B) have effusion resolution rates (conversion to a normal type A tympanogram) of only 20% after 3 months and 28% after 6 months.[43] When the criteria for resolution are relaxed, allowing some degree of negative middle ear pressure, resolution rates remain modest at 28% after 3 months and 42% after 6 months. Although a type B tympanogram is not recommended as the primary diagnostic test for OME (pneumatic otoscopy is easier to use and has comparable sensitivity and specificity),[105] it does have significant utility as a prognostic indicator, even when the prior duration of effusion is unknown.

Understanding tympanometry. Tympanometry provides an objective assessment of tympanic membrane mobility and middle ear function by measuring the amount of sound energy reflected back when a small probe is placed in the ear canal.[106]

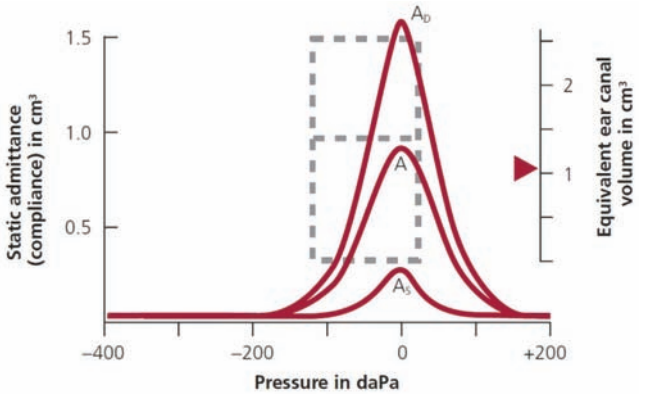


Figure 5. Normal type A tympanogram result. The height of the tracing may vary but is normal when the peak falls within the 2 stacked rectangles. The A_D tracing (upper) indicates an abnormally flexible tympanic membrane, and the A_S tracing (lower) indicates stiffness; the presence of a well-defined peak, however, makes the presence of effusion low. Reproduced with Permission.[106]

The procedure is painless, is relatively simple to perform, and can be done using a handheld unit (slightly larger than a traditional otoscope) or a desktop machine. The resulting graphical display shows how the tympanic membrane responds to varying pressure (negative and positive). A normal type A tympanogram (**Figure 5**), with peak pressure greater than –100 mm water, is associated with effusion in only 3% of ears at myringotomy.[107,108] Proper calibration of the tympanometer is essential for accurate results.

A type B, or flat curve, tympanogram (**Figure 6**) is associated with MEE in 85% to 100% of ears.[107,108] Proper interpretation of a type B tympanogram result must also consider the equivalent ear canal volume, which is displayed on the tympanogram printout and estimates the amount of air in front of the probe. A normal ear canal volume for children is between 0.3 and 0.9 cm and usually indicates MEE when combined with a type B result (**Figure 6A**).[54] A low equivalent ear canal volume (**Figure 6B**) can be caused by improper placement of the probe (eg, pressing against the ear canal) or by obstructing cerumen. The ear canal should be cleaned and the probe repositioned before retesting. Last, a high equivalent ear canal volume (**Figure 6C**) occurs when the tympanic membrane is not intact because of a perforation or tympanostomy tube. When a patent tympanostomy tube is present, the volume is typically between 1.0 and 5.5 cm^3.[54]

Last, clinicians should note that a type B tympanogram may occur in children without MEE because of rigidity or immobility of the tympanic membrane, which can occur because of extensive myringosclerosis or after surgical closure of a tympanic membrane perforation with a cartilage graft.

Tympanostomy tubes and at-risk children. Evidence regarding the impact of tympanostomy tubes on at-risk children with OME is limited, because these children are often considered ineligible for randomized trials based on ethical concerns.[18,21,109] The

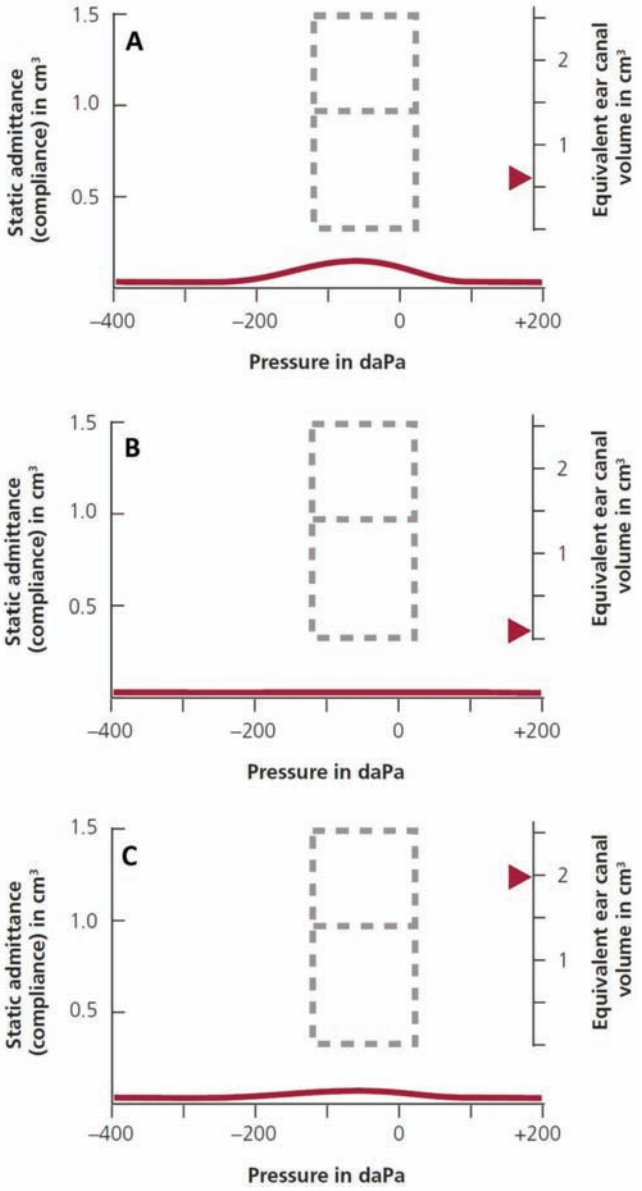


Figure 6. Abnormal type B tympanogram results. (A) A normal equivalent ear canal volume usually indicates middle ear effusion. (B) A low volume indicates probe obstruction by cerumen or contact with the ear canal. (C) A high volume indicates a patent tympanostomy tube or a tympanic membrane perforation. Reproduced with permission.[106]

2004 OME guideline concluded that there was significant potential benefit to reducing OME in at-risk children by "optimizing conditions for hearing, speech, and language; enabling children with special needs to reach their potential; and avoiding limitations on the benefits of educational interventions because of hearing problems from OME." The guideline development group found an "exceptional preponderance of benefits over harm based on subcommittee consensus because of circumstances to date precluding randomized trials."[6]

An observational study of tympanostomy tubes found better outcomes by parental/caregiver report in at-risk children (about 50% of the study sample) for speech, language, learning, and school performance.[21] The odds of a caregiver providing a "much better" response after tubes for speech and language was 5.1 times higher (95% confidence interval [CI], 2.4 to 10.8) if the child was at risk, even after adjusting for age, gender, hearing, and effusion duration. Similarly, the odds of a "much better" response for learning and school performance were 3.5 times higher (95% CI, 1.8 to 7.1). Conversely, caregivers did not report any differences in other outcomes (hearing, life overall, or things able to do) for at-risk versus non–at-risk children, making it less likely that expectancy bias was responsible for the differences in developmental outcomes.

The impact of tympanostomy tubes on children with Down syndrome has been assessed in observational studies[93-96,110] but there are no RCTs to guide management. All studies have shown a high prevalence of OME and associated hearing loss, but the impact of tympanostomy tubes has been variable regarding hearing outcomes, surgical complications (perforated tympanic membrane, recurrent or chronic otorrhea), and need for reoperation. One study achieved excellent hearing outcomes through regular surveillance (every 3 months if the ear canals were stenotic, every 6 months if not stenotic) and with prompt replacement of nonfunctioning or extruded tubes if OME recurred.[110] Hearing aids have been proposed as an alternative to tympanostomy tubes,[58] but no comparative trials have assessed outcomes or to what degree the aids were used successfully by the children.

A systematic review of observational studies concluded that there is currently inadequate evidence to support routine tympanostomy tube insertion in children with cleft palate at the time of surgical repair.[111] The evidence, however, was generally of low quality and insufficient to support not inserting tympanostomy tubes when clinically indicated (eg, hearing loss and flat tympanograms). Whether cleft palate with attendant OME and hearing loss results in speech and language impairment is also unclear, since many of the studies looking at speech and language outcomes studied children who had had tubes inserted.[112] Children with cleft palate require long-term otologic monitoring throughout childhood because of eustachian tube dysfunction and risk of cholesteatoma, but decisions regarding tympanostomy tube placement must be individualized and involve caregivers. Hearing aids are an alternative to tympanostomy tubes when hearing loss is present.

Shared decision making. Whether or not a specific child who is at risk (**Table 2**) should have tympanostomy tubes placed is always a process of shared decision making with the caregiver and other clinicians involved in the child's care. The final decision should incorporate provider experience, family values, and realistic expectations about the effect of reduced MEE and improved hearing on the child's developmental progress. The presence or duration of MEE may be difficult to

establish in some at-risk children because of limited ability to communicate, stenotic ear canals, and lack of cooperation for cerumen removal or tympanometry. These children are candidates for examination under anesthesia with the option of placing tympanostomy tubes if MEE is confirmed.

STATEMENT 10. PERIOPERATIVE EDUCATION: In the perioperative period, clinicians should educate caregivers of children with tympanostomy tubes regarding the expected duration of tube function, recommended follow-up schedule, and detection of complications. *Recommendation based on observational studies, with a preponderance of benefit over harm.*

Action Statement Profile

- Aggregate evidence quality: Grade C, based on observational studies with limitations
- Level of confidence in evidence: Medium; there is good evidence and strong consensus on the value of patient education and counseling, in general, but evidence on how this education and counseling affect outcomes of children with tympanostomy tubes is limited
- Benefits: Define appropriate caregiver expectations after surgery, enable caregivers to recognize complications early, and improve caregiver understanding of the importance of follow-up
- Risks, harms, costs: None
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: Importance of patient education in promoting optimal outcomes
- Intentional vagueness: None
- Role of patient (caregiver) preferences: None, since this recommendation deals only with providing information for proper management
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

Patient and family education is the process of providing verbal and written information to the family and addressing any questions or concerns. Effective communication should aim to improve the family's understanding of optimal care of the child with tympanostomy tubes, improving the child's follow-up care, and allowing prevention or early identification of complications. Not discussing necessary care and follow-up with a patient and family may increase the risk of complications and lead to a negative impact on long-term outcomes. Important points that should be discussed with the family of a child with tympanostomy tubes include the importance of follow-up visits, the management of common tube problems, the expected tube duration, and the potential complications thereof.

The importance of follow-up visits. Routine follow-up ensures that the tubes are in place and functioning and can determine whether the ears are healthy, hearing is maximized, and no complications are present.[62] Generally, the child should be evaluated periodically by an otolaryngologist while the tympanostomy tubes are in place. After extrusion, an additional follow-up appointment with the otolaryngologist should occur to ensure the ears are healthy and to identify any need for further surveillance or treatment.

The primary care provider has an important role in evaluating the child's ears during follow-up visits. Although tympanostomy tubes are safe and beneficial for most children who are candidates for placement, they can be associated with significant sequelae, most of which are easily treated once identified and are not associated with long-term morbidity.[11,19,58] Referral to the otolaryngologist should be made if the tympanostomy tubes cannot be visualized or are occluded, if there are concerns about a change in hearing status, or if other complications are identified (ie, granuloma, persistent or recurrent otorrhea following treatment, perforation at the tube site, persistent tube for greater than 2-3 years, retraction pocket, or cholesteatoma).[11,18,113]

Parents/caregivers of children with tympanostomy tubes should be given information regarding longevity of the tympanostomy tubes. This will vary depending on the type of tube that is placed (short-term versus long-term tubes). Short-term tubes generally last 10 to 18 months, but long-term tubes typically remain in place for several years.[114] It is important for the caregiver to understand that there is no definite way to predict the duration of tube function; some will unfortunately extrude prematurely in the first couple of months, and some will persist and need removal.[11] Rarely, the tube will displace into the middle ear space and require surgical removal.[19] The ultimate goal is for the tubes to last long enough for the child to outgrow his or her middle ear disease. Up to 50% of children, however, will require reoperation within 3 years.[49,50,115]

Managing common tube problems. It is also important to educate parents/caregivers on the presentation and treatment of ear infections with tympanostomy tubes in place. Although tympanostomy tubes reduce AOM incidence, nearly 15% to 26% will have additional episodes.[11,19] Children will rarely experience pain or fever from AOM with tympanostomy tubes in place; otorrhea is typically their only symptom. Management of TTO is fully discussed within Statement 11 of this guideline; however, parents/caregivers should be counseled that TTO may occur, responds to topical antibiotic ear drops, does not usually require oral antibiotics, and benefits from water precautions until the discharge is no longer present.

Although many parents/caregivers may believe they know when to initiate treatment for acute TTO, it is important that they notify the primary care provider or otolaryngology specialist to ensure appropriate action is taken. Parents/caregivers should also be instructed as to how to properly administer ear drops. Pumping of the tragus following placement of the drops

may help with penetration of the drops to the ear canal and middle ear space.[116] Aural toilet may be required prior to drop administration when otorrhea is filling the canal. If the drops are not able to penetrate the canal because of debris or crusting, the child may require suctioning of the canal by the otolaryngologist. When drainage is persistent following treatment, or recurs frequently, the child should be evaluated by an otolaryngologist. Caution should be advised regarding prolonged use of ototopical drops, as this may potentiate a fungal infection requiring different treatment.

Clinicians should review expectations with families. Parents/caregivers and children are frequently concerned about the possibility of discomfort. Educating and reassuring parents/caregivers/children regarding comfort, tube extrusion, and appropriate circumstances for reevaluation are important. As well, reminding families and children that the ear will typically clear cerumen naturally and does not require any special cleaning with cotton swabs or other manipulation is important.[117] Furthermore, families should be told to use only eardrops that are specifically approved for use with tympanostomy tubes, because nonapproved ear drops may induce pain, infection, or even damage hearing. Over-the-counter otic drops are not safe for use with tympanostomy tubes, regardless of the indication (eg, earwax, swimmer's ear, discomfort).

Families should also be educated concerning water exposure, as discussed in Statement 11. Water precautions are unnecessary for most children with tympanostomy tubes but should be implemented for children who develop TTO or experience discomfort upon exposure to water. Protection with earplugs, headbands, or water avoidance may be necessary during periods of active TTO.[118]

In summary, parent/caregiver and patient education is a fundamental component of the care of children with tympanostomy tubes. Education is essential at the time of tympanostomy tube insertion, and ideally, the information should be discussed and reviewed at all subsequent visits. Spoken information should be supplemented by clear, concise written information specific to the needs of the child with tympanostomy tubes **(Figures 7** and **8)**, and there should be ample opportunity for families to ask questions and review their concerns. Education and efficient communication will improve the family's understanding of how to best care for the child with ear tubes, encourage follow-up care, and allow prevention or early identification of complications, all of which will ultimately improve outcomes (**Figure 9**).

STATEMENT 11. ACUTE TYMPANOSTOMY TUBE OTORRHEA: Clinicians should prescribe topical antibiotic eardrops only, without oral antibiotics, for children with uncomplicated acute tympanostomy tube otorrhea. *Strong recommendation based on randomized controlled trials with a preponderance of benefit over harm.*

Action Statement Profile

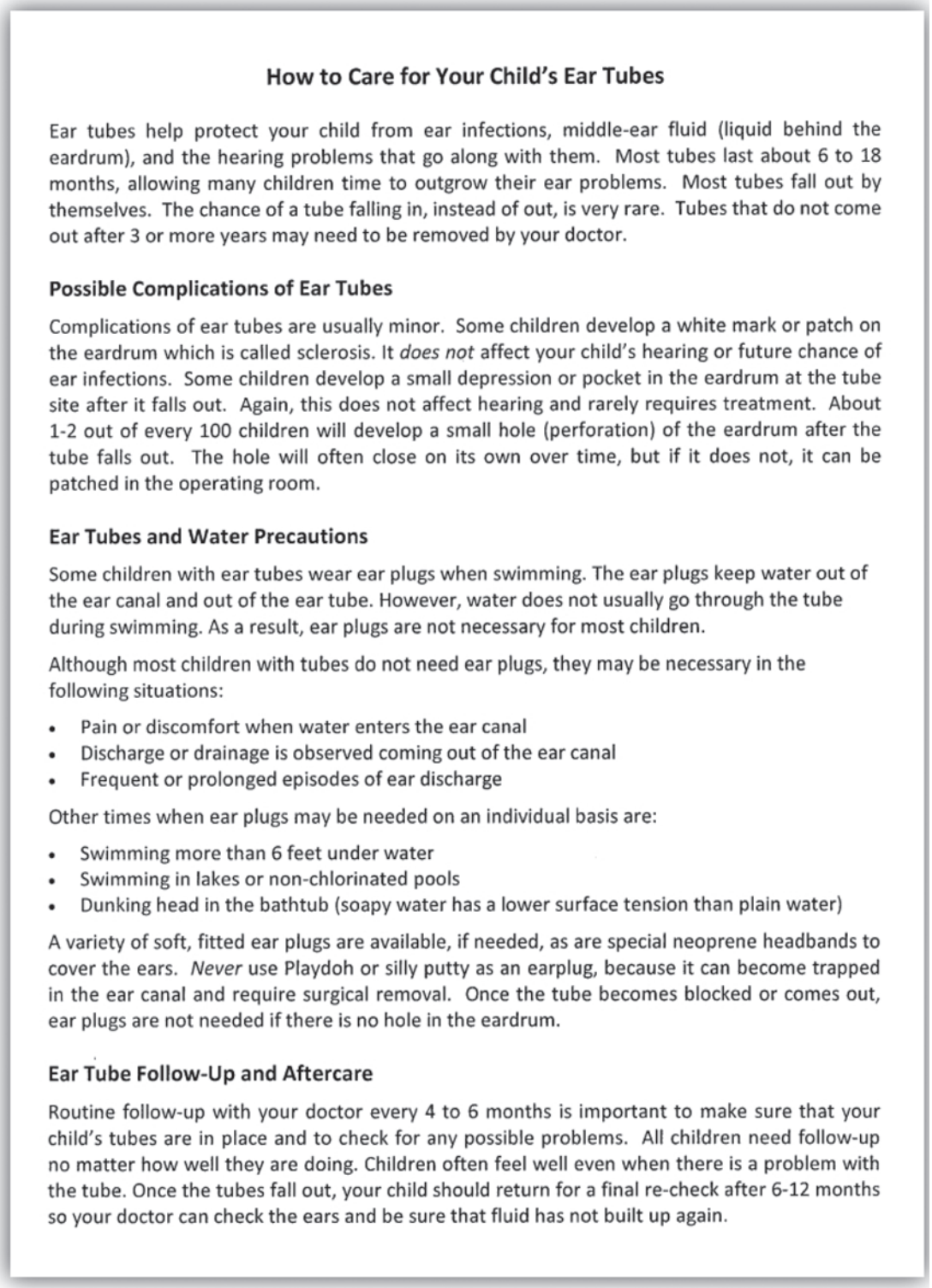
- Aggregate evidence quality: Grade B, based on RCTs demonstrating equal efficacy of topical versus oral antibiotic therapy for otorrhea as well as improved outcomes with topical antibiotic therapy when different topical preparations are compared
- Level of confidence in evidence: High
- Benefits: Increased efficacy by providing appropriate coverage of otorrhea pathogens, including *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA), avoidance of unnecessary overuse and adverse effects of systemic antibiotics, including bacterial resistance
- Risks, harms, costs: Additional expense of topical otic antibiotics compared with oral antibiotics, potential difficulties in drug delivery to the middle ear if presence of obstructing debris or purulence in the ear canal
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: Emphasis on avoiding systemic antibiotics due to known adverse events and potential for induced bacterial resistance
- Intentional vagueness: None
- Role of patient (caregiver) preferences: Limited, because there is good evidence that topical antibiotic eardrops are safer than oral antibiotics and have equal efficacy
- Exceptions: Children with complicated otorrhea, cellulitis of adjacent skin, concurrent bacterial infection requiring antibiotics (eg, bacterial sinusitis, group A strep throat), or those children who are immunocompromised
- Policy level: Strong recommendation
- Difference of opinion: None

Supporting Text

The purpose of this statement is to promote topical antibiotic therapy and discourage systemic antibiotics in managing uncomplicated acute TTO. In this context, *acute* refers to otorrhea of less than 4 weeks' duration, and *uncomplicated* refers to TTO that is not accompanied by high fever (38.5°C, 101.3°F), concurrent illness requiring systematic antibiotics (eg, streptococcal pharyngitis, bacterial sinusitis), or cellulitis extending beyond the external ear canal to involve the pinna or adjacent skin.

Otorrhea is the most common sequela of tympanostomy tubes, with a mean incidence of 26% (range, 4%-68%) in observational studies[13] and up to 83% with prospective surveillance.[119] Otorrhea may be further categorized as early postoperative otorrhea (within 4 weeks of tympanostomy tube insertion), delayed otorrhea (4 or more weeks after tympanostomy tube insertion), chronic otorrhea (persisting 3 months or longer), and recurrent otorrhea (3 or more discrete episodes). Most otorrhea is sporadic, brief, and relatively painless, with recurrent otorrhea affecting only about 7% of patients and chronic otorrhea occurring in about 4%.[11]

Acute delayed TTO in young children with tympanostomy tubes is usually a manifestation of AOM and is caused by the typical nasopharyngeal pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.[120,121]



How to Care for Your Child's Ear Tubes

Ear tubes help protect your child from ear infections, middle-ear fluid (liquid behind the eardrum), and the hearing problems that go along with them. Most tubes last about 6 to 18 months, allowing many children time to outgrow their ear problems. Most tubes fall out by themselves. The chance of a tube falling in, instead of out, is very rare. Tubes that do not come out after 3 or more years may need to be removed by your doctor.

Possible Complications of Ear Tubes

Complications of ear tubes are usually minor. Some children develop a white mark or patch on the eardrum which is called sclerosis. It *does not* affect your child's hearing or future chance of ear infections. Some children develop a small depression or pocket in the eardrum at the tube site after it falls out. Again, this does not affect hearing and rarely requires treatment. About 1-2 out of every 100 children will develop a small hole (perforation) of the eardrum after the tube falls out. The hole will often close on its own over time, but if it does not, it can be patched in the operating room.

Ear Tubes and Water Precautions

Some children with ear tubes wear ear plugs when swimming. The ear plugs keep water out of the ear canal and out of the ear tube. However, water does not usually go through the tube during swimming. As a result, ear plugs are not necessary for most children.

Although most children with tubes do not need ear plugs, they may be necessary in the following situations:

- Pain or discomfort when water enters the ear canal
- Discharge or drainage is observed coming out of the ear canal
- Frequent or prolonged episodes of ear discharge

Other times when ear plugs may be needed on an individual basis are:

- Swimming more than 6 feet under water
- Swimming in lakes or non-chlorinated pools
- Dunking head in the bathtub (soapy water has a lower surface tension than plain water)

A variety of soft, fitted ear plugs are available, if needed, as are special neoprene headbands to cover the ears. *Never* use Playdoh or silly putty as an earplug, because it can become trapped in the ear canal and require surgical removal. Once the tube becomes blocked or comes out, ear plugs are not needed if there is no hole in the eardrum.

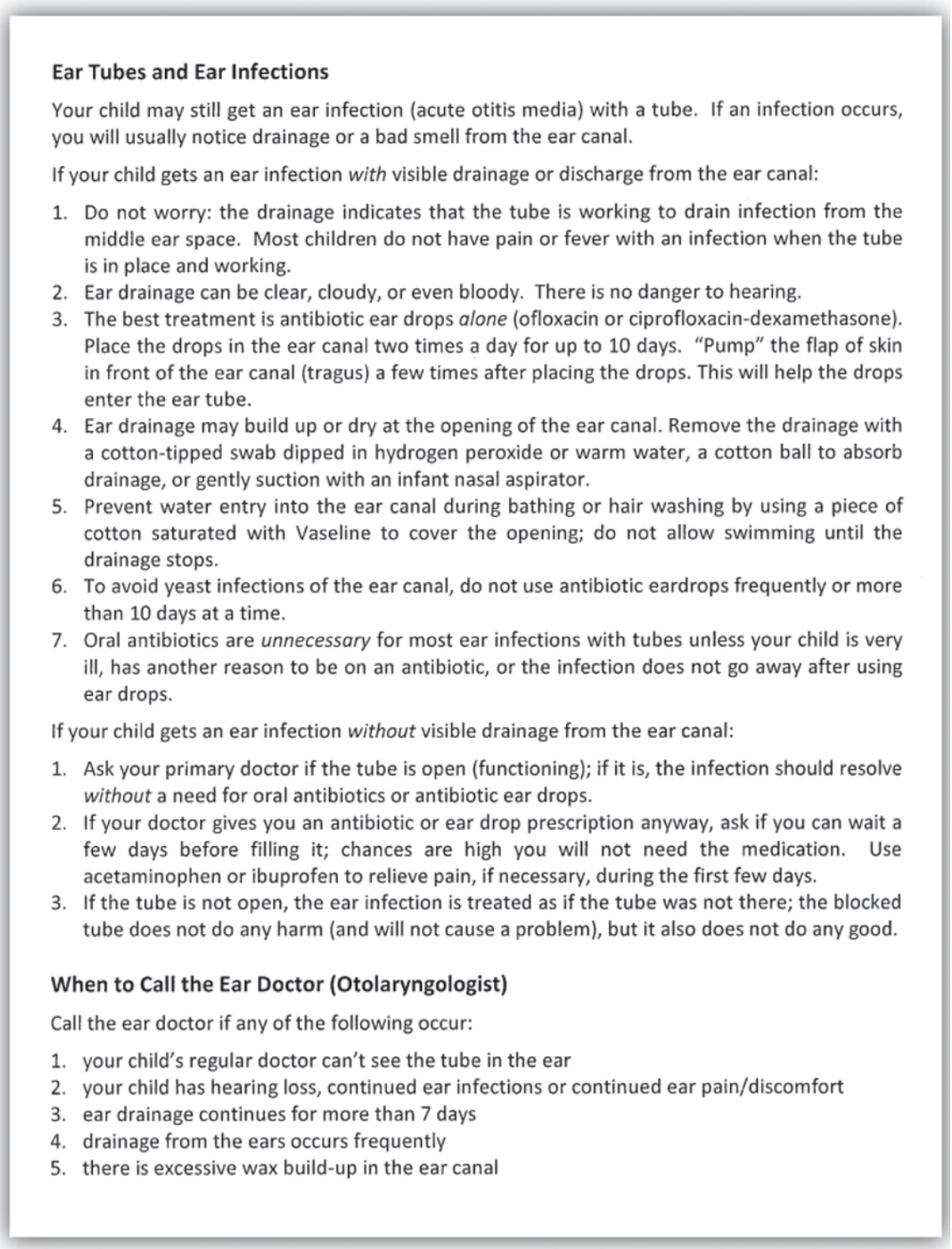
Ear Tube Follow-Up and Aftercare

Routine follow-up with your doctor every 4 to 6 months is important to make sure that your child's tubes are in place and to check for any possible problems. All children need follow-up no matter how well they are doing. Children often feel well even when there is a problem with the tube. Once the tubes fall out, your child should return for a final re-check after 6-12 months so your doctor can check the ears and be sure that fluid has not built up again.

Figure 7. Sample education sheet (page 1) for tympanostomy tube care, which may be modified to suit individual needs.

Conversely, when acute TTO occurs after water exposure (bathing, head dunking, underwater swimming) or in older children, it is often caused by external auditory canal pathogens such as *P aeruginosa* and *S aureus*.[120,121] Viral co-infection is often present when young children present with acute TTO.[122]

Three RCTs have compared topical antibiotic eardrops (ofloxacin, ciprofloxacin, or ciprofloxacin-dexamethasone) to



Ear Tubes and Ear Infections

Your child may still get an ear infection (acute otitis media) with a tube. If an infection occurs, you will usually notice drainage or a bad smell from the ear canal.

If your child gets an ear infection *with* visible drainage or discharge from the ear canal:

1. Do not worry: the drainage indicates that the tube is working to drain infection from the middle ear space. Most children do not have pain or fever with an infection when the tube is in place and working.
2. Ear drainage can be clear, cloudy, or even bloody. There is no danger to hearing.
3. The best treatment is antibiotic ear drops *alone* (ofloxacin or ciprofloxacin-dexamethasone). Place the drops in the ear canal two times a day for up to 10 days. "Pump" the flap of skin in front of the ear canal (tragus) a few times after placing the drops. This will help the drops enter the ear tube.
4. Ear drainage may build up or dry at the opening of the ear canal. Remove the drainage with a cotton-tipped swab dipped in hydrogen peroxide or warm water, a cotton ball to absorb drainage, or gently suction with an infant nasal aspirator.
5. Prevent water entry into the ear canal during bathing or hair washing by using a piece of cotton saturated with Vaseline to cover the opening; do not allow swimming until the drainage stops.
6. To avoid yeast infections of the ear canal, do not use antibiotic eardrops frequently or more than 10 days at a time.
7. Oral antibiotics are *unnecessary* for most ear infections with tubes unless your child is very ill, has another reason to be on an antibiotic, or the infection does not go away after using ear drops.

If your child gets an ear infection *without* visible drainage from the ear canal:

1. Ask your primary doctor if the tube is open (functioning); if it is, the infection should resolve *without* a need for oral antibiotics or antibiotic ear drops.
2. If your doctor gives you an antibiotic or ear drop prescription anyway, ask if you can wait a few days before filling it; chances are high you will not need the medication. Use acetaminophen or ibuprofen to relieve pain, if necessary, during the first few days.
3. If the tube is not open, the ear infection is treated as if the tube was not there; the blocked tube does not do any harm (and will not cause a problem), but it also does not do any good.

When to Call the Ear Doctor (Otolaryngologist)

Call the ear doctor if any of the following occur:

1. your child's regular doctor can't see the tube in the ear
2. your child has hearing loss, continued ear infections or continued ear pain/discomfort
3. ear drainage continues for more than 7 days
4. drainage from the ears occurs frequently
5. there is excessive wax build-up in the ear canal

Figure 8. Sample education sheet (page 2) for tympanostomy tube care, which may be modified to suit individual needs.

systemic oral antibiotics (amoxicillin or amoxicillin-clavulanate) for treating acute TTO in children.[123-125] Superior outcomes with topical therapy were achieved in some studies for clinical cure,[123-125] bacterial eradication,[124] and patient satisfaction.[124] Rates of clinical cure upon completion of therapy after 7 to 10 days ranged from 77% to 96% with topical therapy and from 30% to 67% with systemic antibiotic therapy. Explanations for improved outcomes with topical antibiotic therapy include increased drug concentration at the site of infection and improved coverage of likely pathogens,

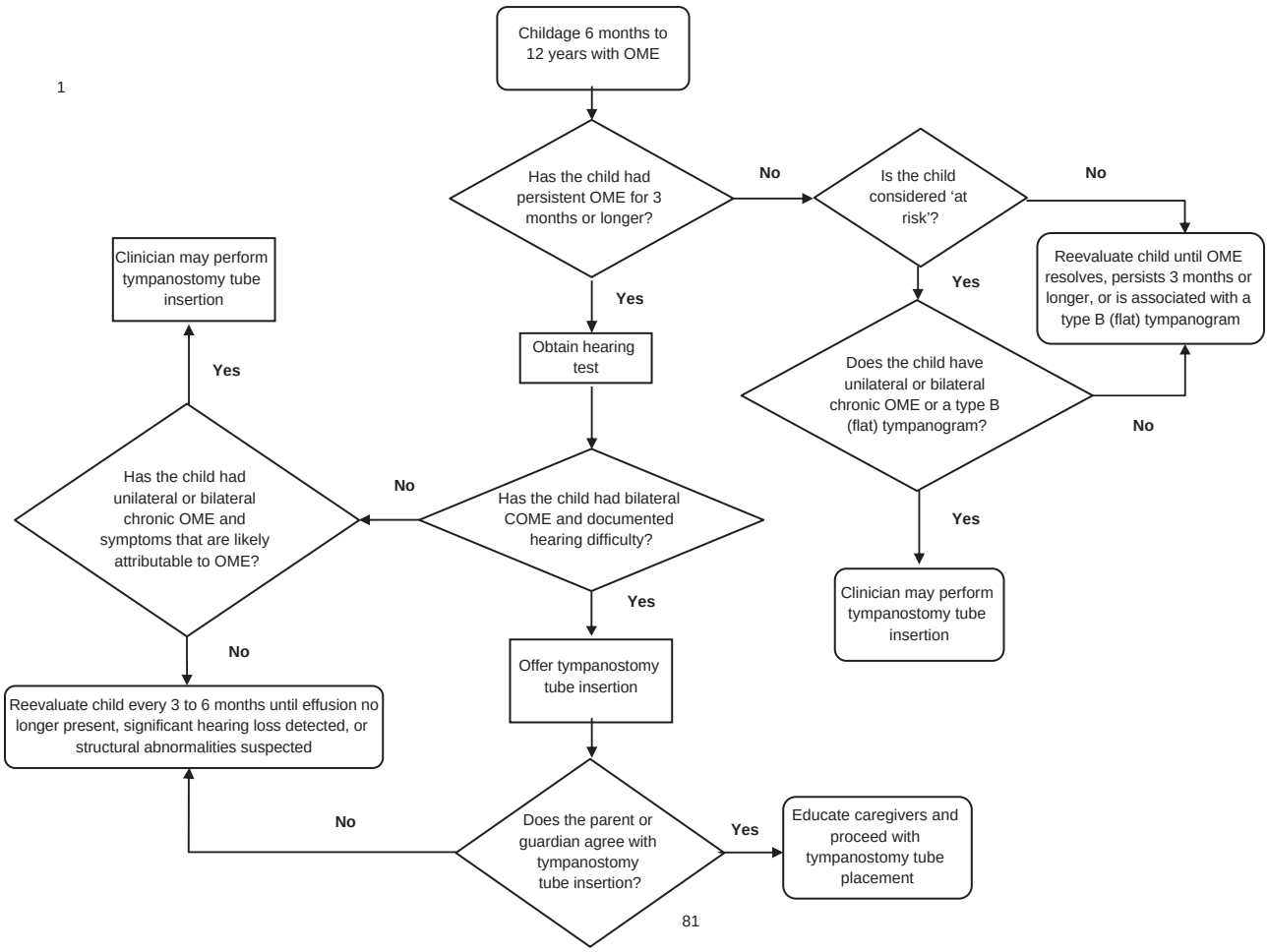


Figure 9. Algorithm of guideline's key action statements for children with otitis media with effusion.

especially *P aeruginosa*. One additional RCT assessed topical antibiotics with and without concurrent oral antibiotics but did not find any advantage to combination therapy.[126]

Topical antibiotic therapy avoids adverse events associated with systemic antibiotics including dermatitis,[123,124] allergic reactions, gastrointestinal upset,[123,124] oral thrush,[124] and increased antibiotic resistance.[121] Only topical drops approved for use with tympanostomy tubes should be prescribed (eg, ofloxacin or ciprofloxacin-dexamethasone) to avoid potential ototoxicity from aminoglycoside-containing eardrops, which are often used to treat acute otitis externa.[127] Otomycosis has not been reported after topical therapy in RCTs of acute TTO,[123-125] but prolonged or frequent use of quinolone eardrops may induce fungal external otitis.[128,129] Caregivers should be advised to limit topical therapy to a single course of no more than 10 days. Last, although systemic quinolone antibiotics are not approved for children aged 14 years or younger, topical drops are approved because they do not have significant systemic absorption.

Acute TTO usually improves rapidly with topical antibiotic therapy, provided that the drops can reach the middle ear space.[18] This is most likely to occur if the ear canal is cleaned of any debris or discharge before administering the drops, by blotting the canal opening or using an infant nasal aspirator to gently suction away any visible secretions.[3] Any dry crust or adherent discharge can be cleaned using a cotton-tipped swab and hydrogen peroxide, which can be used safely when a tympanostomy tube is present.[130] Persistent debris despite these measures can often be removed by suctioning through an open otoscope head or by using a binocular microscope for visualization. In addition, having the child's caregiver "pump" the tragus several times after the drops have been instilled will aid delivery to the middle ear.[116,131] Last, caregivers should be advised to prevent water entry into the ear canal during periods of active TTO.

Systemic antibiotic therapy is not recommended for first-line therapy of uncomplicated, acute TTO but is appropriate, with or without concurrent topical antibiotic therapy, when:

1. Cellulitis of the pinna or adjacent skin is present
2. Concurrent bacterial infection (eg, sinusitis, pneumonia, or streptococcal pharyngitis) is present
3. Signs of severe infection exist (high fever, severe otalgia, toxic appearance)
4. Acute TTO persists, or worsens, despite topical antibiotic therapy

5. Administration of eardrops is not possible because of local discomfort or lack of tolerance by the child
6. A patient has an immune-compromised state
7. Cost considerations prevent access to non-ototoxic topical antibiotic drops

Nearly 4% to 8% of children treated with topical quinolone otic drops require oral antibiotic rescue therapy for persistent symptoms.[123,124] Children who fail topical therapy should be assessed for obstructing debris in the ear canal or in the tympanostomy tube that can impair drug delivery. Culture of persistent drainage from the ear canal may help target future therapy, detecting pathogens such as fungi and MRSA. Most often, however, culture results of persistent TTO despite topical or systemic antibiotic therapy identify organisms (eg, *S aureus*, *S pneumonia*, *P eruginosa*, MRSA) that are susceptible to topical quinolone eardrops.[132] Clinicians should also be aware that sensitivity results from otorrhea culture typically relate to serum drug levels achieved from systemic antibiotic therapy, but the antibiotic concentration at the site of infection with topical drops can be up to 1000-fold higher and will typically overcome this level of resistance.

About 4% of children with tympanostomy tubes develop granulation tissue at the junction of the tympanostomy tube with the tympanic membrane, which can present as persistent, usually painless, otorrhea that is pink or bloody.[11] The treatment of choice is a topical quinolone drop, with or without dexamethasone[133]; systemic antibiotics should not be prescribed.

STATEMENT 12. WATER PRECAUTIONS: Clinicians should *not* encourage routine, prophylactic water precautions (use of earplugs or headbands; avoidance of swimming or water sports) for children with tympanostomy tubes. *Recommendation against based on randomized controlled trials with limitations, observational studies with consistent effects, and a preponderance of benefit over harm.*

Action Statement Profile

- Aggregate evidence quality: Grade B, based on 1 randomized controlled trial and multiple observational studies with consistent effects
- Level of confidence in evidence: High
- Benefits: Allows for normal activity and swimming, reduced anxiety, cost savings
- Risk, harm, cost: Potential for slight increase in otorrhea rates in some children
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: Importance of not restricting or limiting children's water activity in the absence of proven, clinically significant benefits of routine water precautions
- Intentional vagueness: The word *routine* is used to soften the recommendation since individual children may benefit from water precautions in specific situations (eg, lake swimming, deep diving, recurrent otorrhea, head dunking in the bathtub, or otalgia from water entry into the ear canal)
- Role of patient (caregiver) preferences: Significant role in deciding whether or not to use water precautions based on the child's specific needs, comfort level, and tolerance of water exposure.
- Exceptions: Children with tympanostomy tubes and (1) an active episode of otorrhea or (2) recurrent or prolonged otorrhea episodes, as well as those with a history of problems with prior water exposure
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to avoid unnecessary restrictions on child activity because of attempts to theoretically prevent contamination of the middle ear from water exposure during bathing and swimming. These restrictions include avoidance or prohibition of swimming, modification of swimming behaviors (no diving, no swimming in lakes or streams), use of ototopical antibiotics as a prophylactic measure after swimming, and use of earplugs and head bands to limit entry of water into the ear canal. Water precautions have been traditionally advised by most otolaryngologists,[134] but more recent evidence has shown this to be unnecessary.

The most compelling evidence against routine water precautions for tympanostomy tubes comes from a large RCT comparing swimming/bathing with routine ear plug use to swimming/bathing without such plugs over a period of 9 months.[118] Although there were some statistically significant benefits to routine ear plug use, the clinical benefit was trivial: a child would need to wear plugs for 2.8 years, on average, to prevent a single episode of TTO. Routine use of ear plugs slightly reduced the chance of having any otorrhea episodes from 56% to 47%, and the mean incidence of otorrhea episodes decreased from 0.10 per month to 0.07 per month. The authors recommended against routine water precautions for children after tympanostomy tubes because of the large effort involved to obtain an extremely small benefit.

Prior to this RCT, several systematic reviews of observational studies reached similar conclusions. Lee and colleagues[135] examined 5 controlled trials of water precautions after tympanostomy tube placement. The rate of otorrhea was not statistically different between swimmers without water precautions and nonswimmers in any of the trials, and 4 of 5 trials showed favorable trends toward the swimmer groups. With their pooled analysis, these authors concluded that the incidence of otorrhea did not increase for children who swam without water protection.

Carbonell and Ruiz-Garcia[136] reviewed 11 trials and commented on concerns about quality of studies, including inherent inability to blind participants, significant loss of subjects to follow-up, and lack of intention-to-treat analyses. The risk of infection was no different between those children allowed to swim without ear protection and those who did not swim and was also no different between those children instructed to swim with ear plugs or swimming caps and those allowed to

swim without such protection. No difference was found in TTO between those who used ototopical antibiotics after swimming and those who used a swimming cap and/or ear plugs.

While it is appealing to recommend water avoidance or ear plug use for children after tympanostomy tubes, the available clinical evidence in aggregate finds no clinically significant reduction in otorrhea with such practice. Water avoidance is at a minimum a social inconvenience and at worst a detriment to developing water safety skills for young children. It is unlikely that surface swimming or shallow diving creates pressures at the eardrum large enough to allow middle ear penetration.[137] In addition, water contamination in the middle ear does not invariably cause mucosal injury or infection. Ear plugs and other devices can be inconvenient and an unwarranted expense.

Water precautions may be prudent for some children in defined clinical situations. Children with recurrent or persistent otorrhea, particularly those with *P aeruginosa* or *S aureus* in middle ear cultures during such infections, may benefit from measures to keep the middle ear space free from water contamination. In addition, children with risk factors for infection and complications, such as those with immune dysfunction, may benefit from water precautions after placement of tympanostomy tubes. Water precautions may also be useful to avoid exposure to heavily contaminated water (eg, certain lakes), for deep diving, or for children who experience ear discomfort during swimming.

While the evidence against routine water precautions after tympanostomy tubes has solidified, clinical practice has lagged behind. A survey of physicians in the northwestern United States reported 47% of responding otolaryngologists allowed swimming without any water precautions for patients with tympanostomy tubes.[138] Moreover, while 47% of otolaryngologists recommended ear plugs or other barrier devices, 73% of primary care physicians recommended these water precautions. The recommendation for routine water precautions after tympanostomy tubes is unnecessary for the great majority of children. This action statement should be incorporated into the preoperative counseling of families of children before surgery and into the knowledge base of all practitioners who care for children after such surgery.

Implementation Considerations

This clinical practice guideline is published as a supplement to *Otolaryngology—Head and Neck Surgery*, to facilitate reference and distribution. A full-text version of the guideline will also be accessible, free of charge, at http://www.entnet.org. In addition, all AAO-HNSF guidelines are now available via the *Otolaryngology—Head and Neck Surgery* app for smart phones and tablets. The guideline will be presented to AAO-HNS members as a miniseminar at the AAO-HNSF Annual Meeting & OTO EXPO. Existing brochures and publication by the AAO-HNSF will be updated to reflect the guidelines recommendations.

The guideline development group agreed that the recommendations likely to generate the most discussion among clinicians are the 2 statements regarding tympanostomy tube insertion for recurrent AOM. We have distinguished for the first time between recurrent AOM with and without persistent MEE, with tubes indicated only when the effusion persists. This rationale is supported by existing RCTs and evidence about the natural history of recurrent AOM when effusion is absent but is not part of the management paradigm for most practicing clinicians. Education and supporting materials will be required to justify why a child with recurrent AOM but no MEE is unlikely to benefit from tympanostomy tubes, despite parental/caregiver pressure or "traditional" practice.

In the circumstance described, along with other situations in which tympanostomy tubes are not initially recommended, educational materials should be developed to help caregivers and families understand the benefits of watchful waiting instead of immediate tube insertion. This material should include the importance of follow-up visits and monitoring for signs or symptoms related to OME or recurrent AOM that would make the child a potential candidate for tubes and benefit from reassessment by the clinician. Information should also be provided to assist caregivers in detecting child behavior that would suggest a hearing loss is present, which might include the questions for reported hearing difficulty in **Table 7**.

Another implementation concern relates to using topical antibiotic eardrops for acute, uncomplicated TTO. The drops must reach the middle ear space to have the desired benefits, but this can occur only if the drops pass freely through the ear canal and penetrate the tympanostomy tube. An educational video, or other teaching aid, should be developed to illustrate how parents/caregivers should instill the drops (eg, the importance of "pumping" the tragus) and how parents/caregivers or clinicians can clean otorrhea and crusts from the ear canal and adjacent skin, if necessary.

Research Needs

Chronic OME with Hearing Difficulty

- Identify alternatives to formal audiologic assessment, including clinical measures, so that we can identify children with hearing difficulties
- Study of the benefits of postoperative assessment (when, how often, by whom)
- Better understand variations in access to audiometry services, particularly access to pediatric audiometry
- Better understand differential effect on speech and language outcomes based on children's age at intervention for hearing loss
- Study of actual clinical significance of effects of tympanostomy tubes on long-term HLs and the presence of tympanic membrane structural changes

Chronic OME with Symptoms

- Study of differences in effects of OME on children of varying ages
- Study of effects of unilateral versus bilateral OME
- Better understand the effect of unilateral OME on outcomes: vestibular, school performance, behavior, and ear discomfort

- Among children with OME, obtain data on the magnitude and effect size of the long-term hearing deficits well as the presence of tympanic membrane structural changes
- Among children with OME, study of the long-term effects of middle ear fluid on the ear drum in absence of hearing issues—determine the natural history of asymptomatic middle ear fluid

Recurrent AOM without MEE

- Research is needed to develop criteria to identify the subset of recurrent AOM patients, without current effusion, who will develop additional ear infections or long-term effusions in the future

Recurrent AOM with MEE

- Improve documentation of AOM diagnosis and recurrent AOM diagnostic accuracy
- Determine whether the precision with which AOM is diagnosed changes the predicted effectiveness of tympanostomy tubes for recurrent AOM; determine whether studies that demand such diagnostic accuracy and stricter entry criteria show a greater benefit for tympanostomy tubes in children with recurrent AOM
- Characterize QOL for recurrent AOM with tympanostomy tubes versus without tube placement
- Randomized controlled trials to provide effect sizes for benefit of surgery over observation among this patient population; existing studies are deficient in that they have not clearly separated patients with AOM based on presence or absence of fluid at diagnosis

Distinguishing At-Risk Children

- Need better data on the prevalence of at-risk conditions and strategies to identify at-risk children
- Need epidemiological evidence for the prevalence of MEE and sequelae of MEE in at-risk children with conditions other than Down syndrome or cleft palate as well as the acceptability, effectiveness, and consequences of various treatment strategies
- Among at-risk children with OME of medium duration, clarify the role for more aggressive management of ear disease

Tympanostomy Tubes and At-Risk Children

- Better understand the impact of tympanostomy tube placement among children with speech/language delay
- Better understand the indications and outcomes for tympanostomy tube placement in children with Down syndrome or with cleft palate, since existing randomized trials cannot be generalized to these populations; ideally, these studies should be prospective, include long-term follow-up, distinguish children younger than 24 months from older children, and have children treated with tympanostomy tubes matched to control children by age and HLs
- Additional data regarding the efficacy of tubes in preventing sequelae of MEE in at-risk patients
- Compare the efficacy of hearing aids versus tympanostomy tubes for at-risk children with chronic OME and hearing loss
- Determine the role of long-term versus short-term tubes in children with cleft palate or Down syndrome
- Develop educational materials for patients, parents/caregivers, and primary care providers and surgical/medical specialists to raise awareness of the at-risk status of these patients
- Assess whether at-risk children have the same risk profile for surgical and anesthetic complications

Hearing Resting

- Potential implementation hurdles with regard to access to hearing testing and audiometry; need a study to understand possible barriers to audiologic testing
- Determine the role for formal audiologic testing versus a hearing screening test—such as performed by primary care physicians—for follow-up for otherwise low-risk children
- Validation of a clinical proxy for detecting the probable presence of hearing loss when audiology is not available or is unreliable
- Assess the validity of parental/caregiver reports regarding improved hearing following tube placement and whether there is added benefit of objective assessment
- Evidence for best use of postoperative audiologic assessment; determine patient population needs postoperative audiologic assessment: assess all children, only those with preoperative hearing loss, or only those children with parent/caregiver concern regarding persistent hearing loss

Acute TTO

- Determine the impact of tympanostomy tube placement on middle ear bacteriology and whether these changes affect selection of treatment of AOM after tympanostomy tubes
- Determine the ideal duration of topical therapy for posttympanostomy otorrhea
- In the setting of recurrent, persistent, or chronic otorrhea, determine when is it advisable to remove a tube

Water Precautions

- Studies of clinical indicators (swimming locale, host factors such as age, number of AOM episodes, immune status, etc) for more routine recommendation of water precautions after tubes

Perioperative Education

- Research is needed to characterize the effectiveness of various methods of perioperative education about tubes; modalities to include voice, written, video, web-based, other; timing to include preoperative, at

surgery, postoperative; educators to include nurse, surgeon, primary care physician, other

Anesthesia

- Need for more information about the morbidity and mortality of general mask anesthesia for tympanostomy tube placement in children

Disclaimer

The clinical practice guideline is provided for information and educational purposes only. It is not intended as a sole source of guidance in managing children with tympanostomy tubes or being considered for tympanostomy tubes. Rather, it is designed to assist clinicians by providing an evidence-based framework for decision-making strategies. The guideline is not intended to replace clinical judgment or establish a protocol for all individuals with this condition and may not provide the only appropriate approach to diagnosing and managing this program of care. As medical knowledge expands and technology advances, clinical indicators and guidelines are promoted as conditional and provisional proposals of what is recommended under specific conditions but are not absolute. Guidelines are not mandates; these do not and should not purport to be a legal standard of care. The responsible physician, in light of all circumstances presented by the individual patient, must determine the appropriate treatment. Adherence to these guidelines will not ensure successful patient outcomes in every situation. The AAO-HNS, Inc emphasizes that these clinical guidelines should not be deemed to include all proper treatment decisions or methods of care or to exclude other treatment decisions or methods of care reasonably directed to obtaining the same results.

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Age-Dependent Cost-Utility of Pediatric Cochlear Implantation

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Objectives: Cochlear implantation (CI) has become the mainstay of treatment for children with severe-to-profound sensorineural hearing loss (SNHL). Yet, despite mounting evidence of the clinical benefits of early implantation, little data are available on the long-term societal benefits and comparative effectiveness of this procedure across various ages of implantation—a choice parameter for parents and clinicians with high prognostic value for clinical outcome. As such, the aim of the present study is to evaluate a model of the consequences of the timing of this intervention from a societal economic perspective. Average cost utility of pediatric CI by age at intervention will be analyzed.

Design: Prospective, longitudinal assessment of health utility and educational placement outcomes in 175 children recruited from six U.S. centers between November 2002 and December 2004, who had severe-to-profound SNHL onset within 1 year of age, underwent CI before 5 years of age, and had up to 6 years of postimplant follow-up that ended in November 2008 to December 2011. Costs of care were collected retrospectively and stratified by preoperative, operative, and postoperative expenditures. Incremental costs and benefits of implantation were compared among the three age groups and relative to a nonimplantation baseline.

Results: Children implanted at <18 months of age gained an average of 10.7 quality-adjusted life years (QALYs) over their projected lifetime as compared with 9.0 and 8.4 QALYs for those implanted between 18 and 36 months and at >36 months of age, respectively. Medical and surgical complication rates were not significantly different among the three age groups. In addition, mean lifetime costs of implantation were similar among the three groups, at approximately $2000/child/year (77.5-year life expectancy), yielding costs of $14,996, $17,849, and $19,173 per QALY for the youngest, middle, and oldest implant age groups, respectively. Full mainstream classroom integration rate was significantly higher in the youngest group at 81% as compared with 57 and 63% for the middle and oldest groups, respectively ($p < 0.05$) after 6 years of follow-up. After incorporating lifetime educational cost savings, CI led to net societal savings of $31,252, $10,217, and $6,680 for the youngest, middle, and oldest groups at CI, respectively, over the child's projected lifetime.

Conclusions: Even without considering improvements in lifetime earnings, the overall cost-utility results indicate highly favorable ratios. Early (<18 months) intervention with CI was associated with greater and longer quality-of-life improvements, similar direct costs of implantation, and economically valuable improved classroom placement, without a greater incidence of medical and surgical complications when compared to CI at older ages.

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INTRODUCTION

Hearing loss is the most common sensory deprivation in developed countries, with severe-to-profound sensorineural hearing loss (SNHL) affecting 1 in 1000 children born in the United States (Smith et al. 2005). The lifetime cost of onset of deafness before a child acquires speech and language capabilities (approximately 3 years of age) exceeds $1 million per child and currently affects as many as 60,000 children (Mohr et al. 2000; Blanchfield et al. 2001). Cochlear implantation (CI) has been shown to be highly effective in treating deafness, with significantly improved spoken language and auditory outcomes observed at earlier ages of implantation (McConkey Robbins et al. 2004; Svirsky et al. 2004; Nicholas & Geers 2007; Holt & Svirsky 2008; Niparko et al. 2010). An economic evaluation of CI provides an opportunity to model the societal cost-utility of an early intervention for a significant childhood disability. The purpose of a cost-utility analysis is to determine the ratio between the cost of a health-related intervention and the benefits, expressed in quality-adjusted life years (QALYs), which allows for health states that are considered less preferable to full health to be given quantitative values and for those values to vary over time.

Despite increasing evidence in support of early implantation and successful implementation of universal newborn hearing screening programs, implantation at younger ages continues to face considerable resistance. Barriers to early implantation include delayed identification of hearing loss, slow assessment and referrals from interventionists, parental delays, concerns regarding complications with early surgical intervention, lack of health insurance reimbursement for the substantial travel costs, and lost earnings due to CI-related medical visits, which may present a considerable burden for low-income families (Moeller 2000; Lester et al. 2011).

As a result, families and healthcare professionals may devote a substantial amount of time in a developmentally critical period to trials of hearing aids and less expensive and intensive alternatives to CI. Concerns surrounding early CI would be reduced if the perceptual, developmental, and lifetime benefits of early implantation were shown to be substantial.

Previous investigations have shown CI to be highly cost effective in the overall pediatric population in the United States

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but were limited in population size, duration of follow-up, and generalizability of the model (Cheng et al. 2000; Bichey & Miyamoto 2008). In one of the most comprehensive analyses of pediatric CI, a study by the Peninsula Technology Assessment Group (PenTAG) in the United Kingdom identified lack of longer-term health-utility data and analyses of potentially confounding factors such as age at intervention as major limitations to cost-utility analyses of pediatric CI (Bond et al. 2009). Building on these findings, the present study aims to evaluate the comparative societal benefits of pediatric CI by age at implantation through the first cost-utility analysis of pediatric CI using data from a multicenter, longitudinal study in the United States. The effects of long-term postoperative complications, differences in costs of care, and differential educational savings at the three different cohort ages of implantation are analyzed.

MATERIALS AND METHODS

Study Design and Study Population

A detailed discussion of the inclusion and exclusion criteria and the overall study design can be found in a previous publication (Fink et al. 2007). The Childhood Development after Cochlear Implantation (CDaCI) study is a multicenter, prospective cohort study aimed at measuring the outcomes of early childhood CI in the United States. Children with severe-to-profound SNHL were recruited at six academic medical centers, including The Johns Hopkins University, University of Miami, University of Michigan, University of Texas Southwestern, House Research Institute, and University of North Carolina. CI participants in the study had to be under 5 years of age at baseline, be pre- or postlingually deaf (onset of deafness before or after onset of speech and language acquisition), and have developmental scores on the Bayley Scales of Infant Development Mental Scale or Motor Scale (BSID II) of at least 70. A total of 188 children with severe-to-profound SNHL were enrolled in the study. The study was approved by each center's institutional review board, and written informed consent was obtained from the parents of each enrolled child.

For this cost-utility study, 175 cochlear implanted children with up to 6 years of postimplant follow-up, which concluded in November 2008 to December 2011, were grouped in three cohorts corresponding to their age at implantation: younger than 18 months, 18 to 36 months, and older than 36 months of age at implantation. Given that a 3- to 6-month hearing aid trial is required as part of the cochlear implant candidacy evaluation process (Zwolan et al. 1998), 13 cochlear implanted children who had an onset of hearing loss at an age more than 12 months were excluded to minimize selection bias into the three implantation age categories.

This study includes both unilaterally and bilaterally implanted children. As the decision for bilateral implantation was made by the family on an individual basis, the effect of bilateral implantation was factored out in both the costs and the benefits calculations. The health-utility effect of the second implantation was controlled by creating a flag variable within the data set, which was "switched on" whenever a child received a second implantation. This allowed for the isolation of all health-utility gains that were strictly associated with the second implantation. Removing the costs associated with the second implantation was more straightforward because the costs were developed in an itemized "ingredients based" approach.

Perspective and Time Horizon

A societal perspective was adopted for this analysis, in that both direct and indirect costs were examined. All costs, as well as QALYs related to CI were considered over an expected 77.5-year average lifetime (74.9 years for men and 79.9 years for women) of children born in the United States (Expectation of Life at Birth, and Projections 2012). All costs and outcomes were discounted annually at 3%(Gold et al. 1996).

Measurement of Costs

Costs and reimbursements, in U.S. dollars, were collected retrospectively at the individual patient level from the study center with largest number of participants, Johns Hopkins University (JHU). These were further stratified into direct medical costs, including preoperative, operative, and postoperative medical costs; and indirect costs, including lost wages, educational savings, and transportation costs incurred by the families. Full access to cost data from other study centers was prohibited by U.S. antitrust regulations that prevent sharing of medical pricing information among individual hospitals. Instead, costs from other centers were based on clinical care models provided by these institutions, which were priced out according to JHU costs and were incorporated as ranges in sensitivity analyses. In addition, a cost-adjustment factor (see the Appendix, Supplemental Digital Content 1, http://links.lww.com/EANDH/A92), determined by differences between JHU and the national average in payer mix and geographically adjusted healthcare utilization rates, was calculated using data provided by University HealthSystem Consortium (UHC), an alliance of 116 academic centers and 272 of their affiliated hospitals representing approximately 90% of the U.S. nonprofit academic medical centers, to adjust costs collected at JHU into more generalizable ones that reflect the payer mix and healthcare utilization rate of the greater part of the United States (University HealthSystem Consortium 2012). All six of the CDaCI study centers are nonprofit academic medical centers.

The costs used in this study represent direct hospital and physician charges for procedures and medical visits associated with CI and do not represent true economic (opportunity) costs. The latter would be obtained by determining the value of the next best use of each resource that is used to treat the children who receive CI and each resource that is saved as a result of CI rather than not having an implantation. Given the proven clinical superiority of CI over hearing aids in severe-to-profoundly deaf children, enrolling a hearing aided control group for the purposes of the present study would not be ethically justified. As such, direct cost data were not available for hearing aided nonimplanted children. The exclusion of such data yields considerably less favorable cost-utility ratios (as charges are greater than costs) than would be present when considering true economic costs, which are not truly zero for the nonimplantation group.

Educational costs were calculated based on classroom placement, which was tracked through annual parental questionnaires with classroom placement options including: (1) school for the deaf, (2) self-contained program within a mainstream school, (3) partially mainstream classroom placement with at least 50% of children having hearing impairment, and (4) a fully mainstream placement with mostly normal hearing children.

For the youngest cohort, with 6 years of follow-up data, classroom placement distribution was available through second grade. For the middle and oldest cohorts, classroom placement data were tracked through third and fourth grades, respectively. It was noted that beyond 4 years postimplantation, there tended to be little further transition in classroom placement, and therefore, for the remaining school years, an assumption was made that educational placement would hold steady at the last observed distributions. Composite educational costs were calculated based on the weighted proportion of children in each type of classroom setting and the associated costs for these placements as provided by the U.S. Department of Education. Costs were calculated through second, third, and fourth grades for the young, middle, and oldest age cohorts, respectively. Similarly, the educational costs for severe-to-profoundly deaf, nonimplanted children were obtained using data on classroom placement from the Gallaudet Research Institute's (GRI) Annual Survey of Deaf and Hard of Hearing Children and Youth (Gallaudet Research Institute 2009) and applying similar composite educational cost calculations. The GRI survey is conducted annually and offers a representative sample of hearing-impaired children and adolescents in the United States across all levels of hearing impairment. GRI classroom placement data were analyzed for 1517 severe-to-profoundly deaf, nonimplanted, school-aged children, who comprise a subset of the overall population tracked by the GRI annual survey. Educational savings for implanted children were then calculated as the difference between the educational costs for cochlear implanted children in the present study and those calculated for the nonimplanted children derived from the GRI annual survey. All educational costs or savings were discounted annually at 3%.

Average expected cost of complications was stratified by costs of minor (nonsurgical) complications, costs of revisions, and costs of reimplantations, as calculated using prevalence of these events (complication rate) in the CDaCI cohort over 6 years of follow-up. When more than 1 revision/reimplantation event took place, costs for the first and second corrective surgeries were added in determining the average cost of corrective surgery for the overall cohort.

Measurement of Health Utility

Parent-proxy questionnaires were used at baseline and also at yearly postimplantation intervals to assess the health utility of cochlear implanted children in the CDaCI study. The measurement instrument in this study uses questions from both the Health Utility Index (Horsman et al. 2003) Mark II (HUI2) and the Health Utility Index Mark III (HUI3) surveys. These surveys provide measurements of general health status and health-related quality of life stratified by hearing, speech, vision, emotion, pain, ambulation, dexterity, cognition, and self-care domains of health. Respondents' overall health states were calculated using the prescribed methodology provided for the HUI3 instrument. Although not specifically designed for use in children under 5 years of age, parent-proxy questionnaires for HUI2 and HUI3 instruments have been used widely in younger children both in CI and non-CI literature (Barr et al. 1999; Insinga et al. 2002; Oostenbrink et al. 2002; Brisson & Edmunds 2003; Barton et al. 2006b).

Analysis of the repeated measures of health-utility scores at baseline and at 12, 24, 36, 48, 60, and 72 months postimplantation was conducted. Generalized estimating equations (GEE) was used to estimate the parameters of a generalized linear model while allowing for correlation between observations. GEE can be used despite the unknown structure of correlation between measures of health utility at different times since implantation. Children implanted between 18 and 36 months of age were used as the reference group in estimating HUI scores at baseline and at each subsequent follow-up period. This allowed for adjustment for baseline differences in health utilities and projected health utility gains stratified by age at implantation over a 77.5-year average life expectancy in the United States ("Expectation of Life at Birth, and Projections," 2012), taking baseline individual ages and gender into account. Change in QALYs for the three cochlear implanted groups was then calculated by annually compounding the difference in health utility between each of the three cochlear implanted groups and the nonimplanted baseline across the projected life expectancy of each of the three implanted groups.

Cost-Utility Ratios and Sensitivity Analysis

All costs were reported in 2011 U.S. dollars. Base case results were calculated for each age group at implantation, using an average of 4 hours of lost wages based on an average 2-hr hospital stay and a 2-hr round trip travelling time as observed at the JHU study center, a once-a-year lifetime frequency of audiology appointments past study follow-up period, with and without consideration of educational savings, and the partial absorption of the device cost by the manufacturer warranty in instances of reimplantation due to device failures. One-way sensitivity analyses were performed varying these underlying assumptions, with sensitivity analysis parameters centered around those used in the base case.

Statistical Analysis

Baseline demographic, socioeconomic, and medical history factors, as defined in Table 1, were characterized as means and standard deviations for continuous variables and as frequency distributions and percent of total for categorical variables. Baseline comparisons stratified by age at implantation were tested using analysis of variance for continuous variables and χ^2 for categorical variables. Classroom placement and complication rates were compared across age groups at implantation, using analysis of variance.

Health-utility gains from baseline to 72 months, at yearly intervals, after CI were modeled using the results of GEE analysis, allowing for consideration of within-subject correlation over time in the repeated measures. Independent variables included dichotomous indicators for age group at implantation, dichotomous indicators for time of follow-up (a value of 0 or 1 was assigned to indicate whether a given observation occurred at a particular time of follow-up), interaction terms between age group and time of follow-up, and an indicator for bilateral implantation.

A decision tree (Supplementary Fig. 1, Supplementary Digital Content 2, http://links.lww.com/EANDH/A93) was used to compare the costs and outcomes of CI for the three age cohorts. Subsequent to the decision on the age of implantation, each child is faced with a chance node of a CI procedure that results in: no complications, minor complications, revision surgery, or reimplantation surgery. Revision surgeries include surgical procedures that are required to ensure correct functioning of the cochlear device without replacing the initial implanted device. Reimplantations most often result from device failures,

TABLE 1. Characteristics of cohorts

	Cochlear Implantation		
	<18 mos (n = 60)	18–36 mos (n = 71)	>36 mos (n = 44)
Characteristics, No.			
Age at implantation, mos, mean (SD)	13.2 (2.4)	26.4 (5.7)	47.0 (7.9)
Duration of deafness, mos, mean (SD)†	13.0 (2.8)	25.4 (6.8)	45.2 (8.3)
Female (%)†	25 (42)	36 (51)	31 (70)
Hispanic (%)	7 (12)	18 (25)	11 (25)
Congenital SNHL (%)†	51 (85)	34 (48)	20 (45)
Four-tone hearing threshold average, dB, better ear†	107.5 (16.3)	106.7 (15.3)	99.6 (16.0)
Race, No. (%)			
White	49 (82)	48 (68)	34 (77)
Black	4 (7)	9 (13)	2 (5)
Asian	2 (3)	4 (6)	3 (7)
Other	5 (8)	10 (14)	5 (11)
Maternal education, No. (%)			
<8th grade	0 (0)	0 (0)	1 (2)
Some high school	1 (2)	5 (7)	5 (11)
Graduated high school	11 (18)	11 (15)	3 (7)
Some college	13 (22)	23 (32)	14 (32)
Completed college	35 (58)	32 (45)	21 (48)
Household income, No. (%)‡			
<$15,000	1 (2)	8 (11)	4 (9)
$15,000–$29,000	7 (12)	9 (13)	5 (11)
$30,000–$49,999	8 (13)	20 (28)	10 (23)
$50,000–$74,999	14 (23)	8 (11)	7 (16)
$75,000–$99,999	12 (20)	10 (14)	3 (7)
>$100,000	11 (18)	10 (14)	9 (20)
Income <$50,000†	16 (27)	37 (52)	19 (43)
HUI scores,* mean (SD)			
Before implantation†	0.26 (0.14)	0.31(0.17)	0.37 (0.21)
Six years after implantation	0.76 (0.14)	0.72 (0.20)	0.71 (0.17)
Change†	0.51 (0.21)	0.41 (0.24)	0.34 (0.24)
Cognitive status score, mean (SD)			
Bayley PDI (<2y)†	96.2 (17.4)	95.0 (18.9)	76.2 (19.0)
Leiter-R Brief IQ (>2y)	113.5 (15.8)	94.8 (16.0)	106.2 (21.0)
Combined**	100.4 (18.1)	95.6 (20.1)	91.4 (25.5)

Bayley PDI, Bayley Psychomotor Development Index; HUI, Health Utilities Index; Leiter-R Brief, Leiter International Performance Scale-Revised; SNHL, sensorineural hearing loss.
**Health Utilities Index was measured using Mark III transforms—unadjusted scores (see Fig. 1A).*
†Statistically significant differences among children undergoing cochlear implantation at <18 months, 18 to 36 months, and >36 months of age (P< 0.05).
‡Although household income was not significantly different among implant age groups using the six aforementioned family income categories, grouping by family income of less than $50,000 results in significantly lower frequencies among families of children implanted at younger ages (p = 0.012).
***Cognitive status measured by the Bayley Physical Developmental Index for children under 24 months of age and by Leiter Brief Intelligent Quotient Composite Score for children 24 months of age or older.*

requiring the surgical team to replace the device in the same or opposite ear. The probabilities and costs of these events were based on clinical outcomes from the CDaCI study.

Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) was used for decision tree modeling, and STATA version 12 (StataCorp, College Station, TX) was used for all other analyses.

RESULTS

Study Population

A total of 175 children were followed for 72 months after CI. Of these, 60 children were implanted before 18 months, 71 between 18 and 36 months, and 44 after 36 months of age, with a mean age at implantation of 13.2, 26.4, and 47.0 months, respectively. Table 1 shows the baseline characteristics of the study population stratified by age of implantation. The three groups differed by gender, age at onset of deafness, duration of deafness, four-tone hearing threshold average (PTA)—a measure of preimplantation residual hearing, socioeconomic status, baseline HUI scores, and baseline Bayley psychomotor development index, but were not significantly different by race, maternal education level, and other measures of baseline IQ.

Measurement of Health Utility

Children implanted at <18 months of age gained an average unadjusted health-utility improvement of 0.51 points in the first 6 years after implantation, compared with 0.41 points for the 18- to 36-month group, and 0.34 points for the >36-month age group at implantation ($p < 0.0001$). Adjusting for differences in baseline HUI3 scores and controlling for rate of bilateral implantation using the GEE model led to a 0.49 point health-utility gain for the youngest group, a 0.44 point gain for the middle group, and a 0.43 point gain for the oldest group, which resulted in lifetime projected QALY gains of 10.7, 9.0, and 8.4 QALYs, respectively (Fig. 1, Supplemental Digital Content 2,

http://links.lww.com/EANDH/A93; and Table 1, Supplemental Digital Content 3, http://links.lww.com/EANDH/A94).

Due to the absence of a specific hearing aided control group in the CDaCI study, these utility gains were calculated relative to a nonimplanted control constructed from the baseline HUI scores of the three cochlear implanted groups as estimated by the GEE model (0.25, 0.30, and 0.38 for the youngest, middle, and oldest groups, respectively). This approach was used for two reasons: (1) this crossover construct helps reduce potential biases that may be present if the nonimplanted data were instead derived from outside literature, and (2) allows for short-run consideration of effect of maturation on health utilities of nonimplanted children. A weakness of this approach arises from the confounding effect of differences in baseline levels of hearing impairment across the three cochlear implanted groups, a variable associated with HUI scores(Barton et al. 2006a). Barton et al. (2006) demonstrated that higher HUI scores were associated with a more favorable level of hearing loss in nonimplanted children. As a result, one would expect the oldest group at CI (group with lowest 4-tone hearing threshold average at baseline) to attain highest preimplantation HUI scores, as was indeed the case in the present study. The incorporation of this group would, therefore, conservatively bias the health-utility gains identified in the present analysis, particularly for the youngest and middle groups, making the results of the study less favorable.

Measurement of Costs

Classroom placement by 7 years of age (last year of follow-up for youngest cohort) differed significantly among the three cohorts, with the youngest having a higher rate of mainstream integration (81%) and a lower rate of school for the deaf attendance (5%) than the two older implantation groups (55% and 50% mainstream integration, respectively) (Table 2 and Fig. 2). Follow-up of the older two cohorts for 6 years allowed for an assessment of their educational placement at ages older than 7 years, with full mainstream integration increasing to 57% and 56% for the middle and oldest groups, respectively by 8 years of age, and to 63% for the oldest group by 9 years of age. As a result, at 6 years of implant use, the youngest group had a significantly higher rate of mainstream integration at 81% as compared with 57% and 63% for the middle and oldest age groups, respectively ($p < 0.05$). Moreover, GRI-derived classroom placement for severe-to-profoundly deaf hearing aided nonimplanted children had lower rates of mainstream integration than all implant cohort groups (12% for full and 14% for partial mainstream), a higher proportion of self-contained placement (28%), and a 46% attendance at schools for the deaf (Gallaudet Research Institute 2009). With these weights, the mean projected educational costs for severe-to-profoundly deaf hearing aided children were $293,070 from first through 12th grade. This represented mean educational cost savings of $191,705, $170,805, and $167,736 per child for the youngest, middle, and oldest implanted groups, respectively, over the same time period.

Direct medical costs were calculated on an individual patient basis for the entire duration of the CDaCI study, with mean costs presented in Table 3. Total medical cost differences between the three age groups were driven by differences in mean reimplantation rates, which were 5.9%, 7.5%, and 11.5% for the youngest, middle, and oldest groups, respectively ($p = 0.40$) across the 6 years of follow-up (see Table 4). However, none of these differences were significant. Revision surgery rates were 2.4%, 3.2%, and 3.9% for the youngest, middle, and oldest groups, respectively; again, none of these differences reached significance ($p = 0.95$). As a result, total medical and surgical complication rates (see Table 4), which also included minor complications, were not statistically different among the three cohorts ($p = 0.59$). The resulting total lifetime medical costs were $160,453 for the youngest group, $160,638 for the middle group, and $161,056 for the oldest group (Table 5). Incorporating the significantly different educational cost savings from first through 12th grade across the three groups resulted in net lifetime societal savings of $31,252, $10,217, and $6,680 for the youngest, middle, and oldest cohorts, respectively. That is, early CI is estimated to yield more than $20,000 per child lifetime societal savings over implantation at older ages.

Cost-Utility Ratios and Sensitivity Analyses

Driven by these findings, CI for the youngest subgroup dominated the other two alternatives in the base case and sensitivity analyses (Table 5). The base case analysis yielded $14,996/QALY gained when compared with nonimplantation alternatives for the youngest group, $17,849/QALY for the middle group, and $19,173/QALY for the oldest age group at implantation. When incorporating lifetime educational cost savings, these net costs become negative (reflecting net societal savings from pediatric CI), preventing the use of cost-utility ratios as outcome measures.

Sensitivity analyses were conducted by varying underlying assumptions of the model. By increasing the lifetime audiology appointments to twice a year, cost per QALY increases slightly to a range of $15,610 to $20,531. In addition, assuming four audiology visits per year increases the $/QALY ratio to $18,312 to $24,071. Relaxing the assumption that a reimplantation is partially covered by manufacturer's warranty increased the cost of reimplantation to be equal to that of the initial surgery and yielded a cost-utility ratio of $14,426 to $19,194 per QALY gained. Last, sensitivity analyses were performed on health-utility attainment of the constructed nonimplanted control group. These included comparing each implanted group only with their own preimplantation baseline on one extreme and allowing for more significant effects of maturation on health utility in the nonimplanted group on the other extreme. In the latter scenario, a new nonimplanted baseline was modeled after the HUI3 attainment of a group of hearing aided adults reported by Barton et al. (2005).

The study reported an average HUI3 health-utility score of 0.56 for a group of patients with a mean age of 69.5 years and four-tone hearing threshold average of 39 dB (better ear). Despite the considerably lower average level of hearing loss in the study by Barton et al. (2005) than in the present study, a conservative assumption was made to linearly model a health-utility increase from the last known HUI3 score of the nonimplanted group (0.38 at 46 months of age) to an HUI3 score of 0.56 by 21 years of age, after which the health utility of the nonimplanted control does not continue to grow. This scenario yielded cost-utility ratios of $23,254, $30,892, and $35,012 for the youngest, middle, and oldest groups, respectively. Of note, cost-utility ratios for the youngest age group consistently outperformed those for the older cohorts across all the sensitivity analyses. Moreover, even in the most conservative scenarios, these ratios did not approach the $50,000/QALY threshold for cost-effective procedures used in the United States (Owens 1998).

TABLE 2. Educational placement and cost savings

	Classroom Placement*				Difference From Nonimplanted Cohort				Costs and Savings†	
Age Group	Full Mainstream (%)	Partial Mainstream (%)	Self-Contained (%)	School for Deaf (%)	Full Mainstream (%)	Partial Mainstream (%)	Self-Contained (%)	School for Deaf (%)	Grade 1–12 Educational Costs ($)	Educational Cost Savings ($)
<18 mos (n = 42)	81	14	0	5	69	0	–28	–41	101,365	**191,705**
18–36 mos (n = 53)	55	28	2	15	43	14	–26	–21	122,215	**170,805**
36+ mos (n = 32)	50	34	0	16	38	20	–28	–30	125,334	**167,736**
Not implanted‡	12	14	28	46	0	0	0	0	293,070	**0**

*Second-grade classroom placement (average age 7 yrs for each of the groups) is reported in this table. Mean classroom placement was statistically different between the three age groups; p = 0.04. A portion of the children did not report classroom placement in each age group (18 children for youngest group, 18 for middle group, and 12 for oldest group at implantation).
†On the basis of costs provided by the U.S. Department of Education, inflation adjusted to 2011 U.S. dollars: $7, 042 for full mainstream, $8, 540 for partial mainstream, $20,300 for self-contained in a regular school, and $39,480 for school for deaf placement. Educational costs and savings were calculated using differences between annually reported classroom placement for each of the three age groups at implantation during the Childhood Development after Cochlear Implantation study follow-up period. Costs were discounted annually at a 3% rate for entire duration of secondary schooling.
‡Classroom placement of severe-to-profoundly deaf, nonimplanted children obtained from data provided by Gallaudet Research Institute.

DISCUSSION

These data show that even without considering improvements in lifetime earnings, pediatric CI remains cost effective in any age group (<$50,000/QALY; Owens 1998). The $50,000/QALY threshold also translates to approximately one times the per capita U.S. gross domestic product, which is noted by the World Health Organization to be highly cost effective (World Health Organization 2012). Early implantation (<18 months) consistently dominated all quality of life and societal cost outcomes, with equal or lower rates of postoperative complications when compared with 18 to 36 months and >36 months of age at implantation. Although the middle cohort consistently outperformed the oldest age group at implantation, the differences in outcome metrics between these two groups were marginal and significantly lower than the difference between the middle to youngest age group at implantation. This suggests the presence of a critical age threshold below 18 months of age, after which benefits from CI are significantly reduced and are not regained with longer-term experience with the implant.

Barriers to early implantation are, in part, due to concerns of heightened risk in implanting young children. The present analysis demonstrates that, when performed at academic medical institutions with large, established CI programs, early implantation is as safe as implantation at later ages, with statistically equivalent, though lower rates of revision and reimplantation surgeries. Across all age groups at intervention, implanted children had no mortalities or life-threatening postoperative complications; encountered complications were minor, but there were several that required reoperation. These findings are in agreement with recent literature demonstrating the safety of CI in children under 12 months of age (James & Papsin 2004; Colletti et al. 2005; Miyamoto et al. 2005; Dettman et al. 2007; Valencia et al. 2008). In contrast to the present analysis, these studies reported lower or no complications after implantation but were limited to a smaller and less representative sample (less than 25 children, all from 1 study center; James & Papsin 2004; Colletti et al. 2005; Miyamoto et al. 2005; Valencia et al. 2008) and shorter follow-up duration (Dettman et al. 2007). Previous studies using larger patient populations (all pediatric cochlear implant recipients) and longer duration of follow-up reported similar rates of complications to those observed in the present analysis (Kempf et al. 1999; Bhatia et al. 2004; Kandogan et al. 2005).

Another barrier to early implantation relates to potential uncertainty surrounding the initial diagnosis and treatment

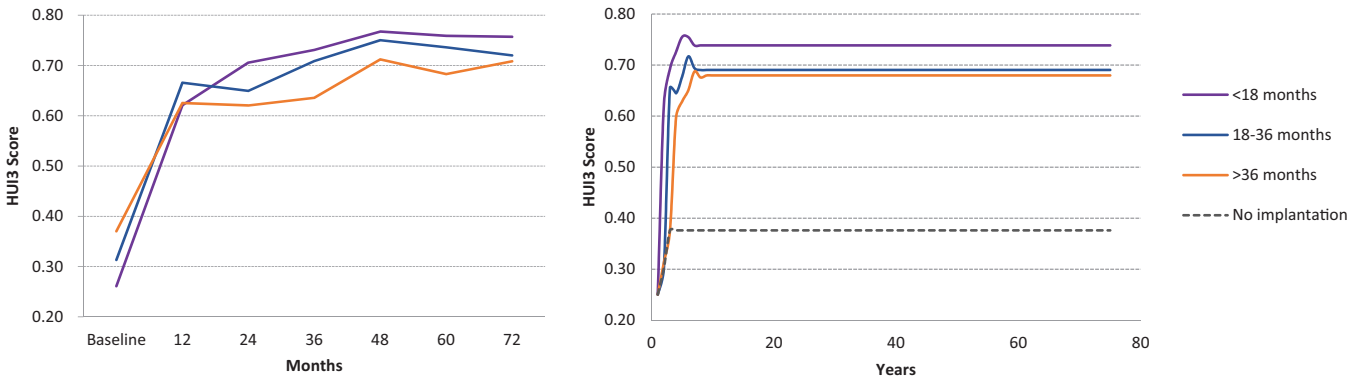

Fig. 1. Health-utility gains after cochlear implantation by age at baseline. Left panel shows unadjusted HUI Mark III gains in the first 6 years after implantation as observed in the Childhood Development after Cochlear Implantation study. Right panel includes lifetime health-utility projections after adjusting for differences in baseline HUI scores and rates of bilateral implantation between the three age groups. Health-utility differences and gains from baseline were significantly different among all three age groups at implantation through 6 years of follow-up on generalized estimating equations analysis ($p < 0.05$). Average projected lifetime quality-adjusted life years gained: 10.7 for <18 month group, 8.9 for 18–36 month group, and 8.2 for >36 month group. HUI, Health Utilities Index.

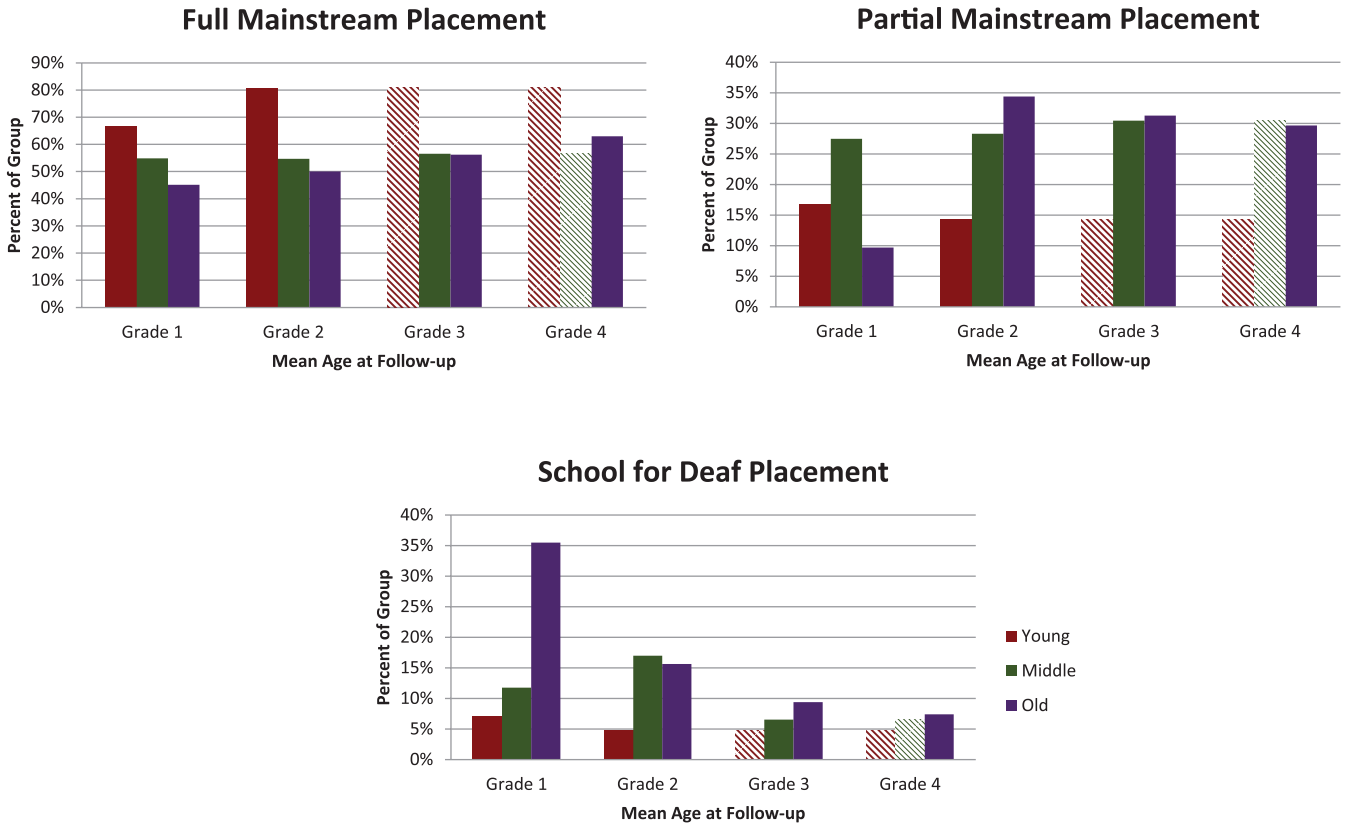

Fig. 2. Classroom placement after cochlear implantation by primary school grade level and age at implantation. Top left panel shows full mainstream placement, top right panel shows partial mainstream placement, and bottom panel shows school for deaf placement. Young, middle, and old correspond to <18 months, 18–36 months, and >36 months of age at implantation, respectively. Mean classroom placement was significantly different among the three groups ($p < 0.05$) in grades 1 and 2. All groups were followed for 72 months after implantation—striped bars are projections based on last known observation for that age group. Self-contained placement omitted because of small subgroup size.

follow-up (White et al. 2010). Though newborn hearing screening (NBHS) programs have been widely adopted in the United States since the early 1990s, increasing the detection of congenital hearing loss in infants from 3% to 94% over the last two decades, a nearly 2% false-positive rate (Clemens et al. 2000) requires further audiologic testing to rule out transient hearing loss and artifact-associated test errors, and to determine the etiology of hearing loss in those with confirmed hearing impairment. Despite the importance of early intervention, significant delays continue to exist in patient follow-up for confirmatory testing and in subsequent treatment for prelingual deafness (Morton & Nance 2006; White et al. 2010). The main factors associated with these delays include shortage of qualified pediatric audiologists, lack of knowledge among health providers about the importance and urgency of follow-up testing (particularly primary care physicians who rarely encounter pediatric hearing loss), and family delays in seeking treatment (Shulman et al. 2010; Lester et al. 2011). Recognizing these delays, the seven national goals for Early Hearing Detection and Intervention (EHDI) programs developed by the CDC include implementation of a confirmatory audiologic evaluation before 3 months of age and appropriate early intervention services by 6 months of age for all infants who screen positive on NBHS (Kemp 1978). The success of these initiatives will largely depend on additional training of health professionals (Sorkin 2011) and implementation of more effective patient tracking and record-management systems to enable timely follow-up and treatment compliance on the part of the patient's family.

These data also show that families with lower annual income were less likely to seek early implantation (in our study setting where onset of all SNHL was before 1 year of age), which may present a critical target for national hearing care initiatives. Prior literature has identified a similar association between delays in implantation and lower socioeconomic class (Fortnum et al. 2002), with some studies specifically linking delayed CI to the presence of Medicaid insurance, likely serving as an indicator for socioeconomic status (Lester et al. 2011). Although patients with Medicaid may receive the same access to medical care as those using private insurance (Morton & Nance 2006), the considerable expenses imposed on families of implanted children by the indirect and downstream costs of implantation, as shown in our analyses, are not reimbursed by health insurance and may present a challenge for low-income families (Chang et al. 2010). Specifically, the preimplantation evaluation process and extensive follow-up require considerable parental involvement and missed time from work, involving several hours of travel to the nearest CI center. Several of the centers participating in this study, for example, recommend at least 2 years of weekly rehabilitation appointments after surgery to achieve maximal benefit from implantation. In turn, these responsibilities are communicated to parents during the initial screening process and may serve as a deterrent to early

TABLE 3. Average lifetime costs of unilateral pediatric cochlear implantation (2011 U.S. dollars)*

Direct Costs	Number of Years	Probability (%)	Reimbursement (US$)
Preoperative			
Audiology	1	100	1284
Physician	1	100	100
Other	1	100	287
Operative			
Cochlear implant device	1	100	34,440
Hospital and surgery charges	1	100	5,724
Medical complications cost			
Minor complications	1–6	4.76	459
Revision	1–6	3.03	5,534
Reimplantation cost	1–6	7.79	9,370
Processor upgrade	1–75	100	11,743
Extended warranty	3–75	100	11,859
Insurance	1–75	100	8,671
Rechargeable batteries	1–75	100	1,485
Postoperative			
Physician	1–75	100	125
Audiology	1–75	100	23,291
Rehab	1–75	100	12,151
Total Direct Costs			126,523
Indirect Costs			
Lost wages†	1–75		30,799
Transportation cost‡	1–75		17,789
Educational savings	1–75		–176,944
Total Indirect Costs			–128,356
Total Costs			–1,833

*Using average age at implantation of 2.3 yrs, 75.2 remaining years of life, a 3% discount rate, once-a-year lifetime frequency of audiology follow-up, 4 hrs of lost wages per medical visit, seven processor upgrades at $2,834 average reimbursement for each upgrade, a $50 annual battery replacement cost, $400 annual extended warranty fee, and $289 annual device insurance fee.
†Lost wages were calculated based on a $23.50 hourly rate and 4 hrs away from work. Wage rate was obtained from the Bureau of Labor Statistics (http://www.bls.gov/eag/eag.us.htm).
‡Transportation cost was calculated based on 100 miles in travel and a travel reimbursement rate of $0.555/mile.

implantation and lead to the alternative of placing a longer emphasis on treatments requiring less intensive follow-up. Unfortunately, prolonging the decision to seek implantation incurs greater downstream costs to the implanted children, their families, and the society at large.

These data also show that the major cost drivers related to CI included the cost of the device and warranty, the surgery, and postoperative rehabilitation and audiology follow-up. Varying all of these factors to 150% of the base case level continued to yield favorable cost-utility ratios—under $25,790/QALY for all age groups at implantation—among the most cost-effective procedures undertaken in the United States (Tengs et al. 1995). Improvements in postimplantation classroom placement were among the largest value drivers of the present analysis. Though limited in duration of follow-up, these data show that early CI had a significantly higher and sustained rate of mainstream integration than the two older groups. This result agrees with the findings of a previous analysis by Schulze-Gattermann et al. (2002), which tracked classroom placement of 158 children in Germany by age at implantation (Schulze-Gattermann et al. 2002). When considering these differential educational cost savings, early pediatric CI actually leads to net societal savings up to $31,000 per child relative to nonimplantation (negative cost-utility ratios). This finding can be put in perspective with the following results: beta blocker therapy to reduce mortality from cardiovascular disease has a positive cost-utility ratio of $5,000/QALY (Weinstein & Stason 1985); combination antiretroviral therapy for human immunodeficiency virus—$23,000/QALY (Freedberg et al. 2001); and dialysis for end-stage renal disease—$50,000–$60,000/QALY (Garner & Dardis 1987).

TABLE 4. Postoperative complications

Age Group	Number of People Implanted	Number of Ears Implanted	Minor Complications* n (%)	Revision Surgeries* n (%)	Reimplantation Surgeries* n (%)	Total Complications* n (%)
<18 mos	60	85	5 (5.88)	2 (2.35)	5 (5.88)	12 (14.12)
18–36 mos	71	94	4 (4.26)	3 (3.19)	7 (7.45)	14 (14.89)
36+ mos	44	52	2 (3.85)	2 (3.85)	6 (11.5)	10 (19.23)
All groups	175	231	11 (4.76)	7 (3.03)	18 (7.79)	36 (15.58)

All complication rates are shown as a percentage of number of ears implanted; none of the complication rates was statistically different at the 5% level between age groups—analysis of variance p *values of 0.80, 0.95, 0.40, and 0.59 for minor complications, revision surgeries, reimplantation surgeries, and total complications across all age groups at implantation, respectively.*

TABLE 5. Cost utility and sensitivity analysis

Cost-Utility Ratios	Total Lifetime Cost Without Educational Savings	Total Lifetime Savings With Educational Savings	QALYs Gained	Cost/QALY Without Educational Savings	Interpretation
<18 mos	$160,453	$31,252	10.7	$14,996	Dominated
18–36 mos	$160,638	$10,217	9.0	$17,849	—
36+ mos	$161,056	$6,680	8.4	$19,173	—
Sensitivity Analysis			<18 mos	18–36 mos	36+ mos
Variables	Base Estimate	Range of Estimate (Best to Worst)	Cost-Utility Cost per QALY (Base $14,996)	Cost-Utility Cost per QALY (Base $17,849)	Cost-Utility Cost per QALY (Base $19,173)
Discount rate	3%	0–6	$10,716–$29,005	$12,761–$34,504	$13,723–$37,018
Direct medical cost					
Frequency of lifetime audiology	1/yr	1–4	$14,996–$19,060	$17,849–$22,681	$19,173–$24,351
Reimplantation cost	$9,370	$0–$40,164	$15,165–$14,944	$18,103–$17,771	$19,045–$19,596
Extended warranty	$400/yr	$300–$500	$14,718–$15,273	$17,519–$18,178	$18,820–$19,526
Frequency of device upgrade	7/lifetime	5–10/lifetime	$14,660–$15,452	$17,448–$18,387	$18,740–$19,615
Total lifetime medical cost	$111,968	$55,984–$167,953	$9,801–$20,190	$11,673–$24,024	$12,557–$25,790
Time off work, hours per visit	4	3–5	$14,304–$15,686	$17,026–$18,669	$18,292–$20,053
Parent salary, hourly wage	$23.50	18–30	$14,322–$15,792	$17,048–$18,795	$18,315–$20,187
Nonimplanted health utility	0.38	0.26–0.56	$11,143–$23,254	$14,472–$30,892	$19,173–$35,012

QALY, quality-adjusted life year.

The use of the national CDaCI study, with access to baseline and long-term multicenter data, detailed tracking of educational placement, direct medical costs and reimbursements, and long-term quality-of-life outcomes, allows for greater generalizability of results than previously feasible. In particular, the inclusion of longer-term health-utility follow-up and subgroup analysis by age at implantation addresses two of the limitations of the PenTAG report (Bond et al. 2009). By tracking actual hospital and physician reimbursement data at the individual patient level across the entire duration of the study, this model expands prior analyses of pediatric CI, which relied on Centers for Medicare and Medicaid Services reimbursement data or shorter-term patient follow-up—factors that appear to understate the costs associated with this procedure. As a result, at approximately $112,000 across all age groups, the total direct lifetime cost of CI was considerably higher after inflation adjustment than that reported by Cheng et al. (2000). Despite these higher costs, the substantial gains in health utility over the lifetime of an implanted child still resulted in highly favorable cost-utility ratios, particularly at younger ages.

The approximate average increment of $20,000 of realized lifetime savings from early CI, relative to that observed with implantation in the two older groups, results in nearly $1.26 billion of societal savings over the lifetime of the current 60,000 pediatric cochlear implant candidates in the United States. An average 1.5-yr delay in CI, the age difference between the youngest and middle groups, would diminish these savings to $212 million and would abolish all saving with a 3-yr delay in implantation. This steep transition from the youngest to middle groups at implantation further supports the presence of a critical threshold period, which has also been suggested from a spoken language and auditory perspective (McConkey Robbins et al. 2004; Svirsky et al. 2004; Nicholas & Geers 2007). The significant association between baseline PTA threshold and age at implantation in the present study, with children implanted at younger ages having more severe hearing impairment at baseline, is in agreement with the results of the aforementioned investigations. These investigations concluded that age at implantation was strongly influenced by progression and degree of hearing loss, and, therefore, related to the extent of auditory experience with hearing aids preimplant. Although potentially confounding the effect of age at implantation on post-CI outcomes, these findings suggest that despite allowing for higher preimplantation PTA thresholds from longer hearing aid use, delaying CI in the hope of longitudinally assessing hearing aid benefit can lead to significant and sustained declines in patient quality of life, poorer educational outcomes, and, in turn, lost educational and societal savings.

There are several limitations to the use of CDaCI data, which may influence our findings. The inability to conduct a randomized controlled trial because of ethical considerations forces the use of preimplantation health-utility scores as proxies for quality-of-life attainment of children who would be cochlear implant candidates. The inability to measure costs directly from all study centers due to antitrust regulation led to the need to estimate these by using adjustment factors from a third-party source to generalize the detailed cost data collected at the JHU study center to other geographically dispersed academic medical centers. In addition, classroom placement was used as a proxy for educational costs, but truly assessing costs associated with each type of classroom placement for cochlear implanted children requires more detailed data than currently available. As noted, the use of parent-proxy questionnaires in measuring HUI score is recommended in children over 5 years of age (Horsman et al. 2003), which could decrease the reliability of the utility measures used in our study. However, because the present study longitudinally compares health-utility gains between three implanted groups and a nonimplanted control constructed from their preimplantation baselines, these potential biases would be systematically present across all age groups and time periods, and should be partially mitigated in the ensuing comparisons (Franks et al. 2006).

CONCLUSIONS

The results of this study add an important dimension to existing evidence on the benefits of early CI on auditory and language outcomes, informing policy makers and clinicians of the societal savings and improved economic outcomes that arise from earlier critical assessment and implantation of cochlear implant candidates. As a result, emphasizing intensive early intervention and bolstering early support of families of implanted children could help mitigate the factors associated with auditory deprivation and permanent delays in spoken language learning associated with delayed intervention, thus improving the lives of implanted children and leading to considerable societal savings.

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Dr. Niparko reported serving on advisory boards without remuneration for two cochlear implant manufacturers, Advanced Bionics Corporations and the Cochlear Corporation, and serving on the board of directors for a school for children with hearing loss, which has received gifts from cochlear implant manufacturers. The terms of these arrangements are being managed by The Johns Hopkins University in accordance with its conflict-of-interest policies. External advisors received honoraria for their review of the study protocol and progress reports.

The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of this article.

The members of the CDaCI Investigative Team are listed in the Appendix (Supplemental Digital Content 4, http://links.lww.com/EANDH/A113).

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Benefits of ultrasound vs. computed tomography in the diagnosis of pediatric lateral neck abscesses☆

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ABSTRACT

Objective: There are no studies comparing the accuracy of ultrasound and computed tomography in the same population of pediatric patients with lateral neck abscesses. This case series assesses the accuracy of the two imaging techniques.

Methods: One hundred and forty imaging studies (ultrasound $n = 39$ or CT $n = 101$) that were performed from 2005 to 2011 prior to incision and drainage of a lateral neck mass at a tertiary care academic institution were retrospectively reviewed. All children 0–18 years of age with lateral neck abscesses who underwent CT or ultrasound imaging prior to drainage were included. Sensitivity, specificity, and positive and negative predictive values of ultrasound and CT were determined as compared to the gold standard, incision and drainage of the suspected abscess.

Results: In children undergoing incision and drainage, the prevalence of an abscess was 89%. Ultrasound has a high specificity (100%) but a low sensitivity (53%). The positive predictive value (96%) is high while the negative predictive value is low (16%), assuming a positive abscess prevalence of 0.9. In contrast, CT has low specificity (18%) but slightly higher sensitivity (68%) compared to ultrasound. Similar to ultrasound, CT had low negative (6%) and high positive (88%) predictive values.

Conclusions: This study demonstrates that ultrasound may be an equivalently sensitive and more specific diagnostic tool when compared to CT in the work-up of lateral neck abscesses in children. It is safe and effective in diagnosis when there is an undetermined probability of an abscess.

1. Introduction

Lateral neck abscesses are increasing in incidence in the pediatric population [1]. Ultrasound and computed tomography (CT) are currently used to screen patients for the presence or absence of a lateral neck abscess. While there have been some evaluations of ultrasound and CT in the literature, there is no standard protocol at our institution and many others. A recent examination of 36 patients ages 2–62 years undergoing ultrasound prior to attempted drainage of an abscess demonstrated 96% sensitivity and 82% specificity. Positive predictive value was 92% and negative predictive value was 90% [2]. These are promising results, but the application to pediatric neck abscesses is limited by the wide variability in the ages of subjects included in this study. A retrospective ultrasound study of 41 surgically confirmed pediatric neck abscesses revealed 31 true positive cases, 6 reported as probable for an abscess, and 4 false negative results. CT was positive for an abscess on 4/5 children prior to a surgically confirmed abscess [3]. The major limitation is that only children with abscess confirmed on drainage were included. There were no false positives or true negatives to report. These patients had widely variable pathology including odontogenic, otogenic, and tonsillogenic sources, one following an insect bite, and another associated with tuberculosis. The majority of infectious sources were unknown. Another pediatric study showed a relatively low sensitivity of ultrasound (65%) but a high specificity (88%), a positive predictive value of 81%, a negative predictive value of 77%, and concluded that a clinical evaluation is integral in the diagnosis alongside the use of ultrasound [4]. The specific locations of the neck masses were not provided. The sensitivities and specificities in these three ultrasound studies were not comparable to those of CT.

In a study of 38 children and adults with deep neck infections, CT has been shown to have a sensitivity of 88% in diagnosing an

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abscess [5]. As this study did not include abscesses from all of the lateral neck, it is difficult to directly compare these findings with the ultrasounds studies. A similar study of 16 CT scans of deep and lateral neck abscesses demonstrated a sensitivity of 91% but a specificity of 60% [6]. This study was limited by its small sample size and mixed pathology.

A comparison of ultrasound and CT in the diagnosis of pediatric lateral neck abscesses is necessary in order to establish a practice guideline for this population. CT is used more often at this institution, most likely because there is a CT technician available at all times whereas ultrasound readings are only available during the day. If it can be shown that ultrasound and CT are comparable in accuracy for the diagnosis of lateral neck abscesses, then a practice guideline can be developed based upon the cost and safety profiles of the two procedures. This study compares the accuracy of ultrasound and CT to the gold standard outcome of attempted drainage in order to promote judicious and individualized use of ultrasound and CT in the diagnosis of children with lateral neck abscesses.

2. Materials and methods

IRB approval was granted by the University of Oklahoma for a retrospective study of all children 0–18 years of age with lateral neck abscesses who underwent preoperative imaging prior to attempted drainage at an academic tertiary care center from 2005 to 2011. This allowed evaluation of the accuracy of CT and ultrasound relative to the surgical finding of presence or absence of pus, the gold standard for determination of an abscess. To appropriately power the study, it is necessary to compare approximately 40 ultrasound and 40 CT imaging studies. This goal was recommended by our statistician and is consistent with the power of previous evaluations of CT or ultrasound. Subjects were located by a search of the medical center billing database by Current Procedural Terminology codes. The patients were evaluated in two groups based on whether an ultrasound or a CT was performed prior to surgery. There are no specific preferences besides availability that determined which children received an ultrasound or a CT in this study. Currently there is no institutional protocol; rather the decision is influenced by when a child presents and which physician initially sees the patient. When clinically indicated, some children are taken to the operating room without receiving either imaging study.

The majority of ultrasounds and CT scans were performed at this institution and some were performed at outside medical facilities prior to transfer. All imaging studies were read at the same academic tertiary care center. The initial final report from the department of radiology was used, and only studies performed within 3 days of surgery are included. All incision and drainages were performed at this facility. In accordance with this institution's protocol, stable children presenting with suspected neck abscesses are given 48 h of intravenous clindamycin before drainage is attempted. Lateral neck abscess locations in this study include the anterior and posterior triangles, submandibular, submental, parotid, and parapharyngeal spaces.

Clinical and demographic characteristics were summarized for each group of subjects (CT or ultrasound). The mean age was compared between groups using a 2-sample *t*-test. The distribution of gender was compared between groups using a Chi-square test. Demographic characteristics of the CT and ultrasound groups were compared after excluding patients who underwent both CT and ultrasound screening tests. The sensitivity, specificity, positive predictive value and negative predictive value were calculated for each method separately. The accuracy of the imaging method is summarized using a two-sided 95% exact confidence interval. Positive and negative predictive values were calculated assuming a positive abscess prevalence of 0.90.

3. Results

One hundred thirty-two patients are included in the analysis with 31 who underwent ultrasound, 93 who underwent CT, and 8 who underwent both ultrasound and CT scans. The median age of the sample was 1.5 years (range one month to 18 years) with a mean age of 2.9 years (standard deviation 3.5 years). Although those who underwent a CT scan were on average one year older than the ultrasound group, this difference was not statistically significant. The gender distribution was well balanced between the groups (Table 1).

A total of 140 imaging studies were available for review, including 39 ultrasound studies with gold standard results of 34 positive and 5 negative and 101 CT studies with gold standard results of 90 positive and 11 negative. The overall prevalence of a pus-positive abscess in children undergoing the gold standard, incision and drainage, was 89%. Table 2 presents the estimated sensitivity, specificity, positive predictive value and negative predictive value for each method along with a 95% confidence interval for the estimate.

The CT scan test method has very low specificity (2/11, 18%) and a very low negative predictive value (6%) assuming a positive abscess prevalence of 0.9. The sensitivity is reasonable (61/90, 68%). The positive predictive value (88%) is slightly lower than the assumed prevalence of 90%. Based on the assumed prevalence value, the probability of a pus-positive abscess is 90% (without knowledge of the CT test result) while the positive predictive value suggests that the probability of a pus-positive abscess is 88% among those with a positive CT scan. Similarly, the estimated negative predictive value (6%) is less than the assumed prevalence of a pus-negative abscess (10%). The ultrasound test method has a high estimated specificity (5/5, 100%) but a low sensitivity (18/34, 53%). The positive predictive value (96%) is high while the negative predictive value is low (16%) assuming a positive abscess prevalence of 0.9.

Table 3 demonstrates the sensitivity and specificity of ultrasound and CT by location of the abscess. Twelve of 140 imaging studies were excluded from this analysis because they included

Table 1
Demographic characteristics of patients who underwent ultrasound and computed tomography.

Baseline values[a]	All patients[b] ($n=132$)	Diagnostic screening approach		p-Value[c] (comparing CT to ultrasound)
		CT ($n=101$)	Ultrasound ($n=39$)	
Age in years	2.9 (3.5) 1.5 [0.04–18]	3.2 (3.5) 2.0 [0.08–18]	2.2 (2.9) 1.3 [0.04–16]	$p=0.16$
Male sex	69 (52%)	55 (54%)	19 (49%)	$p=0.53$

Legend: CT – computed tomography; n – total number in category.
[a] Distributions summarized using the mean (standard deviation) and median [range] for continuous measures and count (column %) for categorical measures.
[b] Data are available for 132 patients, eight of whom underwent both CT and ultrasound screening.
[c] Statistical comparisons of the mean or proportions were made after excluding eight patients undergoing both CT and ultrasound screening.

Table 2
Sensitivity, specificity, positive and negative predictive values of ultrasound and computed tomography as compared to the gold standard, drainage of abscess.

Method	Sensitivity			Specificity			Positive predictive value[a]		Negative predictive value[a]	
	Counts positive/total[b]	Estimate	95% CI	Counts negative/total[c]	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Ultrasound	18/34	0.53	0.35–0.70	5/5	1.0	0.48–1.00	0.96	0.86–0.99	0.16	0.10–0.23
CT scan	61/90	0.68	0.57–0.77	2/11	0.18	0.02–0.52	0.88	0.85–0.91	0.06	0.02–0.19

Legend: CI – confidence interval; CT – computed tomography.
[a] Assuming abscess prevalence of 0.90.
[b] Sensitivity data presented as the number of positive tests out of the total number with a gold standard positive status.
[c] Specificity data presented as the number of negative tests out of the total number with a gold standard negative status.

Table 3
Sensitivity and specificity of ultrasound and computed tomography by abscess location.[a]

Abscess location (total)	Method	Sensitivity			Specificity		
		Counts positive/total[b]	Estimate	95% CI	Counts negative/total[c]	Estimate	95% CI
Anterior cervical (32)	Ultrasound	8/14	0.57	0.29–0.82	0/0	Not estimable	
	CT scan	9/16	0.56	0.30–0.80	0/2	0	0–0.84
Posterior cervical (21)	Ultrasound	1/3	0.33	0.008–0.91	1/1	1.0	0.025–1.0
	CT scan	11/16	0.69	0.41–0.89	0/1	0	0–0.98
Submandibular and submental (30)	Ultrasound	7/12	0.58	0.28–0.85	1/1	1.0	0.025–1.0
	CT scan	12/16	0.75	0.48–0.93	0/1	0	0–0.98
Parapharyngeal (37)	Ultrasound	2/3	0.66	0.094–0.99	1/1	1.0	0.025–1.0
	CT scan	21/27	0.78	0.58–0.91	2/6	0.33	0.04–0.78
Parotid (8)	Ultrasound	0/0	Not estimable		0/0	Not estimable	
	CT scan	6/8	0.75	0.35–0.97	0/0	Not estimable	

Legend: CI – confidence interval; CT – computed tomography.
[a] Twelve imaging studies included abscesses from multiple lateral neck locations and have been excluded from this subgroup analysis.
[b] Sensitivity data presented as the number of positive tests out of the total number with a gold standard positive status.
[c] Specificity data presented as the number of negative tests out of the total number with a gold standard negative status.

abscesses spanning multiple locations. Confidence intervals around the point estimates are wide, particularly for specificity, due to the small sample sizes of individual locations. No formal comparisons of test performance were made between CT and ultrasound by location given the small subgroup sizes. In general, the site-specific estimates are consistent with the overall estimates in which sensitivity is similar but somewhat lower for the ultrasound method compared to CT.

4. Discussion

This study shows that ultrasound may be as sensitive, yet more specific, than CT in the diagnosis of lateral neck abscesses when compared to the gold standard, drainage of the abscess. As such, practice guidelines may be developed based upon the cost, safety, and discomfort of the two procedures. In 2010 in Oklahoma City, ultrasound cost $79.97 to administer, while CT administration with contrast cost $220.11 [7]. It is often necessary to sedate a child to undergo a CT scan, adding to its cost and associated risk. Contrast associated allergy, although rare, is a potential side effect of CT [8]. For children, there may be an increased fear of CT because they have to be separated from their parent or guardian for an extended period of time. Separation anxiety is avoided when ultrasound is used.

There are many concerns about the negative long-term effects of radiation from CT. Computed tomography-related x-ray doses are large enough that there is statistically-significant epidemiological evidence of a small increase in lifetime attributable risk of cancer incidence, ranging from 0.02% in 80 year old men to nearly 1% in 20 year old women undergoing CT [8]. On average, risks are 0.07% larger for children than adults. Annually, out of 600,000 children in the United States who receive a head or abdominal CT, it is estimated that 500 will die of cancer which is directly related to the CT [9,10]. The cumulative radiation exposure from two to three head CT scans in children under 15 may triple the risk of brain cancer [11]. Ultrasound avoids the risks of radiation. One drawback to ultrasound is that a probe must be placed on the child's neck; this could cause pain or discomfort at the infection site. In the cases examined for this study, the performance of at least one ultrasound and one CT was limited by patient movement. When examining the risks and benefits of both techniques, it is likely that ultrasound may be preferred over CT in many instances for the diagnosis of pediatric lateral neck abscesses.

We demonstrate in this review that ultrasound may have greater specificity when compared to CT in the diagnosis of lateral neck abscesses in children. This is of great importance clinically as our goal for imaging is often to determine who does not need to undergo surgical drainage. In our population of children who were already treated with 24 h of intravenous clindamycin, the prevalence of abscesses in those ultimately requiring incision and drainage was 89%. Considering such a high prevalence, reliably finding those children who do not have an abscess and are unlikely to benefit from surgical drainage is critical. Although our numbers for specificity were small for both ultrasound and CT, ultrasound was superior.

A diagnostic protocol that promotes judicious and individualized use of ultrasound and CT in the diagnosis of neck abscesses would likely prove to be beneficial for these children. To decrease cost, discomfort, and potential harm to the child, an ultrasound may be preferred as the first line imaging technique in many situations. Computed tomography may be useful in some

situations as well, but only after reasonable justification and consideration of side effects to the child.

Currently one of the drawbacks to the use of bedside ultrasound may be its availability. At this institution, an ultrasound technician may not be consistently available overnight or on the weekend although this is changing. The availability of ultrasound may improve as its demand increases across all fields of medicine. To improve availability, it may be necessary to specify the need for an ultrasound technician during extended periods. It also may be beneficial for more physicians including otolaryngologists to become proficient in performing and interpreting ultrasound so that it may be used whenever children present with symptoms of a serious abscess.

The decision to perform an ultrasound was based on clinician preference and availability of ultrasound technicians in this study. In the absence of a truly randomized study, some selection bias may exist. It may not be ethical to perform a randomized controlled trial in the interest of cost and potential harm to the child from a CT. The reported data are based on patients who underwent a diagnostic screening test, CT and/or ultrasound, and the gold standard test, drainage of the abscess. There is potential for verification bias because not all patients who underwent an initial screening test also underwent the definitive gold standard test. Many of our patients with cervical adenitis and a suspected abscess will resolve clinically without undergoing incision and drainage. Also, not all children who underwent the gold standard at this institution underwent an imaging study prior to incision and drainage. These two groups were not evaluated in this study. As previous studies recognize, ultrasound interpretation is operator dependent [2]. Computed tomography is subject to variations in operation and interpretation as well [12]. Therefore, the ability to reproduce the results of this study may be affected by the specialty and level of expertise of the examiner. In the absence of otolaryngologists who are comfortable interpreting ultrasound, studies examining its use in the field may continue to be limited by this factor.

Another limitation of this study is the small number of subjects with pus-negative abscesses ($n = 16$). This decreased the precision of our estimate of the specificity for both ultrasound and CT. Without needlessly imaging patients who have a low probability of an abscess, these numbers are unlikely to increase. Expanding the enrollment through a future multicenter study may address this limitation. It is also important to note that the positive and negative predictive values are influenced by the assumed true prevalence of abscess positivity in the population. We expect the positive predictive value to be high and the negative predictive value to be low in settings with a high prevalence, such as tertiary care centers similar to ours.

5. Conclusion

The sensitivity of ultrasound and CT in the diagnosis of pediatric lateral neck abscesses is similar, yet ultrasound may be more specific when compared to the outcome of attempted drainage. The use of an ultrasound in the diagnosis of a lateral neck abscess in a child may provide similar information to the clinician at a lower cost and lower risk to the child compared to CT. As such, it may be preferred for diagnosis in many situations. We propose that ultrasound should be considered prior to requesting a CT scan.

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Conflict of interest

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Initiation and Use of Propranolol for Infantile Hemangioma: Report of a Consensus Conference

abstract

Infantile hemangiomas (IHs) are common neoplasms composed of proliferating endothelial-like cells. Despite the relative frequency of IH and the potential severity of complications, there are currently no uniform guidelines for treatment. Although propranolol has rapidly been adopted, there is significant uncertainty and divergence of opinion regarding safety monitoring, dose escalation, and its use in PHACE syndrome (PHACE = posterior fossa, hemangioma, arterial lesions, cardiac abnormalities, eye abnormalities; a cutaneous neurovascular syndrome characterized by large, segmental hemangiomas of the head and neck along with congenital anomalies of the brain, heart, eyes and/or chest wall). A consensus conference was held on December 9, 2011. The multidisciplinary team reviewed existing data on the pharmacologic properties of propranolol and all published reports pertaining to the use of propranolol in pediatric patients. Workgroups were assigned specific topics to propose protocols on the following subjects: contraindications, special populations, pretreatment evaluation, dose escalation, and monitoring. Consensus protocols were recorded during the meeting and refined after the meeting. When appropriate, protocol clarifications and revision were made and agreed upon by the group via teleconference. Because of the absence of high-quality clinical research data, evidence-based recommendations are not possible at present. However, the team agreed on a number of recommendations that arose from a review of existing evidence, including when to treat complicated IH; contraindications and pretreatment evaluation protocols; propranolol use in PHACE syndrome; formulation, target dose, and frequency of propranolol; initiation of propranolol in infants; cardiovascular monitoring; ongoing monitoring; and prevention of hypoglycemia. Where there was considerable controversy, the more conservative approach was selected. We acknowledge that the recommendations are conservative in nature and anticipate that they will be revised as more data are made available. *Pediatrics* 2013;131:128–140

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KEY WORDS

infantile hemangioma, propranolol, PHACE syndrome, hypertension, bradycardia, hypoglycemia

ABBREVIATIONS

BP—blood pressure
ECG—electrocardiogram, FDA, US Food and Drug Administration
HR—heart rate
IH—infantile hemangioma
PHACE—posterior fossa, hemangioma, arterial lesions, cardiac abnormalities, eye abnormalities

(Continued on last page)

Infantile hemangiomas (IHs) are common benign tumors composed of proliferating endothelial-like cells. The duration and rate of growth are variable; some infants will have hemangiomas that grow very little, whereas others grow rapidly and at an unpredictable rate. Although most are not worrisome, ~12% of IHs are significantly complex, requiring referral to specialists for consideration of treatment.[1,2] Complications of hemangiomas, for which systemic pharmacotherapy is typically initiated, include permanent disfigurement, ulceration, bleeding, visual compromise, airway obstruction, congestive heart failure and, rarely, death. Despite the relative frequency of IH and the potential severity of complications, uniform guidelines for treatment are lacking.

There are no US Food and Drug Administration (FDA)-approved agents for the treatment of IH, and treatment is currently based on expert opinion and observational studies. Prospective data addressing the efficacy and safety of any pharmacologic interventions for the treatment of IH have not been generated, and available data are confounded by the lack of a consensus on treatment criteria and objective outcome measures. Agents with reported activity in treating IH include corticosteroids, interferon α, vinca alkaloids, and, recently, propranolol.[3–25]

Since the initial report of propranolol use for the treatment of IH in 2008, there has been a flurry of case reports and case series describing its efficacy and potential side effects.[3–6,10–15,18,21,23,24,26–36] These publications were not subjected to the usual stringency of phase I/II/III clinical trials, and most were not prospective, randomized, or controlled. With clinical use, propranolol has been found to be rapidly effective for IH, well tolerated, and better than previous therapies at inducing regression. These observations, coupled with the immediate availability of the medication in a pediatric formulation, have led to a rapid and widespread adoption of propranolol for IH. Propranolol suspension is commercially available in the United States, but it does not currently have an FDA-approved indication for children. Cardiologists have historically used this medication in infants with the diagnosis of supraventricular tachycardia. In contrast to infants with supraventricular tachycardia, for whom initiation of propranolol typically occurs in an inpatient setting with extensive cardiac monitoring, the great majority of infants treated for IH are cardiac healthy and are treated in an outpatient setting. Guidelines for dose initiation, dose escalation, and toxicity monitoring were never generated for use with IH; therefore, each institution designed unique protocols. These protocols vary considerably; some centers hospitalize all children for initiation of treatment, whereas others do so only rarely. Some experts recommend intensive outpatient monitoring of patients, whereas others do little to no monitoring.[3]

The distinct circumstances in which propranolol has become so widely used underscores the importance of bringing multiple specialties together to gain consensus regarding dose initiation, safety monitoring, dose escalation, and its use in specific situations (eg, PHACE syndrome).[3] In this report, we review existing data on the pharmacologic properties of propranolol and all published reports pertaining to the use of propranolol in pediatric patients. With this review as the evidence base, a multidisciplinary, multiinstitutional expert panel met in December 2011 to develop a standardized, consensus-derived set of best practices for the use of propranolol in infants with IH. As more information accumulates, it is expected that this provisional set of best practices will change.

REVIEW

Pharmacologic Properties of Propranolol

Propranolol is a synthetic, β-adrenergic receptor-blocking agent that is classified as nonselective because it blocks both β-1 and β-2 adrenergic receptors. Chronotropic, inotropic, and vasodilator responses decrease proportionately when propranolol blocks the β-receptor site, resulting in a decrease in heart rate (HR) and blood pressure (BP). Propranolol is highly lipophilic and undergoes first-pass metabolism by the liver with only ~25% of oral propranolol reaching the systemic circulation. Multiple pathways in the cytochrome P450 system are involved in propranolol's metabolism, making clinically important drug interactions a potential issue (Table 1).

Propranolol had previously been used in pediatric patients primarily for the treatment or prevention of cardiac arrhythmias, hypertension, outflow obstructions in congenital heart disease, and hypertrophic cardiomyopathy. Its antihypertensive effects result from decreased HR, decreased cardiac contractility, inhibition of renin release by the kidneys, and decreased sympathetic

TABLE 1 Drug Interactions

Increase Blood Levels/Toxicity	Decrease Blood Levels/Decrease Efficacy
Inhibitors of CYP2D6: Amiodarone, cimetidine (but not ranitidine), delavudin, fluoxetine, paroxetine, quinidine, and ritonavir Inhibitors of CYP1A2: Imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton, zolmitriptan, and rizatriptan	Inducers of hepatic drug metabolism: Rifampin, ethanol, phenytoin, and phenobarbital

tone. However, the mechanism of action of propranolol on IH is yet to be clearly defined. Some of the proposed hypotheses include vasoconstriction, decreased renin production, inhibition of angiogenesis, and stimulation of apoptosis.[37–39]

Propranolol Use for IH

A comprehensive review of the literature was undertaken to understand the breadth of current clinical practice. A PubMed search cross-referenced with Google Scholar last performed on December 7, 2011, using the search terms "propranolol" and "hemangioma" yielded 177 articles. Of these, 115 articles were written in English and discussed use in humans. Thirty additional articles were excluded because they were nonapplicable or lacked sufficient clinical data. Eighty-five articles (including 1175 patients) were reviewed in detail.[4,11,13,15,18,21,23,24,26–34,36–38,40–104] The majority of these publications included <5 patients, and nearly all were retrospective reports. There was only 1 prospective trial and 1 meta-analysis.[58,80] Nearly half (35/85; 41%) of the publications were interim reports with patients still undergoing treatment; therefore, adverse events may be underestimated. Although there was significant variability in the details provided by each article, the authors chose to be inclusive to understand the breadth of current clinical practice.

Response to therapy was discussed in 79 articles, and the definitions and measures of response varied widely, from "stabilization" to "complete response." Fewer than 10 articles attempted to quantify the degree of involution.[13,15,23,41,42,58] Positive response in all treated patients was reported in 86% of publications; the remaining 14% discussed at least some treatment failures. In total, 19 of 1175 published patients were reported as treatment failures, suggesting a 1.6% treatment failure rate. This rate may be underestimated because treatment failures may not be as commonly reported. In publications with adequate data from which to calculate age at initiation of therapy, the mean age was 5.1 months, with a median age of 4 months.

Adverse Events of Propranolol in the Pediatric Population

Although propranolol has been well studied in adults, observations of its use in infants and children, nearly 40 years in duration, have been mainly anecdotal. There are no FDA-approved indications for propranolol in pediatric patients in the United States. There is 1 active phase II/III Investigational New Drug application (ClinicalTrials.gov NCT1056341) for the use of propranolol for the treatment of IH. On the basis of case reports and case series, oral propranolol appears to have a favorable safety profile in children. Deaths or acute heart failure have been associated with propranolol initiation only in the settings of intravenous administration or drug overdose.[105,106]

Given the variability in study design and the retrospective nature of most reports, the true incidence of adverse events in IH population is difficult to ascertain. For example, routine screening for bradycardia was only documented in 128 of 1175 (10%) of patients reported. Of the 85 articles, 48 (56%) reported no complications in any patient, although reports of complications with propranolol usage increased over time from 2008 to 2011 (Table 2). The most frequently reported serious complications were asymptomatic hypotension or hypotension for which no additional details were provided; pulmonary symptoms related to direct blockade of adrenergic bronchodilation; hypoglycemia or hypoglycemic seizure; asymptomatic bradycardia; and hyperkalemia. The most commonly reported nonpotentially life-threatening complications were sleep disturbances including nightmares, somnolence, cool or mottled extremities, diarrhea, and gastroesophageal reflux/upset.

Bradycardia and Hypotension

As a β-blocker, propranolol decreases HR and, in part, BP as a result of negative chronotropic and inotropic effects on the heart. Propranolol's effects on BP and HR in children peak

TABLE 2 Complications Due to Propranolol in Hemangioma Patients

Complications Recorded	No. of Patients/ Total No. of Patients in Papers Reporting Complication	Frequency (%) of Complication Among Papers Reporting Said Complication	Overall Frequency (%) of Total of 1175 Patients Reviewed in 85 Papers
Asymptomatic hypotension or hypotension (unspecified)	33/228	14.5	2.8
Symptomatic hypotension	3/46	6.5	0.3
Pulmonary symptoms (bronchoconstriction, bronchiolitis, wheezing, pulmonary obstruction, apneic episode)	16/201	8.0	1.4
Hypoglycemia	10/88	11.4	0.9
Asymptomatic bradycardia or bradycardia (unknown)	11/126	8.7	0.9
Symptomatic bradycardia	1/2	50	0.1
Sleep disturbance (including nightmares)	44/326	13.5	3.7
Somnolence	26/220	11.8	2.2
Cool or mottled extremities	20/225	8.9	1.7
Diarrhea	9/53	17.0	0.8
Gastroesophageal reflux disease or gastrointestinal upset	8/133	6.0	0.7

around 2 hours after an oral dose.[47] The reported protocols for initial dose, dose titration, and prospective monitoring were extremely variable and therefore difficult to compare in a uniform fashion. Three prospective studies, although limited by small patient numbers and significant missing data, provide useful information. During initiation of propranolol for IH in infants, bradycardia (<2 SD of normal) and hypotension (< 2 SD of normal) after the first dose (2 mg/kg/day divided 3 times daily) were infrequent and asymptomatic.[47] Changes (*z* scores >2) in systolic BP from baseline occurred in 7%, 22%, and 13% at 1, 2, and 3 hours postpropranolol dosing, respectively. For HR, there were no changes in *z* scores from baseline >2 at any time point measured. As a group, significant changes in BP occurred only at 2 hours.[47] In 28 patients treated for IH with doses up to 4 mg/kg/day, bradycardia was not noted as a side effect.[59] In a separate study of 25 infants by Schiestl and colleagues, HR was continuously monitored during sleep and transient bradycardia was reported in 4/25 infants. Decrease in diastolic BP <50th percentile was noted in 16 of 28 patients (57%) in 1 study, but only 1 patient developed clinically recognizable changes with cold extremities and prolonged capillary refill.[59]

Hypoglycemia

Symptomatic hypoglycemia and hypoglycemic seizures have been reported in infants with IH treated with oral propranolol (Table 3).[59,61,63,64,86,88,90,107] These cases occurred in both newborns and toddlers but were often associated with poor oral intake or concomitant infection. The mechanisms through which propranolol-induced hypoglycemia develops are not completely understood. Nonselective β-blockers, such as propranolol, may block catecholamine-induced glycogenolysis, gluconeogene-

TABLE 3 Hypoglycemia in IH Patients Treated With Propranolol

	Age at Time of Hypoglycemic Episode	Dose	Duration of Propranolol Therapy Before Hypoglycemia	Time From Last Dose to Detection of Hypoglycemia	Symptoms	Glucose	Other Factors
Lawley Case 2	36 d	2 mg/kg/day divided TID	10 d	Unknown	Asymptomatic; detected on routine blood work	48 mg/dL	Timing of last meal not specified
Holland Case 1	12 mo	2 mg/kg/day divided TID	3 wk	2 h	Pale, cold, clammy, increasingly unresponsive	55 mg/dL	Fussiness attributed to teething NI po intake reported
Holland Case 2	18 mo	1.25 mg/kg/day divided BID	Few months	13 h (overnight fast)	Cool, unresponsive after overnight fast; seizures	24 mg/dL	Recent resolution of illness with decreased po intake
Holland Case 3	10 mo	2 mg/kg/day divided TID	8.5 mo	2.5 h	Found limp, pale	20 mg/dL	Setting of RSV, but po intake preceding days reportedly normal
Breur	15 mo	2 mg/kg/day divided BID	3 wk	Several (overnight fast)	Unresponsive in AM	32 mg/dL	Concurrent treatment with prednisone with recent taper; significant HPA axis suppression demonstrated with undetectable AM cortisol
de Graaf Patient 13	32 mo	4 mg/kg; dosing interval NS	NS	NS	Less responsive	48 mg/dL	Prolonged fasting
Bonifazi	6 mo	2 mg/kg/day divided TID	160 d	Propranolol at 3 AM; did not wake at 6 AM	Irritability and seizures upon waking	15 mmol/L	Last meal at 11 PM
Fusilli	6 mo	2 mg/kg/day divided TID	5 mo	Propranolol at 6:30 AM w/o eating, developed seizures at 10 AM (10-h fast)	Seizures	15 mg/dL	
Blatt	8 mo	2.5 mg/kg/day divided BID	2 wk	NS	NS	NS	Dose administered may have been higher because patient had 2 prescriptions (20 mg/5mL and 40 mg/5mL)
Price	NS	NS	NS	NS	NS	NS	Hypoglycemia reported in 1 of 68 patients in study

BID, twice daily; HPA, hypothalamic-pituitary-adrenal; NS, not specified; po, oral administration; RSV, respiratory syncytial virus; TID, 3 times daily.

sis, and lipolysis, predisposing to hypoglycemia. Most of the reported patients who developed hypoglycemia were prescribed relatively low doses (1.25–2.0 mg/kg/day), suggesting that hypoglycemia associated with propranolol may not be dose-dependent. Historically, the 1 reported pediatric fatality from an accidental overdose of oral propranolol had a documented blood glucose level of 0 mg/dL, suggesting that hypoglycemia may be the most serious complication in children.[106] Patients with IH may be at increased risk if they have received or are concomitantly receiving treatment with corticosteroids, because adrenal suppression may result in loss of the counterregulatory cortisol response and increase the risk of hypoglycemia.[88] Children, infants, and especially preterm infants appear to be at higher risk for this hypoglycemia as their glucose utilization rates are threefold higher in the fasting state and their glycogen stores are lower.[108]

Clinical manifestations of hypoglycemia in infants can vary widely. Mild hypoglycemia produces symptoms associated with counterregulatory epinephrine action, including sweating, shakiness, tachycardia, anxiety, and hunger. With propranolol-induced β-adrenergic blockade, early symptoms may be masked. Therefore, because sweating is not typically blocked by β-blockers, this may be a more reliable symptom for diagnosis. More severe hypoglycemia produces symptoms of neuroglycopenia, including lethargy, stupor, poor feeding, seizures, apnea, loss of consciousness, and hypothermia.

Bronchospasm

Bronchial hyperreactivity, described as wheezing, bronchospasm, or exacerbation of asthma/bronchitis, is a recognized side effect of propranolol as the result of its direct blockade of adrenergic bronchodilation. Certainly, the use of propranolol in the setting of known reactive airway disease must be considered cautiously. The development of bronchial hyperreactivity in the setting of an acute viral illness in patients on propranolol has necessitated temporary discontinuation of therapy.[59]

Hyperkalemia

Hyperkalemia (without electrocardiographic changes) was reported in 2 children on propranolol for IH.[72,109] The cause of the hyperkalemia is not known, but the authors postulate that it was tumor lysis from the large ulcerated IH combined with impaired potassium uptake into cells as the result of β blockade. Dental caries have been reported in 2 pediatric patients treated with propranolol, although this may be related to the formulation of the suspension (if it contains sucrose). β-adrenergic antagonism of salivary gland function resulting in decreased salivation has also been postulated as a contributing factor.[58,70]

SURVEY OF PROPRANOLOL USE FOR IH

A survey was designed and was distributed to established prescribers of propranolol in Fall 2011 for IH by Drs Sarah L. Chamlin, Beth A. Drolet, Anita N. Haggstrom, and Anthony J. Mancini.

The response rate was 76%, and most respondents were pediatric dermatologists (88%), academicians (84%), and experienced clinicians with a mean of 15.25 years in practice. Before starting propranolol, the following studies were obtained with the noted frequency: electrocardiogram (ECG; 81%), BP measurement (41%), echocardiogram (38%), and HR measurement (38%). Cardiology consultation was "always obtained" by 34% of respondents and "never obtained" by 25%, with the remainder (41%) stating that they "sometimes obtained" such consultation. Seventeen (53%) prescribers "always" or "sometimes" admitted patients to the hospital to initiate therapy, with only 3 of these prescribers stating that they always admitted. The other respondents admitting children did so under special circumstances, including young age (under 6–8 weeks), extreme prematurity, significant comorbidity, PHACE syndrome, airway hemangioma, and poor social situations. Most respondents (81%) started propranolol at 0.5 to 1.0 mg/kg per day, with a goal dose of 2.0 mg/kg per day in 84% of patients. Dosing was twice daily for 38% and 3 times daily for 47%, with the remaining 15% dosing 3 times daily initially with a change to twice daily when the child was older (6–12 months of age).

CONSENSUS METHODS

A consensus conference was held in Chicago, Illinois, on December 9, 2011. This conference was sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (1R34AR060881-01). Twenty-eight participants attended from 12 institutions, representing 5 specialties. Collectively, the group has treated >1000 infants with propranolol for IH. Given the inconsistencies in current institutional policies, consensus was difficult to obtain on all issues. Because of the especially vulnerable patient population of infants aged 1 to 6 months, the group chose to remain cautious in the approach to these recommendations. Where there was considerable controversy, the more conservative approach was selected until additional safety data can be obtained.

Results of the survey were shared, and participants were asked to review all existing literature on the use and adverse effects of propranolol in the treatment of IH, PHACE syndrome, and other indications in the pediatric population. These data were summarized, and work groups were assigned specific

topics to propose protocols on the following subjects: contraindications, special populations, pretreatment evaluation, dose escalation and monitoring, and patient education. These protocols were presented to the entire group and debated using an iterative process (nominal group technique).[110] Consensus protocols were recorded during the meeting, refined after the meeting, and resubmitted to the entire group for discussion by teleconference and electronic review. Comments were recorded and discussed, and when appropriate, protocol clarifications and revisions were made and agreed on by the group via teleconference.

Because of the absence of high-quality clinical research data, evidence-based recommendations are not possible at the present time, and these are not American Academy of Pediatrics–endorsed recommendations. However, the multidisciplinary team agreed on a number of recommendations that arose from a review of existing evidence. It is acknowledged that, in many areas, evidence is generally confined to expert opinion, case reports, observational or descriptive studies, and uncontrolled studies. We acknowledge that the following recommendations are conservative in nature, and we anticipate that they will be revised as more data are made available.

CONSENSUS RECOMMENDATIONS

When to Treat IH

Given the wide spectrum of disease and the natural tendency for involution, the greatest challenge in caring for infants with IH is determining which infants are at highest risk for complications and in need of systemic treatment. Medical management is highly individualized, and treatment with oral propranolol is considered in the presence of ulceration, impairment of a vital function (ocular compromise or airway obstruction), or risk of permanent disfigurement. Before the initiation of therapy, the potential risks of adverse effects are carefully considered and weighed against the benefits of intervention. A medical team with expertise in both the management of IH and the use of oral propranolol in infants provides the most optimal care to patients in need of systemic therapy with propranolol.

Contraindications and Pretreatment History

Before initiating propranolol therapy for IH, screening for risks associated with propranolol use should be performed. Relative contraindications are listed in Table 4. The prescribing physician should perform, or obtain documentation of, a recent normal cardiovascular and pulmonary history and examination. Key elements of the history are poor feeding, dyspnea, tachypnea, diaphoresis, wheezing, heart murmur, or family history of heart block or arrhythmia. The examination should be performed by a care provider with experience in evaluating infants and children. The examination should include HR, BP, and cardiac and pulmonary assessment.

Pretreatment ECG

Routine ECG screening before initiation of propranolol for hemangiomas has been advocated, although the utility of ECG screening for all children with hemangiomas before initiation of propranolol therapy is unclear. In the future, a more indication-driven ECG strategy is likely to develop because the incidence of ECG abnormalities that would limit propranolol use in children with IH appears low.[4,7,10,13,15,18,21,25,27,29] For example, congenital complete heart block is rare, with an estimated prevalence of 1 in 20 000 live births,[111] and this is most commonly associated with maternal connective tissue disease.[112] Consensus was not achieved on the use of ECG for all children with IH, but ECG should be part of the pretreatment evaluation in any child when

1. the HR is below normal for age[113]:
   - newborns (<1 month old), <70 beats per minute,
   - infants (1–12 months old), <80 beats per minute, and
   - children (>12 months old): <70 beats per minute.
2. there is family history of congenital heart conditions or arrhythmias (eg, heart block, long QT syndrome, sudden death), or maternal history of connective tissue disease.
3. there is history of an arrhythmia or an arrhythmia is auscultated during examination.

Because structural and functional heart disease have not been associated with uncomplicated IH, echocardiography as a routine screening tool before initiation of propranolol is not necessary in the absence of abnormal clinical findings.

TABLE 4 Contraindications to Propranolol Therapy

Cardiogenic shock
Sinus bradycardia
Hypotension
Greater than first-degree heart block
Heart failure
Bronchial asthma
Hypersensitivity to propranolol hydrochloride

Propranolol Use in PHACE Syndrome

PHACE syndrome (Online Mendelian Inheritance in Man database ID 606519) is a cutaneous neurovascular syndrome present in one-third of infants with large, facial hemangiomas; it is characterized by large, segmental hemangiomas of the head and neck and congenital anomalies of the brain, heart, eyes, and/or chest wall.[114]

Arterial anomalies of the head and neck are the most common noncutaneous manifestation of PHACE syndrome, and acute ischemic stroke is a known

complication.[115] Although the arterial anomalies are widely variable, infants with PHACE syndrome believed to be at highest risk for stroke are those with severe, long-segment narrowing or nonvisualization of major cerebral or cervical arteries in the setting of inadequate collateral circulation, especially when there are coexisting cardiac and aortic arch anomalies (Table 5).[116] Theoretically, propranolol may increase the risk of stroke in PHACE syndrome patients by dropping BP and attenuating flow through absent, occluded, narrow, or stenotic vessels. Furthermore, nonselective β-blockers, such as propranolol, have been shown to increase variability in systolic BP to a greater degree than β1-selective agents, and labile BP is a known risk factor for stroke.[117] There are 2 reports of acute ischemic stroke in PHACE syndrome patients on propranolol to date. Both patients were concomitantly on oral steroids and had severe arteriopathy.[116] Cardiac and aortic arch anomalies are also commonly seen in PHACE syndrome and require echocardiography to assess intracardiac anatomy and function. Propranolol administration in these patients should be managed in close consultation with cardiology.

Infants with PHACE syndrome represent a unique management challenge because most affected infants have extensive facial hemangiomas, with high risk for both medical morbidities and permanent facial scarring. Such patients are thus prime candidates for propranolol therapy.[4] The potential benefits of treatment must be weighed against the risks. The safe use of propranolol in individuals with PHACE has been described in several small case reports and case series, although no clinical trials have been conducted to assess the overall safety.[27,115]

It is recommended that infants with large facial hemangiomas at risk for PHACE be thoroughly evaluated with MRI/magnetic resonance angiography of the head and neck and cardiac imaging to include the aortic arch before considering propranolol. If imaging results place a patient into a higher risk category for stroke (Table 5), consultation and comanagement with neurology is appropriate. If the potential benefits of propranolol outweigh the risks, the consensus group recommends use of the lowest possible dose, slow dosage titration upward, close observation including inpatient hospitalization in high-risk infants, and 3 times daily dosing to minimize abrupt changes in systolic BP.

TABLE 5 Imaging and Clinical Features and Stroke Risk in PHACE Syndrome

Risk Category	Cerebrovascular Anomalies
High[a]	• Multiple vessels with severe narrowing or non-visualization without adequate collateral circulation and Moyamoya disease and Cardiac or Aortic arch anomalies • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation and Moyamoya disease and Cardiac or Aortic arch anomalies • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation and Moyamoya disease • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation and Cardiac or Aortic arch anomalies • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation
Standard	• Severe narrowing/stenosis[b] of major vessels[c] *with* adequate collateral circulation • Mild narrowing/stenosis[d] of major vessels[c] *with* adequate collateral circulation • Hypoplasia, dysplasia, aberrant origin or course of major vessels[c, e] • Persistent embryonic arteries • Aberrant subclavian artery

[a] risk further increased if coexistent cardiac or aortic arch anomalies.
[b] defined as vessel narrowing >75%.
[c] internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, basilar artery, vertebral artery.
[d] defined as vessel narrowing <75%, and categorized as standard risk given known frequency of overdiagnosis with MRA.
[e] any degree of severity.

Formulation, Target Dose, and Frequency

Propranolol is currently commercially available in propranolol hydrochloride oral solution (20 mg/5 mL and 40 mg/5 mL). It is recommended that the 20 mg/5 mL preparation be used because of the small volumes required for this indication. The consensus group recommends a target dose of 1 to 3 mg/kg per day with most members advocating 2 mg/kg per day, the median dose reported in the literature. Given the fact that dose escalation is required with propranolol and that IH often respond rapidly to even low doses, physicians will often use dose response to determine an individual's optimal target dose. Dose escalation from a low starting dose is always recommended even in the presence of inpatient monitoring as the initial cardiac response to β blockade may be pronounced.

The consensus group advocates that the daily dose of propranolol be divided into 3 times daily dosing with a minimum of 6 hours between doses, balancing considerations of safety, efficacy, and convenience.

Initiation of Propranolol in Infants With IH

Some facilities may have the resources and expertise to safely monitor all patients in an outpatient setting, and some practitioners continue to admit all infants. The following suggestions were made regarding monitoring for potential side effects while initiating oral propranolol for the treatment of problematic IH (Fig 1). We acknowledge that the data for safe outpatient initiation is mounting but still relatively limited for this indication. The recommendations are age-dependent with patients divided into 2 age groups.

Inpatient hospitalization for initiation is suggested for the following: Infants $\leq$8 weeks of gestationally corrected age, or any age infant with inadequate

social support, or any age infant with comorbid conditions affecting the cardiovascular system, the respiratory system including symptomatic airway hemangiomas or blood glucose maintenance.

Outpatient initiation with monitoring can be considered for infants and toddlers older than 8 weeks of gestationally corrected age with adequate social support and without significant comorbid conditions.

Cardiovascular Monitoring

The peak effect of oral propranolol on HR and BP is 1 to 3 hours after administration. Patients should be monitored with HR and BP measurement at baseline and at 1 and 2 hours after receiving the initial dose, and after significant dose increase (>0.5 mg/kg/day), including at least 1 set of measurements after the target dose has been achieved. If HR and BP are abnormal, the child should be monitored until the vitals normalize. Dose response is usually most dramatic after the first dose; therefore, there is no need to repeat cardiovascular monitoring multiple times for the same dose unless the child is very young or has comorbid conditions affecting the cardiovascular system or the respiratory system including symptomatic airway hemangiomas. Bradycardia is important to recognize because the accurate measurement of BP in infants may be challenging. HR is simple to measure, and normative data for inappropriate bradycardia have been established as follows:

- Newborns (<1 month old), <70 beats per minute
- Infants (1–12 months old), <80 beats per minute
- Children (>12 months old), <70 beats per minute

Systolic BP varies significantly between 1 month and 6 months of age, so normative data are difficult to interpret. Moreover, most pediatric normative BP tables were designed to evaluate for hypertension, not hypotension, and are based on auscultatory measurements.[118] Oscillometric devices are convenient and minimize observer error, but they do not provide measures that are identical to auscultation. Obtaining accurate BP measurements in neonates and infants may be challenging, and BP measurements should be obtained by experienced personnel. The infant should be in a warm room and in a resting state, awake or asleep. The use of an appropriately sized infant cuff is essential. The

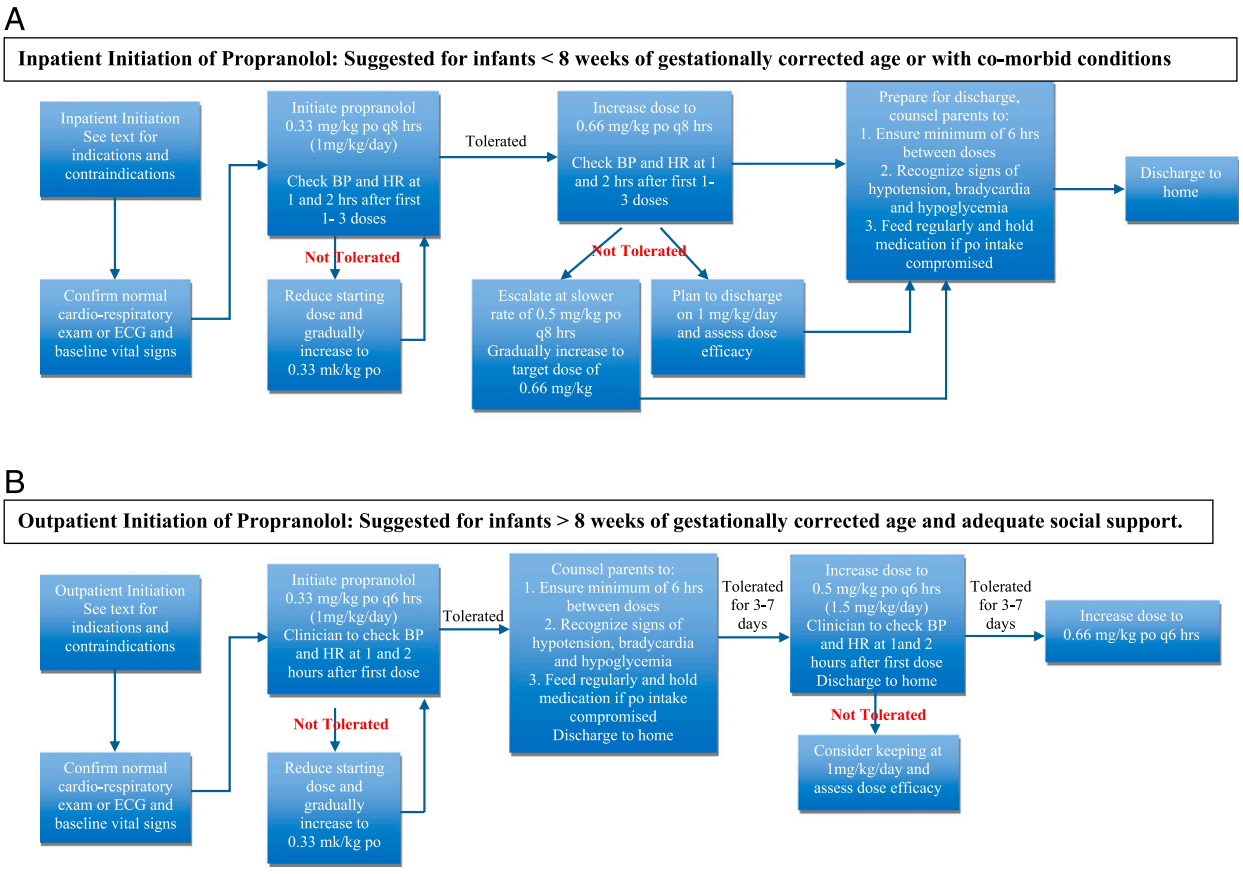

FIGURE 1

(A) Summary of recommended dose initiation for inpatient scenario. (B) Summary of recommended dose initiation for outpatient scenario. PO, oral administration; q6, every 6; q8, every 8.

inflatable portion of the cuff should encircle ≥75% of the limb circumference, and the length of the cuff should be at least two-thirds of the length of the upper limb segment. Specific age-based normative parameters for identification of systolic hypotension in infants are difficult to provide; as a general guide, we would describe systolic BP that is below normal (less than fifth percentile oscillometric or <2 SD of normal auscultation)[119] as follows:

- Newborn: <57 mm Hg (<5th percentile oscillometric) or 64 mm Hg (2 SD auscultation)
- 6 months: <85 mm Hg (<5th percentile oscillometric) or 65 mm Hg (2 SD auscultation)
- 1 year: <88 mm Hg (<5th percentile oscillometric) or 66 mm Hg (2 SD auscultation)

Patients who have HR and systolic BP measurements below these values during propranolol initiation/dose escalation warrant careful evaluation for additional evidence of cardiovascular compromise and should be considered at higher risk for continued propranolol use at that dose/continued dosage escalation.

The inpatient and outpatient dose escalation recommendations are age-dependent with patients divided into 2 age groups, as shown in Fig 1.

Ongoing Monitoring

As discussed earlier, patients should be monitored with HR and BP measurement at baseline and at 1 and 2 hours after a significant dose increase (>0.5 mg/kg/day), including at least 1 set of measurements after the target dose has been achieved. There is no published information on the utility of Holter monitoring in infants after initiating propranolol to identify occult bradycardia or arrhythmias, and this group has not reached consensus on a recommendation for Holter monitoring after reaching a steady dose. Most centers represented at the conference do not perform or recommend Holter monitoring in this setting on a routine basis.

Preventing Hypoglycemia

Although recognition of signs or symptoms of hypoglycemia may prompt early intervention, measures should be taken to decrease the risk of hypoglycemia. Because asymptomatic hypoglycemia was not detected in studies that included a random serum glucose as part of routine monitoring, and the timing of hypoglycemic events, as outlined in Table 3, has been variable and unpredictable, routine screening of serum glucose is not indicated. Propranolol should be administered during the daytime hours with a feeding shortly after administration. Parents should be instructed to ensure that their child is fed regularly and to avoid prolonged fasts. In otherwise healthy children, the risk of hypoglycemia is age-dependent and begins after 8 hours of fasting in children 0 to 2 years of age.[47] Infants <6 weeks should be fed at least every 4 hours, between 6 weeks and 4 months of age should be fed at least every 5 hours, and >4 months of age should be fed at least 6 to 8 hours. Propranolol should be discontinued during intercurrent illness, especially in the setting of restricted oral intake. Children undergoing procedures or radiologic imaging requiring fasting for sedation should be supported with Pedialyte (Abbott Nutrition, Abbott Laboratories, Columbus, OH) or glucose-containing IV fluids during periprocedural periods. Preoperative blood glucose levels may identify additional patients whose symptoms might otherwise be masked by preoperative medications and anesthesia. Particular care should be taken in using propranolol in preterm infant, patients prescribed other medications known to be associated with hypoglycemia or with medical conditions known to produce hypoglycemia.

CONCLUSIONS

Currently, the most significant barrier to the implementation of a multiinstitutional clinical trial for the treatment of IH with oral propranolol is the lack of standardized toxicity monitoring in infants without anatomic cardiac/vascular anomalies, as well as in infants with PHACE syndrome. Despite the widespread use of this drug, no

TABLE 6 Consensus Meeting Key Learnings

- There are no FDA-approved indications for propranolol in pediatric patients in the United States.
- There is significant uncertainty and divergence of opinion regarding safety monitoring and dose escalation for propranolol use in IH.
- ECG should be part of the pretreatment evaluation in any child when the HR is below normal, arrhythmia is detected on cardiac exam, or there is a family history of arrhythmias or maternal history of connective tissue disease.
- Cardiac and aortic arch anomalies are commonly seen in PHACE syndrome and require echocardiography to assess intracardiac anatomy and function in at-risk children.
- It is recommended that the 20 mg/5 mL preparation of propranolol be used.
- The consensus group advocates that the daily dose of propranolol be divided into 3 times daily.
- Regardless of the setting in which propranolol is initiated, it is recommended that the propranolol dose be titrated up to a target dose, starting at 1 mg/kg/day divided 3 times daily.
- The peak effect of oral propranolol on HR and BP is 1 to 3 h after administration.
- Dose response is usually most dramatic after the first dose of propranolol.
- Bradycardia may be the most reliable measurement of toxicity because obtaining accurate BPs in infants may be challenging, and normative data for bradycardia are better established.
- If a major escalation in dosage (>0.5 mg/kg/day) is indicated, the patient's HR should be assessed before, 1 and 2 h after the increased dose is administered.
- Hypoglycemia may be the most common serious complication in children treated with propranolol for IH.
- Propranolol should be discontinued during intercurrent illness, especially in the setting of restricted oral intake to prevent hypoglycemia.

systematic strategy currently exists to identify toxicities of therapy for infants with IH. The consensus team agreed on a number of recommendations that arose from a review of existing evidence supplemented by expert opinion and clinical experience (Table 6). These recommendations will provide the platform for large-scale phase II/III clinical trials to determine optimal dosing regimens and long-term safety profiles. We anticipate that these guidelines will be modified as more data are made available from these future studies.

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The Laryngoscope

BRAF V600E Does Not Predict Aggressive Features of Pediatric Papillary Thyroid Carcinoma

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Objectives/Hypothesis: This study aimed to review the prevalence of the BRAF V600E mutation in pediatric papillary thyroid carcinoma (PTC) and any possible association with aggressive tumor behavior.

Study Design: A retrospective chart review and post hoc BRAF V600E mutational analysis of archived tumor tissue.

Methods: Patients 0 to 18 years old who underwent surgery for PTC from 1999 to 2012 were selected for a retrospective chart review to assess for aggressive disease characteristics. Microdissection was performed on archived tumor tissue, which was analyzed for the BRAF V600E mutation by pyrosequencing.

Results: Archived tumor specimens were available for 19/27 pediatric patients who fit the inclusion criteria. Ages ranged from 2.8 to 18 years (median, 13.7 years). Thirteen patients (68.4%) had central neck metastases, eight (42.1%) had lateral neck metastases, and five (26.3%) had pulmonary metastases. The BRAF V600E mutation was present in seven patients (36.8%). There were 11 patients with classic PTC, seven with a follicular variant of PTC, and one with an oncocytic variant. Seven (63.6%) with classical PTC were BRAF V600E positive. All histologic variants were wild type. PTC histology significantly correlated with the BRAF mutation ($P = .013$). The BRAF mutation was associated with a lower metastases, age at diagnosis, completeness of resection, invasion, and size of the tumor score, which trended toward significance ($P = .087$). Presence of lymphatic or pulmonary metastases, tumor size, overall age, lymphovascular invasion, or extrathyroidal extension were not associated with BRAF V600E. Our results are combined with existing studies for a combined incidence of 28.4%.

Conclusions: BRAF V600E mutations may be more prevalent than previously thought in pediatric patients with PTC, but do not correlate with aggressive disease characteristics.

Key Words: Papillary thyroid cancer, pediatric, BRAF V600E mutation.

Level of Evidence: 4.

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INTRODUCTION

Thyroid cancers comprise 0.5% to 3% of all childhood malignancies,[1] and papillary thyroid cancer (PTC) is the predominant histologic subtype.[2] Children often present at a more advanced disease stage than adults; 35% to 83% present with cervical lymphatic disease and 9% to 30% with pulmonary metastases.[2] Potentially, tumor markers could help identify patients at higher risk for more aggressive disease and serve as a treatment target, or could be used as a diagnostic adjunct to help identify malignant disease on fine-needle aspiration (FNA) biopsy.

B-type RAF kinase (BRAF) is a member of a family of serine-threonine kinases that regulates intracellular growth signals.[3] The T1799A/V600E mutation leads to 500-fold higher activation of this signaling pathway in vitro than the wild-type protein.[4] In vivo, the mutation is thought to constitutively activate the pathway, leading to malignant transformation.[3,5] BRAF V600E is the most common gene mutation in PTC, with a prevalence of 29% to 83% in adult PTC.[6] Two recent meta-analyses estimated its prevalence in classical PTC at 45% and 50.9% and found a significant association with several aggressive disease characteristics.[7,8] BRAF mutations are not found in benign adenomas or follicular carcinomas, making it a highly specific marker for PTC.[9]

To our knowledge, only five series have examined the frequency of BRAF in non–radiation-associated pediatric PTC; these series have shown a 0% to 37% prevalence of BRAF mutations.[7,10–13] Two of these studies examined the relationship between BRAF status and aggressive tumor behavior, and did not find a positive correlation.[11,14] The overall prevalence of the BRAF mutation in the pediatric literature is variable, and correlation with aggressive tumor characteristics remains unclear. We aimed to review the prevalence of this tumor marker in our pediatric population, and to

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BRAF codon 600 primers:	
Forward	5'-ACTACACCTCAGATATATTTCTTC-3'
Reverse	5'-biotin-AATCAGTGGAAAAATAGCCTCAAT-3'
Sequencing	5'-GTGATTTTGGTCTAGCTACA-3'

Fig. 1. Primers used the polymerase chain reaction to amplify exon 15 of the *BRAF* gene.

determine its association with aggressive disease characteristics. Better understanding of the relevance of this tumor marker in this population has possible implications for adjuncts in diagnosis, treatment planning, and targeted therapy.

MATERIALS AND METHODS

Patients 0 to 18 years old were selected for a retrospective chart review if they underwent surgery for PTC at our institution (Primary Children's Medical Center, The University of Utah Hospital, Huntsman Cancer Hospital) between 1999 and 2012. Institutional review board approval was obtained (The University of Utah IRB 00057453).

A retrospective chart review was performed using institutional electronic medical records. Patient demographic factors and disease characteristics (tumor size, lymphatic/distant metastases, surgical and adjuvant treatment rendered, lymphovascular invasion, extrathyroidal extension, recurrence, histology) were obtained and kept in a secure patient database. Metastases, age at diagnosis, completeness of resection, invasion, and size of the tumor (MACIS) score was calculated.[15]

Tumor samples for the study subjects were obtained from archived pathologic specimens. Formalin-fixed paraffin-embedded (FFPE) tissue blocks were used to prepare hematoxylin and eosin slides to identify areas of tumor cells. Aniline blue-stained slides were processed from adjacent slices of FFPE tissue, and microdissection of tumor cells was performed. A single pathologist (A.M.A.) performed all tumor microdissection. DNA was then extracted using a standardized technique.[16]

Exon 15 of the BRAF gene was amplified using polymerase chain reaction with primers as shown in Figure 1. After the amplification, mutation status was determined by pyrosequencing using the Qiagen PyroMark Q24 pyrosequencer (Qiagen, Venlo, the Netherlands) following the manufacturer's instructions, as has been outlined previously.[17] Sequence analysis was performed using the Pyromark Q24 version 1.0.10 software in the allele quantification (AQ) analysis mode, using pyrograms as shown in Figure 2. The assay operates with a sensitivity of 5% of alleles.

Statistical analysis was performed with SPSS software (IBM, Armonk, New York). Fischer exact test was used to measure the association of the BRAF V600E mutation between binary variables (lateral and central neck metastases, pulmonary metastases, histology, lymphovascular invasion, extrathyroidal extension, recurrence). A two-tailed t test was used to measure association between the BRAF mutation and continuous data (tumor size, age, MACIS score).

A review of the literature was performed by searching PubMed for "papillary thyroid carcinoma" and "BRAF" with limits applied for patients aged 0 to 18 years, as well as additional text search strings for "children" or "pediatric" or "adolescent." Results of these relevant studies were summarized.

RESULTS

Archived tumor specimens were available for 19 of 27 pediatric patients who initially fit inclusion criteria. Demographic data are shown in Table I. Ages ranged from 2.8 to 18 years (median, 13.6 years). Two patients had previously undergone thyroidectomy, whereas the remainder had thyroidectomy performed at our facility. Average tumor size was 2.18 cm (range, 3 mm to 4.2 cm). Five patients had papillary microcarcinoma, whereas the remainder had tumors >1 cm. The average MACIS score was 5.1. Thirteen patients underwent central compartment neck dissection, nine underwent lateral neck dissection, including two who underwent bilateral neck dissections. Thirteen patients (68.4%) had metastases to the central neck, eight (42.1%) had lateral neck metastases, and five (26.3%) had pulmonary metastases. Two patients experienced regional recurrence. The BRAF V600E mutation was present in seven patients (36.8%). Eleven patients had classic PTC (including one with partial tall cell morphology), seven had a follicular variant of PTC, and one had an oncocytic variant. Seven of the 11 (63.6%) samples with classical PTC were BRAF V600E positive. All samples with variant pathology showed wild-type BRAF.

PTC histology was significantly associated with the presence of the BRAF V600E mutation ($P = .013$, Cramer's effect size V = 0.651). Similarly, FVPTC histology was negatively associated with the BRAF V600E mutation ($P = .017$). There was no association of the following variables with wild type or BRAF V600E (Table II): presence of lateral neck metastases (50.0% vs. 28.5%, $P = .633$), central neck metastases (75.0% vs. 57.1%, $P = .617$), pulmonary metastases (42% vs. 0%, $P = .106$), average tumor size (2.23 cm vs. 2.08 cm, $t = 0.176$, $P = .863$), average age (12.9 years vs. 14.8 years, $t = -1.221$, $P = .239$), lymphovascular invasion (77.8% vs. 60.0%, $P = .580$), extrathyroidal extension (62.5% vs. 60%, $P = 1.00$), and incidence of papillary microcarcinoma (36.4% vs. 16.7%, $P = .851$). MACIS score approached significance (5.59 vs. 4.23, $P = .087$)

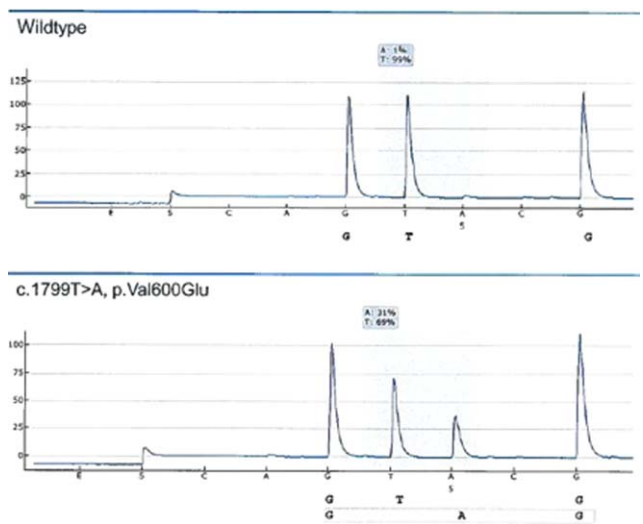

Fig. 2. Sequence analysis using the Pyromark Q24 version 1.0.10 software in the allele quantification analysis mode using pyrograms.

TABLE I.
Patient Characteristics.

Patient No.	Age, yr	Tumor Size, cm	Lateral Neck Disease	Central Neck Disease	Pulmonary Metastases	Recurrence	Histology	Lymphovascular Invasion	Extracapsular Extension	MACIS Score	BRAF Mutation
1	15.2	1.9	N	N	N	NR	PTC	NR	N	3.67	Positive
2	11.2	6	Y	Y	Y	NR	PTC	Y	Y	8.9	Negative
3	10.9	NR	Y	Y	N	Y	FVPTC	Y	Y	—	Negative
4	13.4	3	Y	Y	Y	NR	FVPTC	NR	NR	8	Negative
5	13.7	0.3	Y	Y	N	N	FVPTC	Y	Y	4.19	Negative
6	2.8	2.6	N	Y	Y	N	FVPTC	Y	NR	7.88	Negative
7	12.4	1.3	N	N	N	N	PTC	N	Y	3.49	Positive
8	11.8	3.3	N	N	N	N	FVPTC	NR	NR	4.09	Negative
9	16.2	0.3	N	N	N	NR	PTC	N	N	3.19	Negative
10	13.8	2.7	Y	Y	N	Y	PTC	Y	Y	4.91	Positive
11	18.3	NR	Y	Y	N	N	PTC	NR	NR	—	Positive
12	12.5	3.9	Y	Y	Y	NR	FVPTC	Y	Y	8.27	Negative
13	12.8	1.4	N	N	N	N	FVPTC	N	N	3.52	Negative
14	15.1	0.8	N	N	N	N	PTC	N	N	3.34	Positive
15	13	1.6	N	Y	N	N	PTC	Y	NR	4.58	Positive
16	16.7	2.3	N	Y	Y	N	PTC, oncocytic variant	Y	Y	4.79	Negative
17	15.5	4.2	N	Y	N	N	PTC	Y	Y	5.36	Positive
18	14.8	0.5	Y	Y	N	N	PTC–TCM	Y	N	4.25	Negative
19	17.4	0.9	N	Y	N	N	PTC	NR	NR	4.37	Negative

FVPTC = follicular variant of papillary thyroid carcinoma; MACIS = metastases, age at diagnosis, completeness of resection, invasion, size of the tumor scoring; N = no; NR = not reported; PTC = papillary thyroid carcinoma; TCM = tall cell morphology; Y = yes.

with a higher MACIS score in BRAF wild-type patients. The presence of tumor size >1 cm was not statistically associated with the BRAF V600E mutation ($P = .851$).

Our literature review identified a total of five studies that examined pediatric patients with well-differentiated thyroid cancer and assessed for the BRAF gene mutation. Prevalence was variable ranging from 0% to 36%. Two studies reviewed the disease characteristics of the patients and did not find an association between BRAF V600E and aggressive disease. When the results of our study were added to the existing literature, the cumulative presence of BRAF V600E in pediatric thyroid cancer was 28.4% (Table III).

DISCUSSION

The BRAF V600E gene mutation has been increasingly studied in various disease entities such as thyroid carcinoma, melanoma, astrocytoma, and colon cancers. Chemotherapeutic agents have been successfully used to target this gene mutation in clinical trials in adults. Numerous studies have attempted to correlate the

TABLE II.
Association of BRAF V600E With Disease Factors.

Independent Variable	Wild-Type BRAF	Mutant BRAF	Significance
Percentage with PTC histology	33.3% (4/12)	100% (7/7)	$P = .013$
Percentage with lateral neck metastases	50% (6/12)	28.5% (2/7)	$P = .633$
Percentage with central neck metastases	75% (9/12)	57.1% (4/7)	$P = .617$
Percentage with pulmonary metastases	42% (5/12)	0% (0/7)	$P = .106$
Percentage with lymphovascular invasion	77.8% (7/9)	60% (3/5)	$P = .580$
Percentage with extrathyroidal extension	62.5% (5/8)	60% (3/5)	$P = 1.00$
Percentage with microcarcinoma	36.3% (4/11)	16.7% (1/6)	$P = .851$
Average age, yr*	12.9	14.8	$t = -1.221$, $P = .239$
Average MACIS score*	5.59	4.23	$P = .087$
Average tumor size, cm*	2.23	2.08	$t = 0.176$, $P = .863$

*These continuous variables describe differences between the two groups BRAF V600E and BRAF wild-type.
MACIS = metastases, age at diagnosis, completeness of resection, invasion, size of the tumor; PTC = papillary thyroid carcinoma.

TABLE III.
Literature Review.

Study and Year	Patients With BRAF Mutation	Percentage	Association With Aggressive Disease Characteristics	Country of Origin
Kumagai 2004	1 of 31	3.2%	Factors not associated with BRAF V600E: tumor size, lymphatic or distant metastases, extrathyroidal extension.	Japan
Nikiforova 2004	30 of 82	36.6%	Not examined.	Belarus and Ukraine
Penko 2005	0 of 14	0%	Not examined.	U.S.A.
Rosenbaum 2005	4 of 20	20%	Not examined.	U.S.A.
Sassoulas 2012	21 of 56	20.3%	Factors not associated with BRAF V600E: lymphatic metastases or extrathyroidal extension.	France, Italy
Givens 2014 (current study)	7 of 19	36.8%	BRAF V600E is associated with PTC histology and is negatively associated with FVPTC histology. Factors not associated with BRAF V600E: lymphatic or distant metastases, age, tumor size, extrathyroidal extension, lymphovascular invasion, MACIS score, microcarcinoma. Prevalence in patients with classical PTC is 63.6%.	U.S.A.
Cumulative prevalence	63 of 222	28.4%		

FVPTC = follicular variant of papillary thyroid carcinoma; MACIS = metastases, age at diagnosis, completeness of resection, invasion, size of the tumor scoring; PTC = papillary thyroid carcinoma.

presence of the mutation with aggressive disease characteristics, but no general consensus has been reached. A recent meta-analysis in adults, including 14 studies and 2,470 patients reported that the BRAF mutation was significantly associated with recurrence, lymphatic metastases, extrathyroidal extension, and advanced stage.[7]

Thyroid cancer is rare in pediatric populations, and these patients often present at a more advanced stage. Few studies in children have examined the prevalence of the BRAF gene mutation, or its association with aggressive disease characteristics. In our study, tumor specimens from 19 pediatric patients with PTC were analyzed for the presence of the BRAF gene mutation. The BRAF mutation was present in 7/19 patients (36.8%) overall, and in 7/11 patients (63.6%) with classic PTC. All patients with variant pathology were wild type, which is similar to previous reports of a very low incidence of the BRAF mutation in histologic variants of PTC.[13]

Previous studies of pediatric patients with PTC demonstrated a BRAF mutation prevalence of 0% to 37%.[10–14] The prevalence of the BRAF gene mutation in our sample of patients with classic PTC (63.6%) is much higher than previously reported in the pediatric literature (Table III), and higher than the prevalence reported in two recent meta-analyses of adult patients (45% and 50.9%),[7,8] but similar to rates published in individual studies in adults (27%–73%).[7,18] This study is the most comprehensive of its type in that it attempts to determine an association of the BRAF V600E mutation with aggressive disease features commonly seen in pediatric PTC. Only two previous studies from the US population[12,13] have examined the BRAF prevalence in the pediatric population, and these studies did not comment on aggressive disease characteristics (Table III). The studies from Europe and Japan that did review the clinical course of their patients did not find any association with some aggressive characteristics.[11,14] This question is important to answer in the US population, because oncogene mutations may display variable prevalence in different geographical regions.[14]

The BRAF V600E mutation was significantly associated with malignancy, specifically PTC histology ($P = .013$), as has been reported previously in the adult literature.[8] No patients with other variant pathology, including seven follicular variants of PTC (FVPTC), one tall cell variant, and one oncocytic variant were BRAF V600E mutants. FVPTC histology was significantly negatively associated with BRAF V600E ($P = .017$). This is in agreement with findings from a recent meta-analysis of the adult literature,[8] and is important because this mutation could serve as a diagnostic adjunct in FNA biopsy. Gene panel assays are currently in early phases of use for thyroid cancer diagnosis.[19,20] Some authors have recommended escalating therapy (such as performing a total thyroidectomy instead of lobectomy) in patients with a thyroid nodule that have a known genetic mutation.[21]

In contrast to the adult population, we did not find that the BRAF mutation was associated with other markers of aggressive disease such as lateral neck metastases ($P = .633$), central neck metastases ($P = .617$), pulmonary metastases ($P = .106$), tumor size ($P = .863$), lymphovascular invasion ($P = .580$), or extrathyroidal extension ($P = 1.00$). It was also not associated with older age ($P = .239$). Interestingly, there was a negative association between the BRAFV600E mutation and a higher MACIS score ($P = .087$). This association approached statistical significance, and could become significant with a higher sample size.

MACIS score was chosen as a surrogate for more advanced disease because, unlike the AGES and AMES scoring systems for prognosis, it does not rely as heavily on age to calculate the score. MACIS score is calculated with numerical points added for age, tumor size, incomplete resection, local invasion, and distant metastases. This system has been previously validated in children and adolescents[22] as a useful prognostic indicator. A

MACIS score >4.0 was associated with aggressive PTC.[22] We did not find a difference in BRAF V600E mutations between patients with a MACIS score <4, and with scores of 4 or greater (60% vs. 25%, $P = .56$). Overall MACIS score showed a trend toward negative association with the BRAF V600E mutation ($P = .087$). In adults, BRAF V600E has been shown to be a useful prognostic indicator when added to MACIS[23]; however, another study[24] failed to show a statistical association between a MACIS score of >6 (which is commonly used as a cutoff for aggressive disease in adults) and the presence of the BRAF mutation. No studies previous performed in children with the BRAF V600E mutation have reviewed association with MACIS score.

Children typically present with higher rates of regional metastases (57% in one study[2]) than adults (13% in one study[25]). Two other studies in children examined the presence of lymphatic metastases[14] and tumor size, lymph node invasion, distant metastases, and extrathyroidal extension,[11] and did not find any significant association with BRAF mutation status (Table III). Two recent meta-analyses in adults found a significant association of BRAF V600E with lymphatic metastases,[8] tumor size >1 cm,[8] and extrathyroidal extension.[7,8] One study did not examine association with lymphovascular invasion,[7] whereas one did not demonstrate an association of lymphovascular invasion with BRAF V600E.[8] Our findings are also in agreement with the existing pediatric literature, which found no association of the BRAF V600E mutation with lymphatic or distant metastases[11,14] or extrathyroidal extension.[11]

We acknowledge the limitations of this study in that it is a retrospective review with a small sample size. The study is insufficiently powered to detect a statistically significant association between the BRAF mutation and aggressive disease characteristics, if one truly exists. Additionally, certain variables such as tumor size, lymphovascular invasion, and extrathyroidal or extracapsular extension were inconsistently reported in our pathology reports. Finally, patient follow-up information was not always available, making association with recurrence unclear.

CONCLUSION

The BRAF V600E mutation may be more prevalent than previously thought in pediatric patients with PTC, but it is not associated with aggressive disease characteristics. This is in contrast to the findings in the adult population, where a BRAF gene mutation may be an indication for more aggressive surgical treatment. We cannot support that conclusion in the pediatric population.

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Evaluation and Management of Neck Masses in Children

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Neck masses in children usually fall into one of three categories: developmental, inflammatory/reactive, or neoplastic. Common congenital developmental masses in the neck include thyroglossal duct cysts, branchial cleft cysts, dermoid cysts, vascular malformations, and hemangiomas. Inflammatory neck masses can be the result of reactive lymphadenopathy, infectious lymphadenitis (viral, staphylococcal, and mycobacterial infections; cat-scratch disease), or Kawasaki disease. Common benign neoplastic lesions include pilomatrixomas, lipomas, fibromas, neurofibromas, and salivary gland tumors. Although rare in children, malignant lesions occurring in the neck include lymphoma, rhabdomyosarcoma, thyroid carcinoma, and metastatic nasopharyngeal carcinoma. Workup for a neck mass may include a complete blood count; purified protein derivative test for tuberculosis; and measurement of titers for Epstein-Barr virus, cat-scratch disease, cytomegalovirus, human immunodeficiency virus, and toxoplasmosis if the history raises suspicion for any of these conditions. Ultrasonography is the preferred imaging study for a developmental or palpable mass. Computed tomography with intravenous contrast media is recommended for evaluating a malignancy or a suspected retropharyngeal or deep neck abscess. Congenital neck masses are excised to prevent potential growth and secondary infection of the lesion. Antibiotic therapy for suspected bacterial lymphadenitis should target *Staphylococcus aureus* and group A streptococcus. Lack of response to initial antibiotics should prompt consideration of intravenous antibiotic therapy, referral for possible incision and drainage, or further workup. If malignancy is suspected (accompanying type B symptoms; hard, firm, or rubbery consistency; fixed mass; supraclavicular mass; lymph node larger than 2 cm in diameter; persistent enlargement for more than two weeks; no decrease in size after four to six weeks; absence of inflammation; ulceration; failure to respond to antibiotic therapy; or a thyroid mass), the patient should be referred to a head and neck surgeon for urgent evaluation and possible biopsy. (*Am Fam Physician.* 2014;89(5):353-358.

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 327.

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Primary care physicians commonly see children with a neck mass. These masses often cause significant alarm and anxiety to the caregiver; however, a neck mass in a child is seldom malignant.[1] In a review of children with neck masses that were biopsied in a tertiary referral center, 11% were cancerous.[2] It is likely that the malignancy rate would be much lower in a primary care physician's office. In one series, 44% of children younger than five years had palpable lymph nodes, suggesting that benign lymphadenopathy is common in this population.[3] Recognizing the possibilities within a broad differential diagnosis will allow the experienced physician to effectively evaluate and identify these lesions. Understanding the appropriate workup and indications for intervention will prevent use of unnecessary diagnostic tests and therapies.

History and Physical Examination

Neck masses in children typically fall into one of three categories: developmental, inflammatory/reactive, or neoplastic *(Table 1)*. Important aspects of the history and physical examination can help narrow the differential diagnosis into one of these categories *(Table 2)*.

TIMING

The onset and duration of symptoms should be elicited during the initial history. A mass present since birth or discovered during the neonatal period is usually benign and developmental. Vascular malformations present at birth and grow with the child, whereas hemangiomas develop a few weeks after birth and have a rapid growth phase. Developmental masses may present later in life, either with superimposed infection or with growth over time. A new, rapidly

Table 1. Differential Diagnosis of Neck Masses in Children

	Diagnosis		
Location	*Developmental*	*Inflammatory/reactive*	*Neoplastic*
Anterior sternocleidomastoid	Branchial cleft cyst,* vascular malformation	Reactive lymphadenopathy,* lymphadenitis (viral, bacterial),* sternocleidomastoid tumor of infancy	Lymphoma
Midline	Thyroglossal duct cyst,* dermoid cyst*	—	Thyroid tumor
Occipital	Vascular malformation	Reactive lymphadenopathy,* lymphadenitis*	Metastatic lesion
Preauricular	Hemangioma, vascular malformation, type I branchial cleft cyst	Reactive lymphadenopathy,* lymphadenitis,* parotitis,* atypical mycobacterium	Pilomatrixoma, salivary gland tumor
Submandibular	Branchial cleft cyst,* vascular malformation	Reactive lymphadenopathy,* lymphadenitis,* atypical mycobacterium	Salivary gland tumor
Submental	Thyroglossal duct cyst,* dermoid cyst*	Reactive lymphadenopathy,* lymphadenitis (viral, bacterial)*	—
Supraclavicular	Vascular malformation	—	Lymphoma,* metastatic lesion

*—Type of lesions that are more commonly found in that location.

growing mass is usually inflammatory. If the mass persists for six weeks, or enlarges after initial antibiotic therapy, a neoplastic lesion must be considered. Concern for airway involvement or malignancy should prompt immediate referral or imaging. A slowly enlarging mass over months to years suggests benign lesions such as lipomas, fibromas, or neurofibromas.

ASSOCIATED SYMPTOMS

Fevers, rapid enlargement or tenderness of the mass, or overlying erythema indicates a likely inflammatory etiology *(Figure 1)*. Most malignant neck masses in children are asymptomatic and are not painful.[4] However, acute infection in a necrotic, malignant lymph node can also occur. An upper respiratory tract infection preceding the onset of the mass suggests possible reactive lymphadenopathy or a secondary infection of a congenital cyst. Constitutional type B symptoms such as fever, malaise, weight loss, and night sweats suggest a possible malignancy. Lymphadenopathy with high fever, bilateral conjunctivitis, and oral mucosal changes with a strawberry tongue likely represents Kawasaki disease.

Table 2. History and Physical Examination Clues to Diagnosis in Children with a Neck Mass

Finding	*Diagnosis*
History	
Fevers, pain	Inflammatory
Present at birth	Developmental
Rapidly growing mass	Inflammatory, malignancy
Physical examination	
Hard, irregular, firm, immobile	Malignancy
Larger than 2 cm	Malignancy
Midline location	Thyroglossal duct cyst, dermoid cyst, thyroid mass
Shotty lymphadenopathy	Reactive lymph nodes
Supraclavicular location	Malignancy

RECENT EXPOSURES

Recent upper respiratory tract infections; animal exposures (cat scratch, cat feces, or wild animals); tick bites; contact with sick children; contact with persons who have tuberculosis; foreign travel; and exposure to ionizing radiation should be reviewed.[5] Medications should also be reviewed because drugs such as phenytoin (Dilantin) can cause pseudolymphoma or can cause lymphadenopathy associated with anticonvulsant hypersensitivity syndrome.

LOCATION

The location of the neck mass provides many clues to the diagnosis. The most common midline cystic neck masses are thyroglossal duct cysts and dermoid cysts *(Figure 2)*. Thyroglossal duct cysts are often located over the hyoid bone and elevate with tongue protrusion or swallowing, whereas dermoid cysts typically move with the overlying

skin.[6] Malignant anterior neck masses are usually caused by thyroid cancer. Congenital masses in the lateral neck include branchial cleft anomalies, vascular or lymphatic malformations, and fibromatosis colli. Lymphadenopathy in the lateral neck can be inflammatory or neoplastic. Supraclavicular lymph nodes or those in the posterior triangle (behind or lateral to the sternocleidomastoid muscle) have a higher incidence of malignancy than lymph nodes in the anterior triangle (anterior or medial to the sternocleidomastoid muscle).[2] Generalized or multiple anatomic sites of lymphadenopathy increase the chance of malignancy.[7,8]

PALPATION

The consistency of the mass provides useful information. Shotty lymphadenopathy refers to the presence of multiple small lymph nodes that feel like buckshot under the skin.[9] In the neck, this usually implies a reactive lymphadenopathy from an upper respiratory tract infection. A hard, irregular mass, or a firm or rubbery mass that is immobile or fixed to the deep tissues of the neck may indicate malignancy.

SIZE

Size alone cannot confirm or exclude a diagnosis. However, cervical lymph nodes up to 1 cm in size are normal in children younger than 12 years,[10] with the exception of the jugulodigastric lymph node, which can be as large as 1.5 cm. Persistent enlarged lymph nodes greater than 2 cm that do not respond to empiric antibiotic therapy should be evaluated for possible biopsy.

Initial Diagnostic Testing

The primary care physician ultimately must determine whether further invasive workup or treatment is necessary, or if watchful waiting is appropriate. Laboratory studies may be indicated if there is concern about a systemic disease or to confirm a diagnosis suspected from the history and physical examination. Ordering routine studies in a shotgun style approach is rarely indicated and seldom can reliably rule in or out a specific disease *(Table 3)*. Results of a complete blood

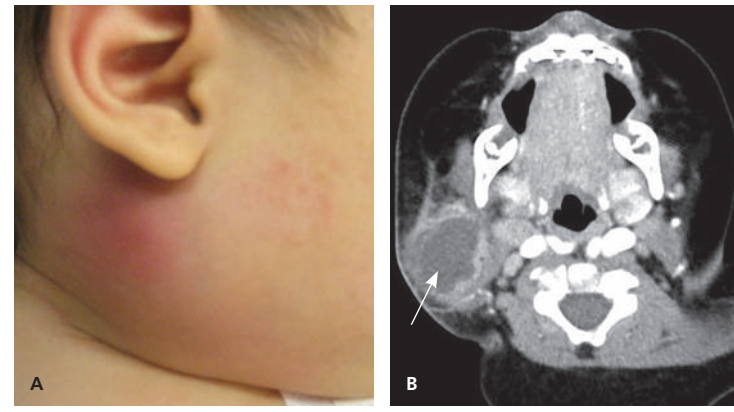

Figure 1. *(A)* Lateral neck mass in a seven-month-old girl. She presented with fever, swelling for three days, overlying erythema, tenderness, and an elevated white blood cell count. *(B)* Computed tomography with contrast media showed a cystic mass (*arrow*) with enhancing rim suggestive of suppurative lymphadenitis. The abscess was incised and drained, and was found to be positive for *Staphylococcus aureus*.

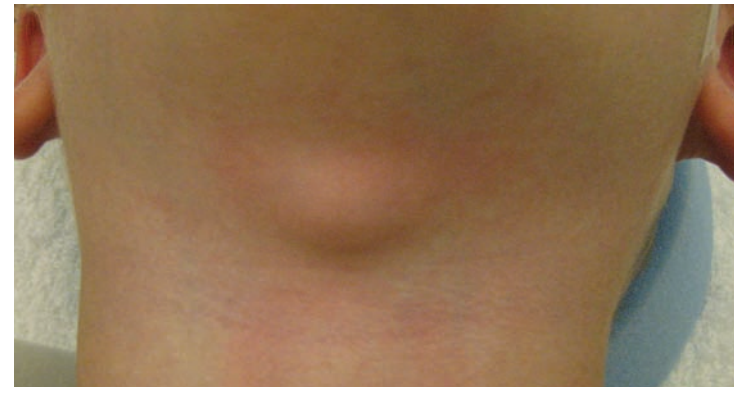

Figure 2. Midline neck mass in a four-year-old boy consistent with a thyroglossal duct cyst.

Table 3. Indications for Ordering Clinical Laboratory or Imaging Studies in the Workup of a Child with a Neck Mass

Test	*Indication*
Bartonella henselae titers	Recent exposure to cats
Complete blood count	Serious systemic disease suspected (e.g., leukemia, mononucleosis)
Computed tomography	Imaging study for retropharyngeal or deep neck abscess, or suspected malignancy
Magnetic resonance imaging	Preferred if vascular malformation is suspected
Purified protein derivative (PPD) test for tuberculosis	Exposure to tuberculosis, young child in rural community (atypical tuberculosis)
Ultrasonography	Recommended initial imaging study for a developmental mass, palpable mass, or suspected thyroid problem
Viral titers (cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, toxoplasmosis)	If history suggests exposure or a suspected inflammatory mass is not responding to antibiotics

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
When indicated, ultrasonography is the preferred initial imaging study for most children with a neck mass.	C	12	Based on expert opinion
Empiric antibiotic therapy with observation for four weeks is acceptable for children with presumed reactive lymphadenopathy.	C	11	Based on a consensus-based practice guideline
Excision of presumed congenital neck masses in children is recommended to confirm the diagnosis and to prevent future problems.	C	1	Based on observational studies
In children, enlarged lymph nodes that are rubbery, firm, immobile, or that persist for longer than six weeks or that enlarge during a course of antibiotics should be considered for biopsy.	C	19, 20	From a consensus guideline based on observational studies

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

count with differential may be abnormal with infectious lymphadenitis. A complete blood count with differential is recommended in patients with a history and physical examination suggestive of infection or malignancy; however, good evidence to support the value of routine complete blood count is lacking. Atypical lymphocytosis can occur in mononucleosis, and pancytopenia with blast cells suggests leukemia.[11] If there was recent exposure to cats, measurement of *Bartonella henselae* titers to evaluate for cat-scratch disease should be considered. Measurement of titers for Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, and toxoplasmosis also should be considered if the history suggests possible exposure or if a presumed inflammatory mass is not responding to antibiotics.

Imaging may help with diagnosis and with planning for invasive intervention. The American College of Radiology considers ultrasonography, computed tomography with intravenous contrast media, and magnetic resonance imaging with or without intravenous contrast media appropriate imaging studies for a child up to 14 years of age presenting with a neck mass.[12] Ultrasonography is the preferred initial imaging study in an afebrile child with a neck mass or a febrile child with a palpable neck mass.[12] Ultrasonography is a relatively quick, inexpensive imaging modality that avoids radiation and helps define the size, consistency (solid vs. cystic), shape, vascularity, and location of the mass. Malignancy is more likely with an abnormally shaped lymph node compared with a lymph node that retains its normal architecture. If fine-needle aspiration is warranted for deep neck masses, ultrasonographic guidance can help. Ultrasonography should be performed when a thyroglossal duct cyst is suspected to determine the presence of a normal thyroid gland. Ultrasonography also should be the initial imaging study for the evaluation of a thyroid mass.

Computed tomography with intravenous contrast media is the preferred study for evaluating a malignancy or a suspected retropharyngeal or deep neck abscess that may require surgical drainage.[12] Computed tomography with contrast media should not be ordered for a thyroid mass; uptake of contrast media by thyroid tissue could delay subsequent radioactive iodine treatment if needed. Magnetic resonance imaging better defines soft tissue anatomy[13] and avoids the radiation exposure from computed tomography. However, the expense and frequent need for sedation often limit magnetic resonance imaging as the initial imaging study of choice. Magnetic resonance imaging is the imaging study of choice when a vascular malformation is suspected.

Fine-needle aspiration may provide critical diagnostic information and avoid the need for open biopsy. Sensitivity of fine-needle aspiration in children is usually greater than 90%[14-16] and specificity is approximately 85%.[16] However, in one series, 76% of the children required general anesthesia; a cytopathologist who has experience with neck lesions in children is essential.[16] Occasionally, fine-needle aspiration does not provide sufficient tissue or adequate evaluation of lymph node architecture, and an open biopsy is needed to determine the diagnosis.

Initial Treatment and Referral

Little evidence exists to definitively determine the best approach for the child with a neck mass. Current suggested algorithms are based on expert opinion.[17] Observation is recommended initially in children with cervical lymphadenitis that is bilateral, whose lymph nodes are

smaller than 3 cm and are not erythematous or exquisitely tender.[18] An empiric course of antibiotics should be considered for patients with cervical lymphadenitis if they have systemic symptoms (e.g., fever, chills), unilateral lymphadenopathy, or erythema and tenderness, or if their lymph nodes are larger than 2 to 3 cm.[18] If an antibiotic is prescribed, a 10-day course of oral cephalexin (Keflex), amoxicillin/clavulanate (Augmentin), or clindamycin is recommended based on expert opinion, because the most common organisms are *Staphylococcus aureus* and group A streptococcus.[11] Empiric antibiotic therapy with observation for four weeks is acceptable for presumed reactive lymphadenopathy.[11] *Figure 3* is an algorithm for the treatment of a child presenting with a neck mass.

Children with congenital neck masses should be referred to a specialist to consider definitive excision *(Table 4)*. Excision is recommended to confirm the diagnosis and to prevent future problems (e.g., potential growth, secondary infection).[1] Patients with suppurative lymphadenitis or a neck abscess that does not respond to oral antibiotic therapy should be referred for intravenous antibiotics, possible incision and drainage, or further workup. If malignancy is suspected (accompanying type B symptoms; hard, firm, or rubbery

Table 4. Indications for Referral in Children with a Neck Mass

Developmental mass requiring excision for definitive therapy
Infectious lymphadenitis requiring incision and drainage
Mass suggests malignancy
Enlarged lymph node persistent for six weeks
Firm, rubbery lymph node > 2 cm in diameter
Hard, immobile mass
Size increasing during antibiotic therapy
Supraclavicular mass
Thyroid mass

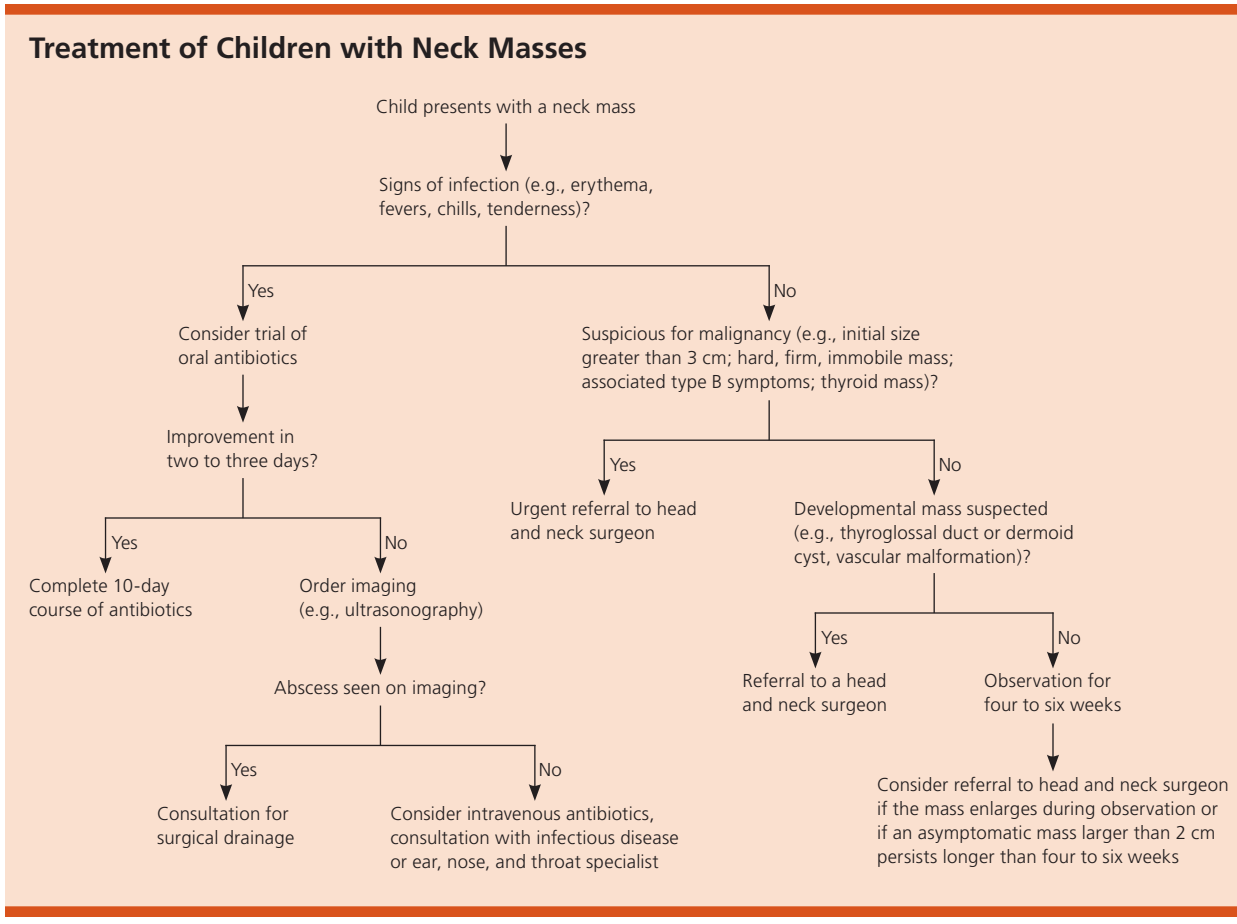

Figure 3. Algorithm for the treatment of children with neck masses.

consistency; fixed mass; supraclavicular mass; lymph node larger than 2 cm in diameter; persistent enlargement for more than two weeks; no decrease in size after four to six weeks; absence of inflammation; ulceration; failure to respond to antibiotic therapy; or a thyroid mass), the patient should be referred to a head and neck surgeon for urgent evaluation and possible biopsy. Although rare, malignant lesions such as lymphoma, rhabdomyosarcoma, thyroid carcinoma, and metastatic nasopharyngeal carcinoma can occur in children.

An asymptomatic lesion that appears to be an enlarged lymph node creates a difficult dilemma for the primary care physician. Usually, the patient or caregiver is anxious for a diagnosis and an intervention. Most cases of lymphadenopathy are self-limited and require only observation and patience.[11] Enlarged lymph nodes that are rubbery, firm, immobile, or that persist for longer than six weeks or enlarge during a course of antibiotics should be evaluated by a head and neck surgeon, and a biopsy is recommended.[19-21]

Data Sources: A PubMed search was completed in Clinical Queries using the key term pediatric neck mass. The search included systematic reviews, meta-analyses, consensus development conferences, and guidelines. Also searched was the Cochrane database. Search dates: August 25, 2011, and December 2, 2013.

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Review

S.E. Mitchell Vascular Anomalies Flow Chart (SEMVAFC): A visual pathway combining clinical and imaging findings for classification of soft-tissue vascular anomalies☆

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Classification of vascular anomalies (VAs) is challenging due to overlapping clinical symptoms, confusing terminology in the literature and unfamiliarity with this complex entity. It is important to recognize that VAs include two distinct entities, vascular tumours (VTs) and vascular malformations (VaMs). In this article, we describe SE Mitchell Vascular Anomalies Flow Chart (SEMVAFC), which arises from a multidisciplinary approach that incorporates clinical symptoms, physical examination and magnetic resonance imaging (MRI) findings to establish International Society for the Study of Vascular Anomalies (ISSVA)-based classification of the VAs. SEMVAFC provides a clear visual pathway for physicians to accurately diagnose Vas, which is important as treatment, management, and prognosis differ between VTs and VaMs.

Introduction

The classification of vascular anomalies (VAs) is confusing to most physicians. Overlapping clinical and imaging findings, rarity of the VAs, lack of physician experience, and multidisciplinary approach in many centres contribute to the chaos in diagnosis and management of VAs. To clarify this situation, correct terminology for each entity should be consistently used amongst all disciplines involved in the care of VAs. Even as recently as 2009, Hassanein et al. found that the term “haemangioma” was used incorrectly in 71.3% of publications that year.[1] This emphasizes the importance of understanding the current classification system that was approved by International Society for the Study of Vascular Anomalies (ISSVA) in 1996 (Table 1), which stems from the biological behaviour-based classification system introduced by Drs Mulliken and

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Table 1
Vascular anomalies (simplified and adapted from ISSVA 1996).

Vascular tumours
Infantile haemangiomas
Congenital haemangiomas
• Rapidly involuting congenital haemangiomas
• Non-involuting congenital haemangiomas
Kaposiform haemangioendothelioma
Others
Vascular malformations
Slow-flow vascular malformations
• Venous malformations
• Lymphatic malformations
• Capillary malformations
Fast-flow vascular malformation
• Arteriovenous malformations/fistulas
Combined complex vascular malformations
• Capillary–venous
• Capillary–arteriovenous
• Lymphaticovenous malformation

Glowacki in 1982.[2] This classification system divides VAs into two separate categories, vascular tumours (VTs) and vascular malformations (VaMs).[3] Congenital soft-tissue VAs can present anywhere in the body from head to toe, with variable size and infiltration; thus, a multidisciplinary approach is crucial in the management and treatment of these patients. Consistent use of correct terminology will improve communication between different specialists and avoid misunderstandings.

Given the rarity of some of the VAs, and overlapping clinical and imaging features, experience of the team taking care of the patient is extremely important. The accurate classification and treatment of VAs is best performed by those groups who see a large volume of patients, and as a consequence can see the patterns of VAs in the clinical appearance coordinated with the imaging appearance. This is why the development of multidisciplinary VAs centres is essential for accurate diagnosis and management of these patients. In the present authors' clinical practice, we often see patients who say that their doctor had never seen anything like that before and had no idea what it was, let alone how to treat it.

VAs can be imaged using ultrasonography (US), computed tomography (CT), CT angiography, digital subtraction angiography, or magnetic resonance imaging (MRI), and MR angiography/venography (MRA/MRV). US is often used as the first line of imaging, given the lack of ionizing radiation, no need for sedation/general anaesthesia, and bed-side imaging capabilities. Structural imaging data can be combined with flow dynamics of the VA, which is valuable in the classification of the lesion. However, operator dependence and small field of view are limiting factors in diagnosis and follow-up. MRI is the reference standard in most cases given the high soft-tissue resolution, different sequences, and fat suppression capabilities enabling clear differentiation/demarcation of the VA from surrounding soft tissues, along with dynamic contrast-enhanced (DCE) imaging information. DCE-MRA provides high temporal resolution and produces imaging of the lesion in the arterial, capillary, venous, and delayed venous phases[4,5] in the order of seconds.[6] Rapid DCE-MRA data acquisition is based on a combination of parallel imaging and k-space undersampling.[7] View-sharing and keyhole techniques are used by fully sampling the central k-space during each acquisition, although only a small fraction of the k-space periphery is acquired at the same time. A full k-space periphery is generated for each image by adding information from previous and subsequent acquisitions to obtain a sharp, high-resolution image with good image contrast. The high-resolution components encoded in the k-space periphery are relatively stable over time, whereas the low-frequency k-space centre carries the significant contrast changes during bolus passage.

The full anatomical extent of the anomaly can be evaluated in relation to adjacent nerves, and MRA/MRV can identify the feeding artery and draining vein (Table 2). Response to treatment can be reliably evaluated over time by changes in size and flow characteristics.[8,9]

Table 2
Key magnetic resonance imaging features of vascular anomalies.

	IH	VM	LM	AVM
Solid mass	Yes	No	No	No
Phlebolith	No	Yes	No	No
Enhancement	Avid homogeneous	Variable	None (cysts' periphery)	Avid serpiginous
DCE-MRA	Arterial	Venous	None	Arterial with early venous drainage

IH, infantile haemangioma; VM, venous malformation; LM, lymphatic malformation; AVM, arteriovenous malformation; DCE-MRA, dynamic contrast-enhanced magnetic resonance imaging.

Vascular tumours

VTs include infantile haemangiomas (IHs), congenital haemangiomas (CHs) including non-involuting congenital haemangiomas (NICHs) and rapidly involuting congenital haemangiomas (RICHs), as well as kaposiform haemangioendotheliomas (KHEs), among others. Age of presentation (prenatal, neonatal, early childhood/adult), presence or absence of overlying telangiectatic vessels, lighter peripheral ring, presence of high flow, and temporal evolution of the mass (involution, no involution) are important clinical criteria to approach diagnosis in VTs.

Haemangiomas

Infantile haemangioma

IHs compromise approximately 90% of all VTs and are the most common VTs of infancy with higher incidence in the white Caucasian infants. The highest incidence is noted in the preterm infants weighing less than 1000 g.[10] The head and neck regions are involved most frequently (60% of cases), followed by the trunk (25% of cases), and extremities (15% of cases).[11]

IH often is not apparent at birth and most appear in the first 6 weeks of life as a soft, non-compressible mass with a typical triphasic evolution: proliferation, plateau, and involution. Superficial haemangiomas are generally cherry red macules and papules; deep haemangiomas are reasonably firm subcutaneous masses sometimes with a bluish skin hue. Compound haemangiomas obviously combine aspects of both types.

Most IHs double in size in the first 2 months of life, and approximately 80% reach their maximum size between by 6 months of age.[12]

Spontaneous regression over the first several years of life is typical[13,14]; however, up to 40% of IHs may have residual skin changes and fibro-fatty residuum, especially in the head and neck region. IHs within the cutaneous lumbosacral region can be associated with tethered cord. In patients with large IHs in the head and neck region there may be concern for airway compromise, ulceration, or bleeding, which can be medically treated, with propranolol as the leading choice of medication (Figs 1 and 2a–b).

The immunohistochemical marker, glucose transporter protein isoform 1 (GLUT1) has become a major tool in the diagnosis of IH, with the endothelial cells staining strongly. The overwhelming majority of other VTs do not stain positive for GLUT-1.[15,16]

Imaging is not required for the majority of IHs but can be useful to confirm the suspected diagnosis in atypical lesions and to determine the extent of deep lesions and to exclude other VTs (such as KHE), or soft-tissue malignancies. US demonstrates a solid mass with increased colour flow within the mass.[17] Arterial feeder and venous drainage can be visualized using Doppler US.[18]

MRI reveals a T2 bright, T1 isointense mass with homogeneous, avid contrast enhancement.[19] Internal serpiginous

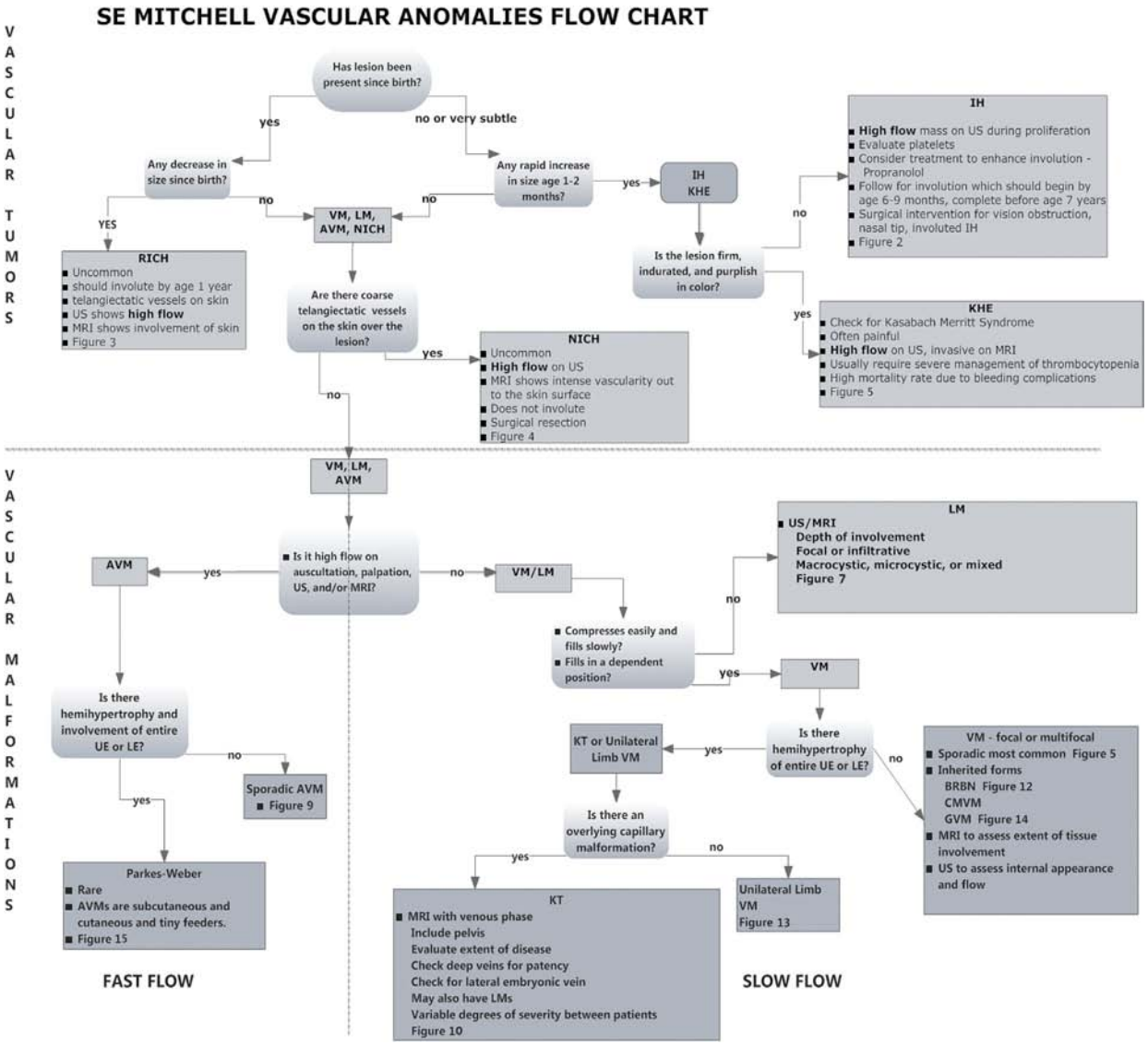

Figure 1 SEMVAFC. IH, Infantile haemangioma; RICH, Rapidly involuting congenital haemangioma; NICH, non-involuting congenital haemangioma; KHE, Kaposiform haemangioendothelioma; VM, Venous malformation; LM, Lymphatic malformation; AVM, Arteriovenous malformation; KT, Klippel–Trénaunay.

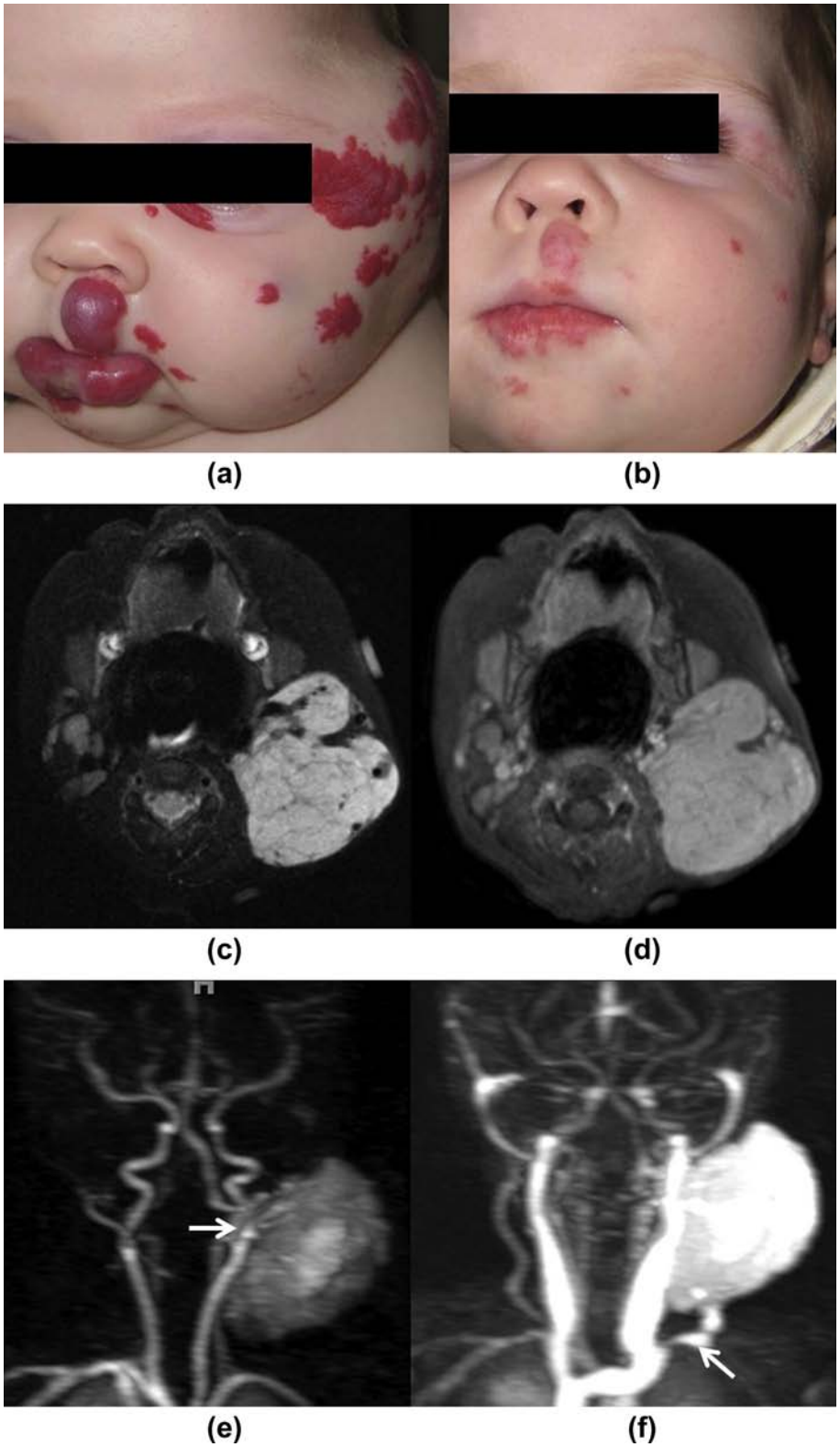

Figure 2 (a) A 10-week-old female infant. Note multiple segmental facial red haemangiomas, the ulceration on the bottom lip, and the subcutaneous haemangioma of the left upper medial eyelid that causes swelling and partial obscuring of the left eye. (b) Same patient after 9 months on propranolol. Note the degree of involution of the lesions shown in c. (c) Another patient, a 6 month-old female, with a palpable soft mass in the left lateral neck, an IH. Axial T2-weighted image with fat saturation demonstrates a well-defined, hyperintense soft-tissue mass in the left neck with few internal serpiginous flow voids. (d) Contrast-enhanced T1-weighted image with fat saturation demonstrates avid, homogeneous internal contrast enhancement of the solid vascular mass. (e–f) Time-resolved DCE-MRA in the arterial phase demonstrate that the avid homogenous enhancement of the IH starts in the arterial phase (note that only the arteries are enhanced, no veins visualized) from a feeding artery taking off from the left external carotid artery (arrow). Serpiginous flow voids noted in c were demonstrated to represent the feeding arteries and draining veins of the IH. Note the draining vein into the left subclavian/IJ junction (arrow) (f).

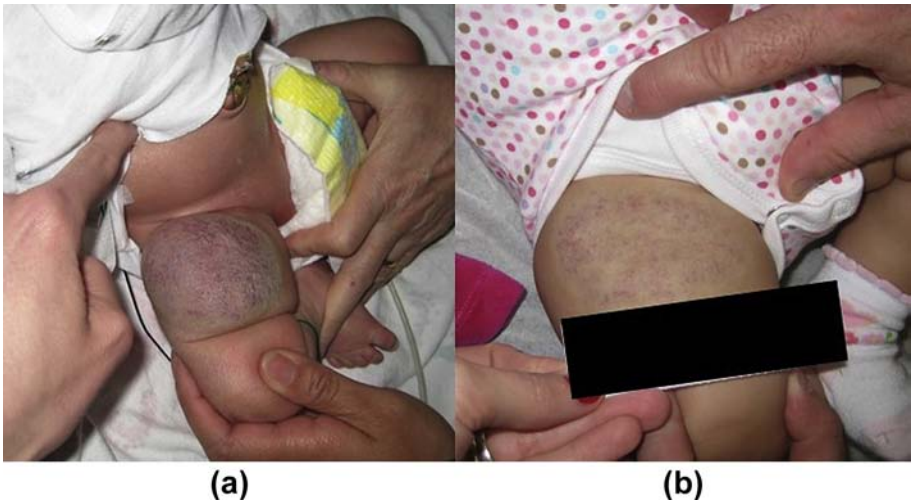

Figure 3 (a) Newborn with a round purple mass on the right thigh. Note that the skin has coarse telangiectasia, and that there is a peripheral pallor typical for CHs. (b) Same patient at 5 months of age. Note that the lesion has spontaneously involuted very rapidly, confirming that this is a RICH.

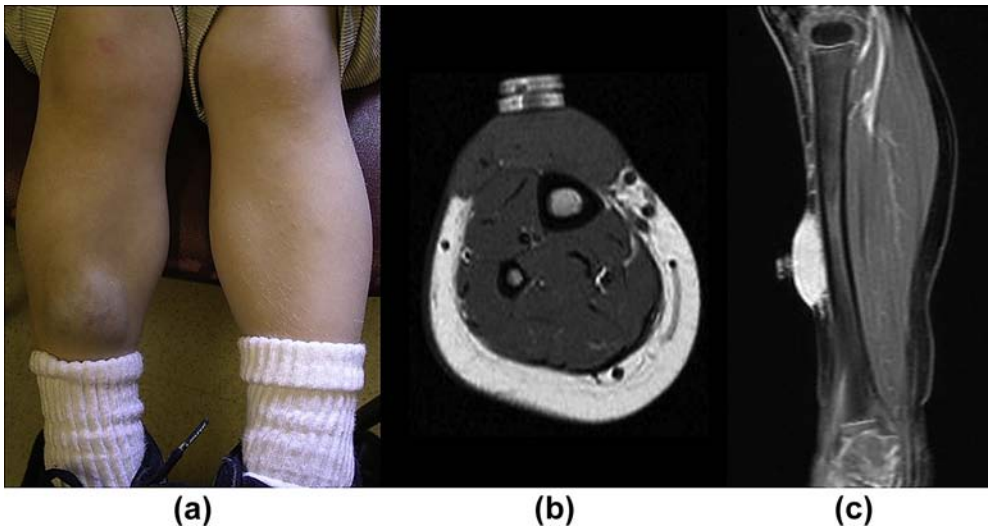

Figure 4 (a) A 4-year-old male patient with a raised, round lesion on the right shin since birth without regression. Note the coarse purple telangiectasia on the skin. (b) Axial T1-weighted image without fat saturation clearly demonstrates the infiltration of the skin, typical for CHs. (c) Axial contrast-enhanced T1-weighted image with fat saturation demonstrates avidly enhancing solid vascular mass with skin infiltration. Constellation of imaging findings with patient's age and no regression since presentation at birth makes the diagnosis of a NICH.

flow void within the IH noted in T2-weighted imaging represents the arterial feeder, an important diagnostic clue. DCE-MRA demonstrates early arterial enhancement in a soft-tissue mass with a draining vein. Typically, no perilesional oedema is observed, which helps differentiation from other soft-tissue malignancies. Fibro-fatty infiltration can be observed during the involuting phase (Fig 2c–f).

Congenital haemangioma

Unlike IHs, CHs are fully formed at birth, with nearly no growth after birth, and lack positive staining with GLUT-1. Clinically, RICHs (Figs 1 and 3) and NICHs (Figs 1 and 4) appear similar, often presenting as violaceous grey tumours with prominent overlying veins or telangiectasias, which extend beyond the periphery of the lesion. Many have a lighter or bluish halo on the surrounding skin. In practice, RICH and NICH are distinguished in retrospect, as the former involutes by 12 months of age, and the latter involutes either partially or not at all and requires surgical excision. RICH, too, can leave significant textural change necessitating reconstructive surgery after involution.[20]

Early and accurate diagnosis is critical to avoid unnecessary biopsy/surgical intervention.[21] Similar histological and clinical features of RICH and NICH raise the possibility that the latter may undergo involutional arrest to become a non-involuting tumour.[22]

Kaposiform haemangioendothelioma

KHE is a rare distinct vascular tumour,[23] which may present at birth or within the first few months of life as an

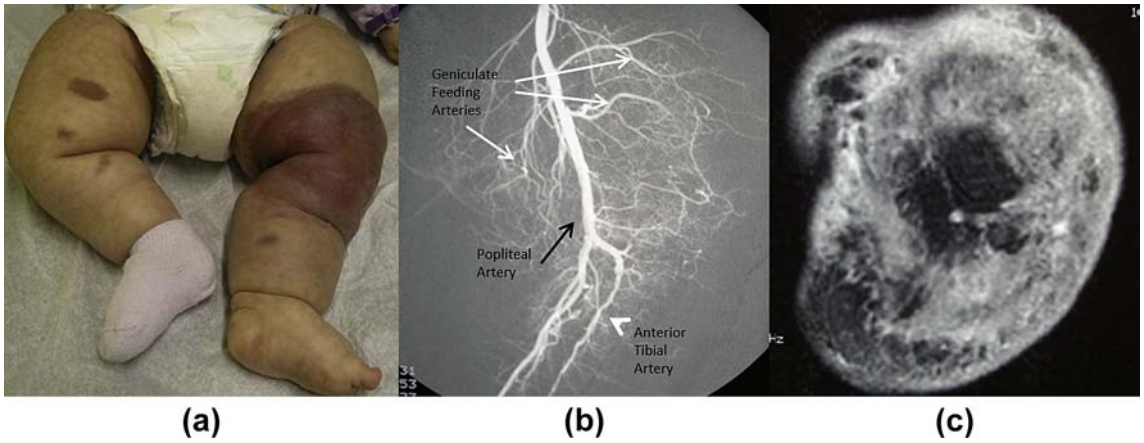

Figure 5 (a) An 11-month-old female patient born with ill-defined purple and firm, indurated lesion overlying the left knee region. The vascular anomaly was notable for being extremely painful, limiting movement of the left lower extremity. (b) This is a lateral view of an arteriogram of the left knee demonstrating enlarged feeders off the lower superficial femoral artery and popliteal filling the hypervascular mass. Multiple hypervascular branches arising from the geniculate artery supplying the blush of the KHE (white arrows). Note that the popliteal artery (black arrow) and anterior tibial artery (arrowhead) are also marked on the image for orientation purposes. (c) Axial contrast-enhanced T1-weighted image with fat saturation demonstrates infiltration of the skin, subcutaneous fat, muscle groups, and cortex of the bone by this enhancing infiltrative vascular anomaly. Infiltrative and aggressive nature of this painful solid mass in a young child confirms the diagnosis of a KHE.

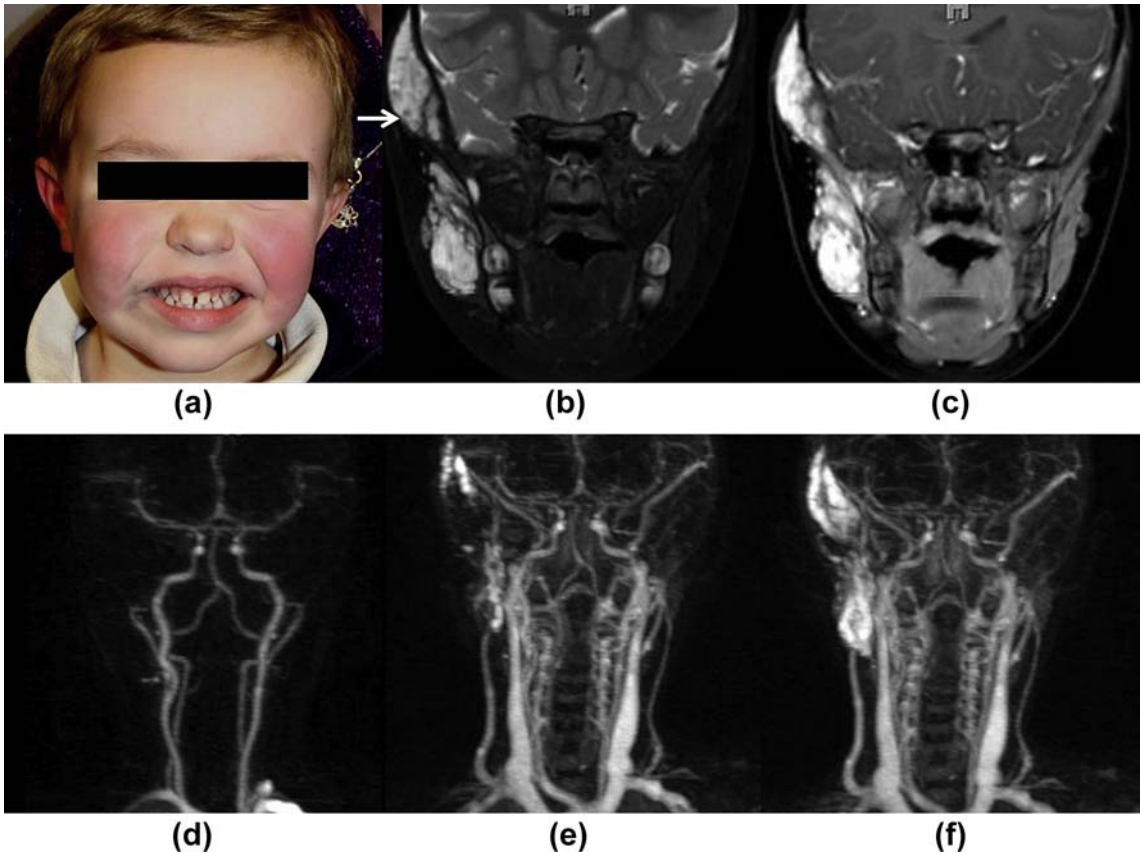

Figure 6 (a) A 4-year-old with blue discolouration of his right cheek and corner of right lip noted to be present since birth and stable. Note that the right cheek is fuller than the left. The lesions are soft and compressible. (b–c) Coronal images show infiltration of the right temporalis muscle and right masticator space by a T2 bright (b) and enhancing mass (c). Note the T2 dark round foci in b representing phleboliths (arrow). (d–f) DCE-MRA demonstrates no enhancement in the arterial phase (d). Enhancement starts in the venous phase (e) and progressively increases in the delayed venous phase (f), typical for VMs.

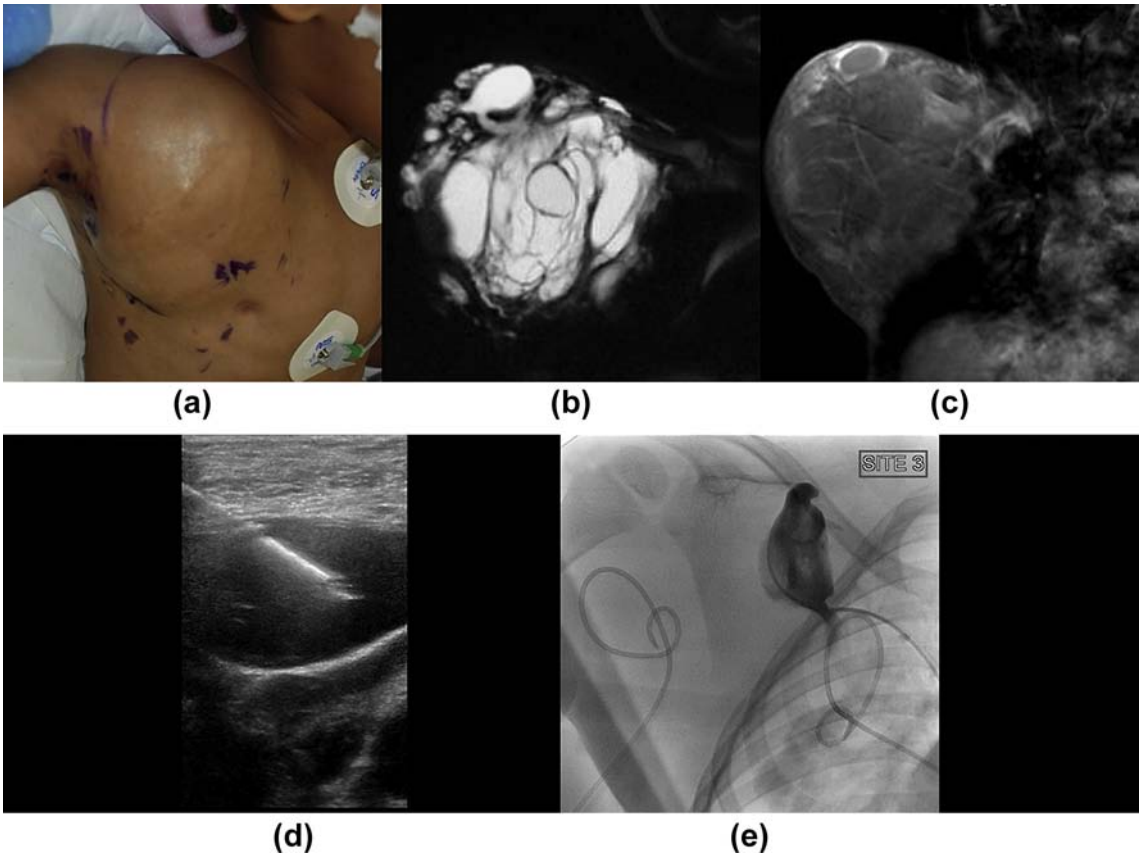

Figure 7 (a) A 4-year-old male patient with a large, firm mass on his right shoulder/chest wall. It was first noted soon after birth, and he underwent surgical debulking at that time. A known LM that recently enlarged in size. (b–c) Coronal T2-weighted image with fat saturation shows a T2 bright multicystic/septate, large mass that only shows enhancement of the cyst walls and septa (c), typical for LMs. Relatively large size of each cyst qualifies for a macrocystic LM. (d) Ultrasound during percutaneous access demonstrates macrocystic LM. (e) Contrast medium injection into one of three macrocysts being treated with doxycycline sclerotherapy.

ill-defined purpuric mass, often painful; however, presentation may be later in childhood.[24] The destructive/infiltrative nature and very rapid growth of the vascular tumour helps differentiation from IH. Kasabach–Merritt phenomenon (KMP) can be seen up to 50% of patients. KHE has a high mortality rate (24%) related to coagulopathy or complications from local tumour infiltration. The firm, indurated lesion has a more invasive appearance and purplish colouration (Figs 1 and 5).

These cells form slit-like lumina containing erythrocytes that resemble Kaposi's sarcoma, thus the name KHE.[25] KHE appears as a solid mass with ill-defined borders and variable echogenicity at US.[26] MRI demonstrates an infiltrative pattern with crossing of multiple soft-tissue planes with

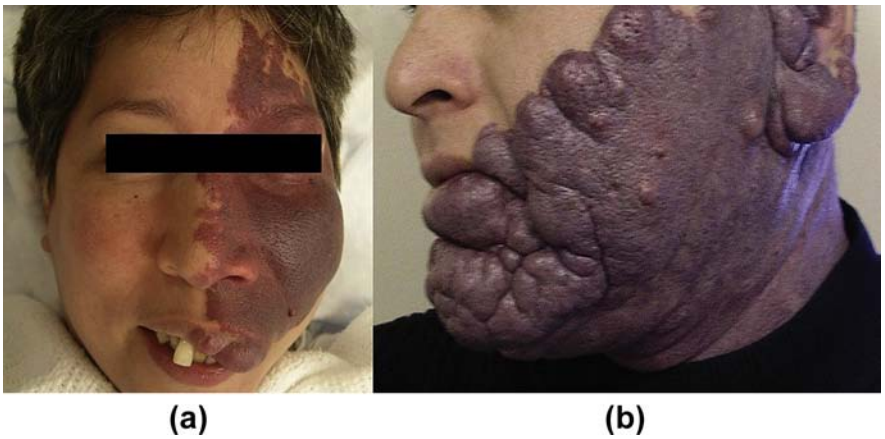

Figure 8 Two patients with Sturge–Weber, (a) 23 years-old, and (b) 35 years old, both with extensive CMs of the face. Note the thickening of the CM especially in b, which can be seen in CMs over time.

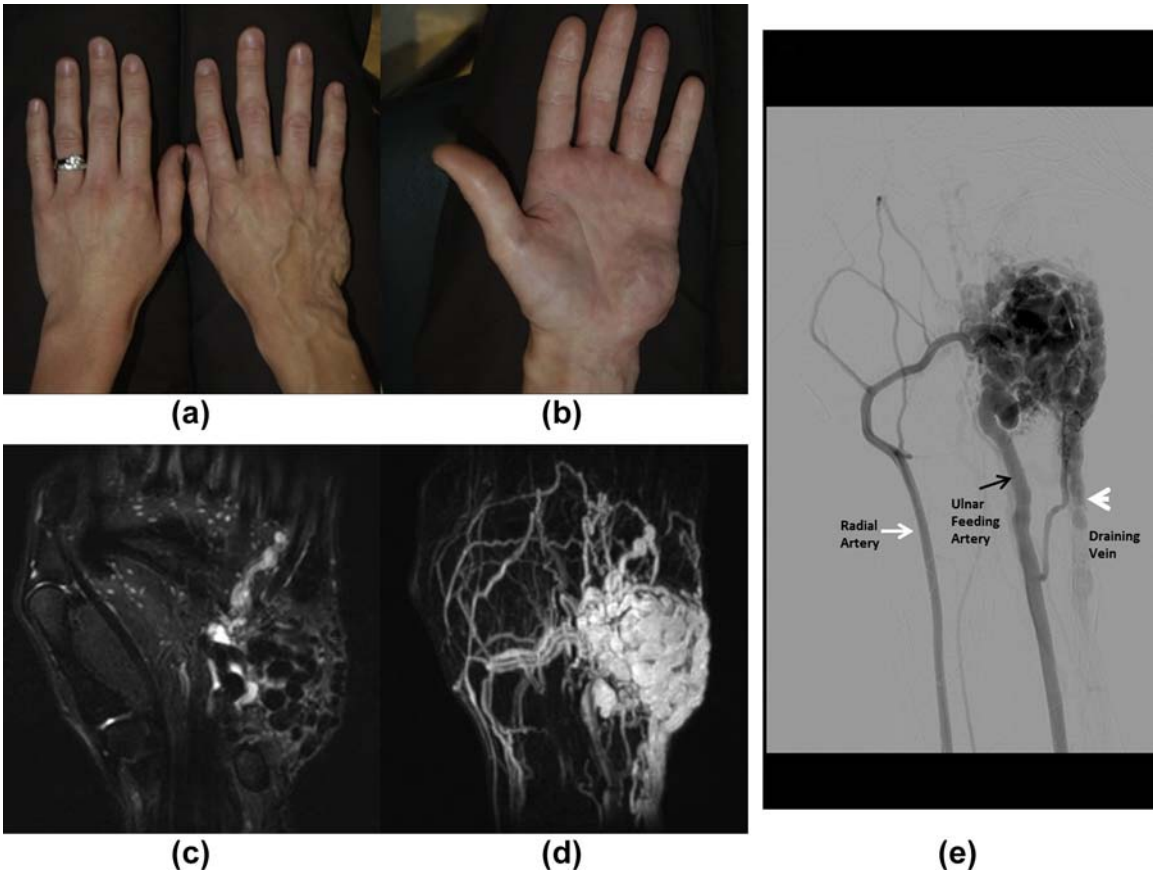

Figure 9 (a) A 30-year-old woman with a swollen pulsatile mass on the hypothenar eminence of her right hand. View of the dorsal surface of the patient's right hand compared to the left. Note the enlarged draining veins and relatively bigger size of the right hand. (b) Note the hypothenar eminence mass on this image of the palmar surface of right hand. (c) Coronal T2-weighted image with fat saturation demonstrates serpiginous tangle of flow voids indicating high flow, infiltration the hypothenar eminence and the subcutaneous fat. Note absence of associated soft-tissue mass. (d) MR angiogram demonstrates strong enhancement of the AVM with arterial feeder from the ulnar artery and venous drainage into the basilic vein. (e) Angiogram demonstrating predominant ulnar feeder (black arrow) to AVM. Note early venous drainage to basilic vein (arrowhead). Enlargement of the ulnar artery becomes more conspicuous when compared to normal radial artery (white arrow). The draining vein is also patoulous (arrowhead).

involvement of the overlying skin and subcutaneous fat. These more aggressive imaging features distinguish KHE from IH, as do the atypical clinical features.

Syndromes associated with haemangiomas

Although the clinical course of the vast majority of haemangiomas is benign, there are some associated abnormalities that should be noted and that may require further diagnostic evaluation. Patients with large segmental facial haemangiomas should be evaluated for signs and symptoms of PHACES syndrome. PHACES syndrome refers to a constellation of *p*osterior fossa brain malformations, *h*aemangiomas, *a*rterial anomalies, *c*oarctation of the aorta and cardiac defects, *e*ye abnormalities, and *s*ternal defects.[27]

Patients with haemangiomas overlying the lumbosacral spine can have associated abnormalities, the most common of which is a tethered spinal cord. MRI should be performed to exclude this abnormality.[28] Genitourinary anomalies are possible, although less common.

Airway haemangiomas should be investigated in patients who have cutaneous cervicofacial haemangiomas distributed in the chin, anterior neck, lower lip, and pre-auricular areas (a "beard" distribution).[29]

Vascular malformations

VAs that are present at birth and grow slowly, proportionally to the patient without spontaneous regression are

Table 3
Schobinger scale of severity of arteriovenous malformations.

Stage	Stage name	Description
I	Quiescence	Only pink–bluish stain and warmth
II	Expansion	Enlarged swelling with pulsation, thrill, and bruit; veins are tense and tortuous
III	Destruction	Same as stage II with ulceration, bleeding, pain, and tissue necrosis
IV	Decompensation	Same as stage III with cardiac failure

Modified from reference 37.

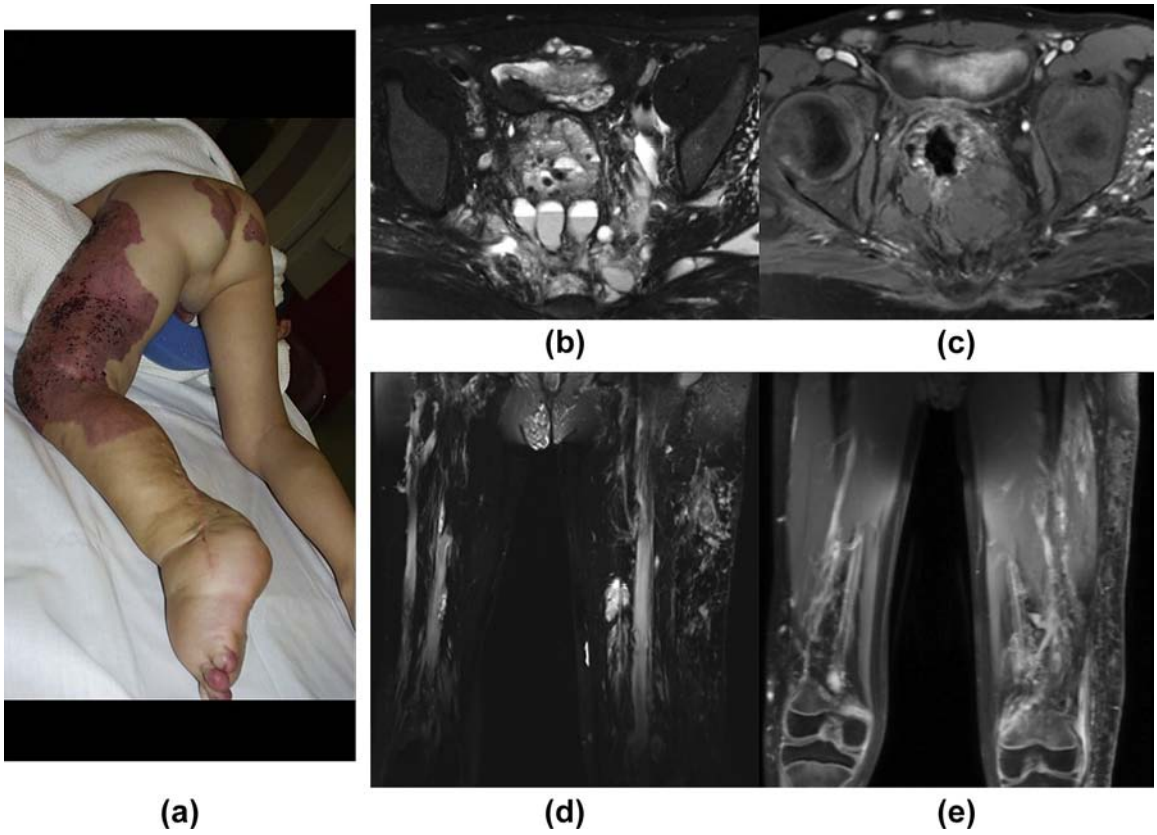

Figure 10 A 4-year-old with hemihypertrophy of left lower extremity, CM, VM, and LM in left lower extremity. Post-surgical resection of lower leg microcystic LM. Note pelvic involvement with perineal swelling. (b) Axial T2-weighted image with fat saturation shows multiple cysts with fluid–fluid levels noted deep in the pelvis. (c) Axial post-contrast T1-weighted image demonstrates lack of contrast enhancement in the cysts confirming that these represent LMs. (d–e) Coronal T2-weighted image with fat saturation shows increased thickness of the subcutaneous fat in the left thigh (d). Note infiltration of the subcutaneous fat, and muscle groups by the VM that shows heterogeneous enhancement on coronal contrast-enhanced T1-weighted images (e). Also note the enlarged/patolous deep venous system.

consistent with VaMs, that is, congenital errors in vascular development. Although they are present at birth, they may remain dormant and present in later childhood, or adult life. Histological evaluation of these lesions supports this classification, with the types of malformations delineated by the basic type of constituent vessel and the presence or absence of arteriovenous shunting. They demonstrate vascular spaces lined with flat, mature epithelium that is

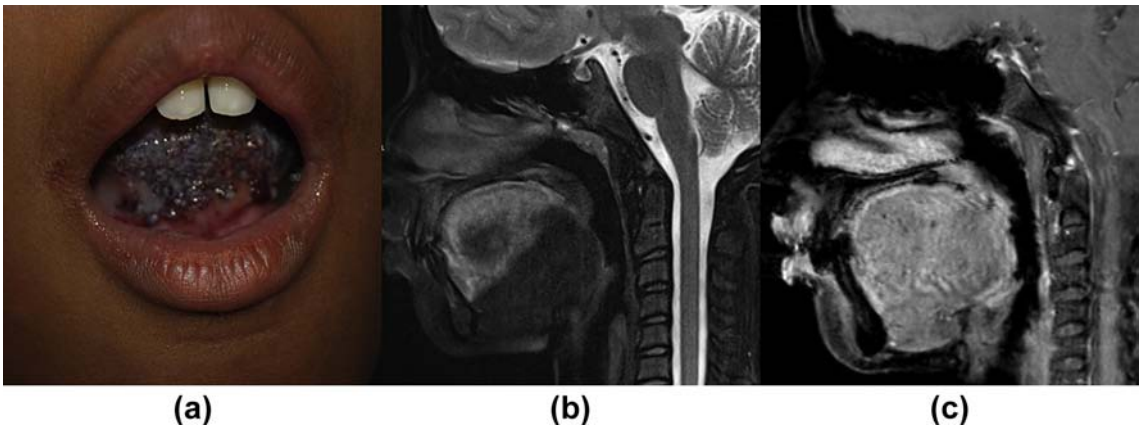

Figure 11 (a) An 11-year-old female patient with LVM of the tongue, status post-tongue reduction surgery and prior laser treatment. Recurrence of the blue–black small numerous tiny cystic lesions on her tongue. They weep clear lymphatic as well as bloody fluid. (b–c) Sagittal T2 Weighted image of the tongue shows increased T2 signal in the intrinsic tongue muscles, that show mild enhancement in contrast-enhanced T1-weighted sagittal image (c). MRI is helpful in identifying the depth of infiltration in this superficial lesion.

Table 4
Syndromes associated with vascular malformations (VMs).

Syndromes associated with VM
• Klippel–Trénaunay
• Blue rubber bleb nevus
• Maffucci syndrome
Syndromes associated with CM
• Klippel–Trénaunay
• Sturge–Weber
Syndromes associated with LM
• Gorham syndrome
Syndromes associated with AVM
• Parkes–Weber
• Rendu–Osler–Weber
• Bannayan–Riley–Ruvalcaba syndrome

VM, Venous malformation; LM, Lymphatic malformation; CM, Capillary malformation; AVM, Arteriovenous malformation.

mitotically quiescent. VaMs are subclassifed based on flow dynamics, as slow-flow, and fast-flow VaMs.[30]

Slow-flow vascular malformations

Venous malformation

Venous malformations (VMs) are the most common of all types of VaM. They present as soft, compressible lesions that typically infiltrate multiple tissue planes. Physical examination generally reveals bluish lesions (Figs 1 and 6) that may enlarge with Valsalva manoeuvre or gravity. There may be overlying skin involvement. They usually present during mid to late childhood and become more symptomatic as time passes. The lesions vary in size from very small to extensive involving multiple body parts. The can appear as sacs filled with venous blood or as dilated venous channels with or without communication of systemic veins. Generally, even when large, VMs tend to be continuous in nature. They tend to extend within the muscle groups of extremities, along the nerves and major arteries or veins.

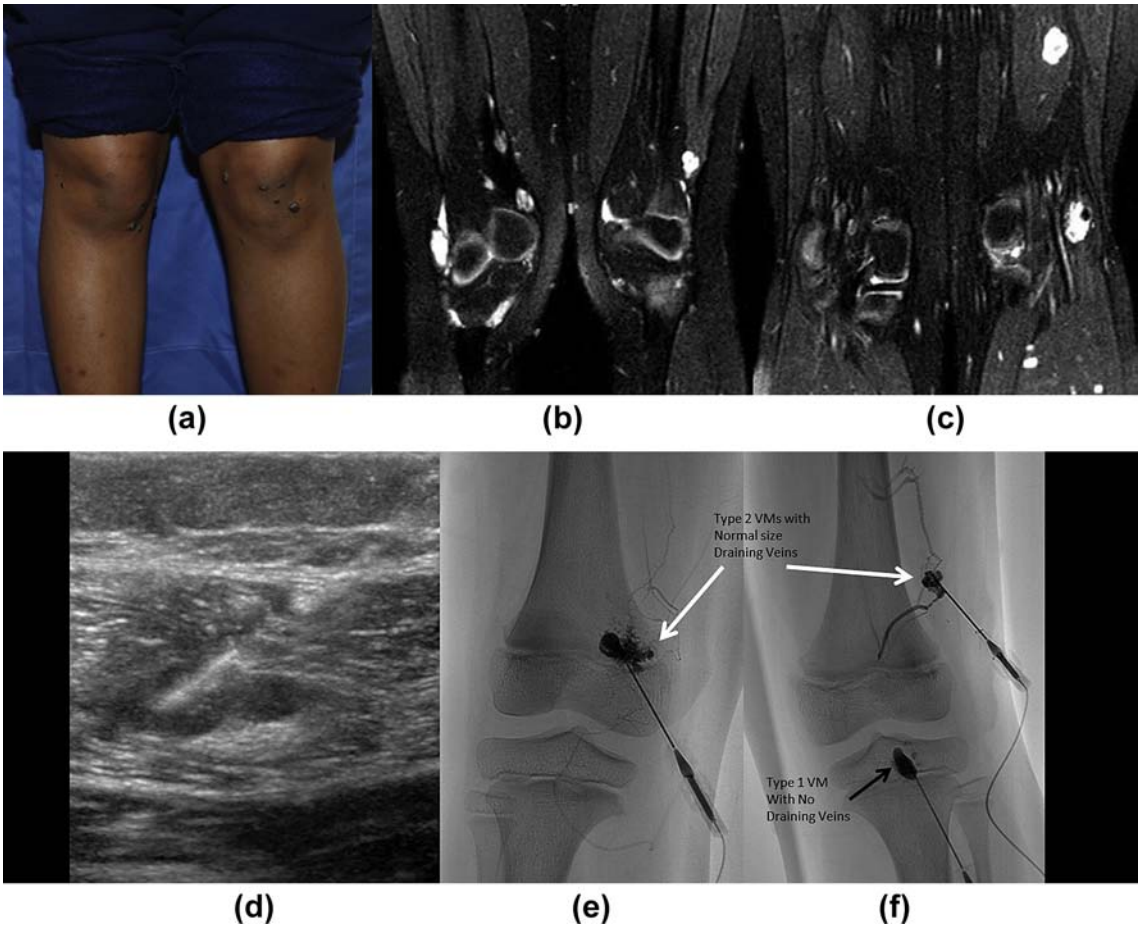

Figure 12 (a) A 7-year-old female patient with multiple dark, slightly raised, firm skin lesions on both knees, and over entire body as well. These are the skin lesions of BRBNS. She has multiple deep VMs on the shoulder and right arm that have been previously percutaneously sclerosed. She recently reported severe pain around both knees and thighs that prompted MRI. (b–c) Coronal T2-weighted images demonstrate multiple small, lobular T2-bright lesions in the muscle groups and medulla of the bones representing VMs. (d) Ultrasound showing intramuscular VM with needle accessing it for percutaneous sclerotherapy. (e) Percutaneous venogram of right leg intramuscular VM demonstrating type II drainage into normal veins (white arrow). (f) Percutaneous venogram of left leg intramuscular VM and infrapatellar VM. Note again the type II VM with drainage into normal veins (white arrow), and additional type I VM without a draining vein (black arrow).

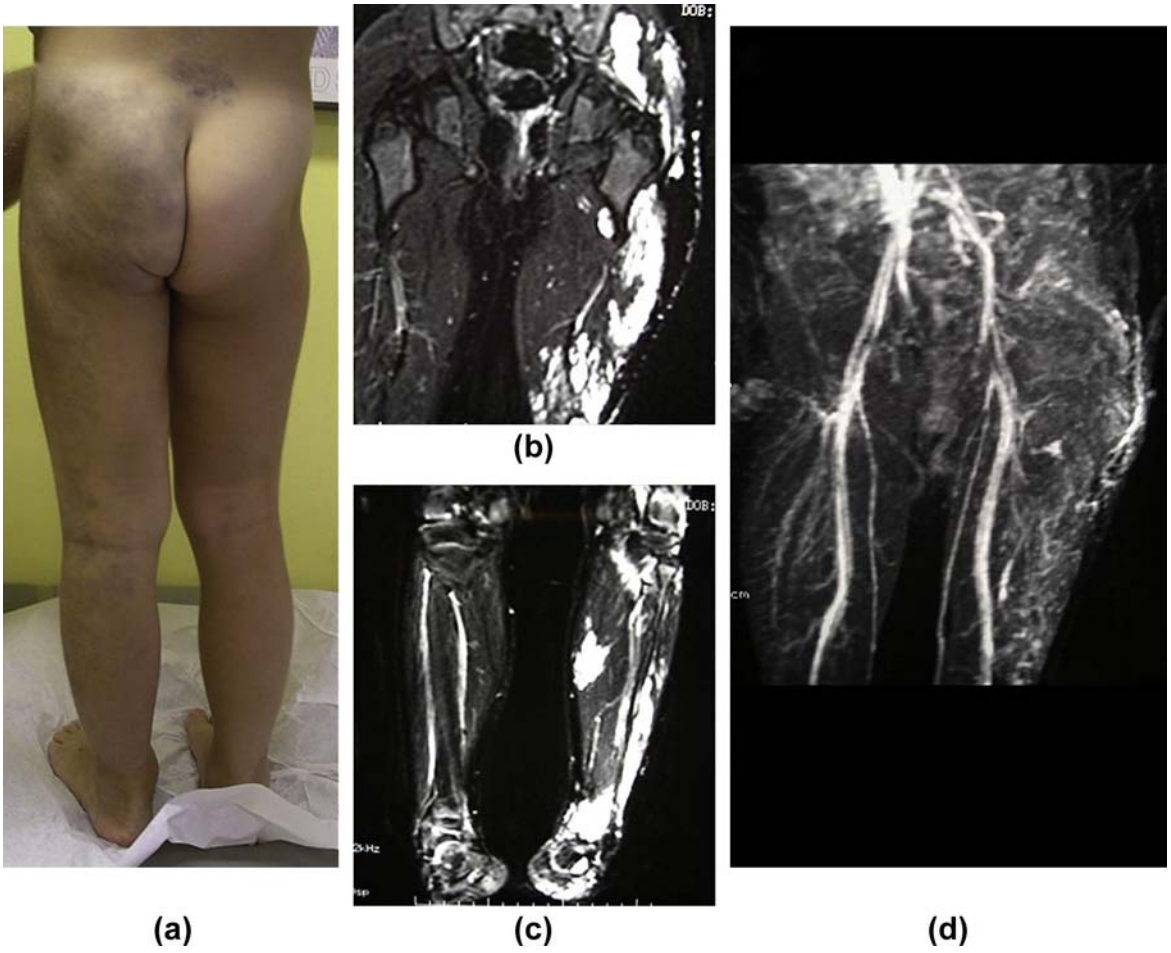

Figure 13 (a) A 4-year-old female patient with extensive blueness to her left leg and buttock region. She had no leg length discrepancy on measurement. (b–c) Coronal T2-weighted image shows extensive VM infiltrating the muscle groups in the left lower extremity and buttock. Note infiltration in the skin. (d) DCE-MRA shows enhancement of the VM in the venous phase.

US of VMs demonstrate a sponge-like network of tubular structures with low velocity or no venous flow. The vessels are easily compressible with the US probe.

MRI is the best imaging method to define the full anatomical extent of VMs.[31] VMs are serpiginous T2 hyperintense lesions, which often show phleboliths. Haemorrhage, thrombosis, or phleboliths may reveal variable degree of pre-contrast high T1 hyperintensity. Some degree of fat tissue or muscle tissue may be observed interspersed between the venous channels. Spontaneous thrombosis and thrombolysis can occur with VMs, which results in elevated D-dimer levels (>0.5 μg/ml) in approximately 42% of patients. D-dimer levels are often very high even in otherwise healthy patients.[32] Phleboliths are often observed (round/oval shaped T2 hypointense foci) representing calcification within the veins. DCE-MRA demonstrates enhancement in the venous phase that may be progressive in nature, typical for VMs (Figs 1 and 6).[33]

Lymphatic malformation

Lymphatic malformations (LMs) are soft, compressible lesions of lymphatic origin (Figs 1 and 7). These have also been referred to as cystic hygromas or lymphangiomas, but these terms are confusing and should be avoided. LMs are collections of cystic spaces filled with chylous material.[34] These cystic spaces may be macrocystic, microcystic, or mixed. Microcystic LMs are not as compressible as macrocystic LMs. The microcysts may be so small that they are indistinguishable on cross-sectional imaging.

US evaluation shows no flow within the major spaces, although small arteries and veins can traverse the interstitial spaces. MRI appearance can be variable on T1-weighted imaging for LMs depending on internal haemorrhage and inflammation, but usually of high signal on T2 weighting and shows mild peripheral enhancement with no internal enhancement with gadolinium. Diffuse microcystic LM may result in mild diffuse enhancement of the cyst walls and may be challenging diagnosis for the radiologist.

Capillary malformation

Capillary malformations (CMs) are commonly known as "port wine stains" as well as nevus flammeus and can be confused with IH. They are typically red or pink in infancy and may darken with age. They grow in proportion with the patient and do not resolve spontaneously. CMs in certain locations can be associated with other abnormalities. For

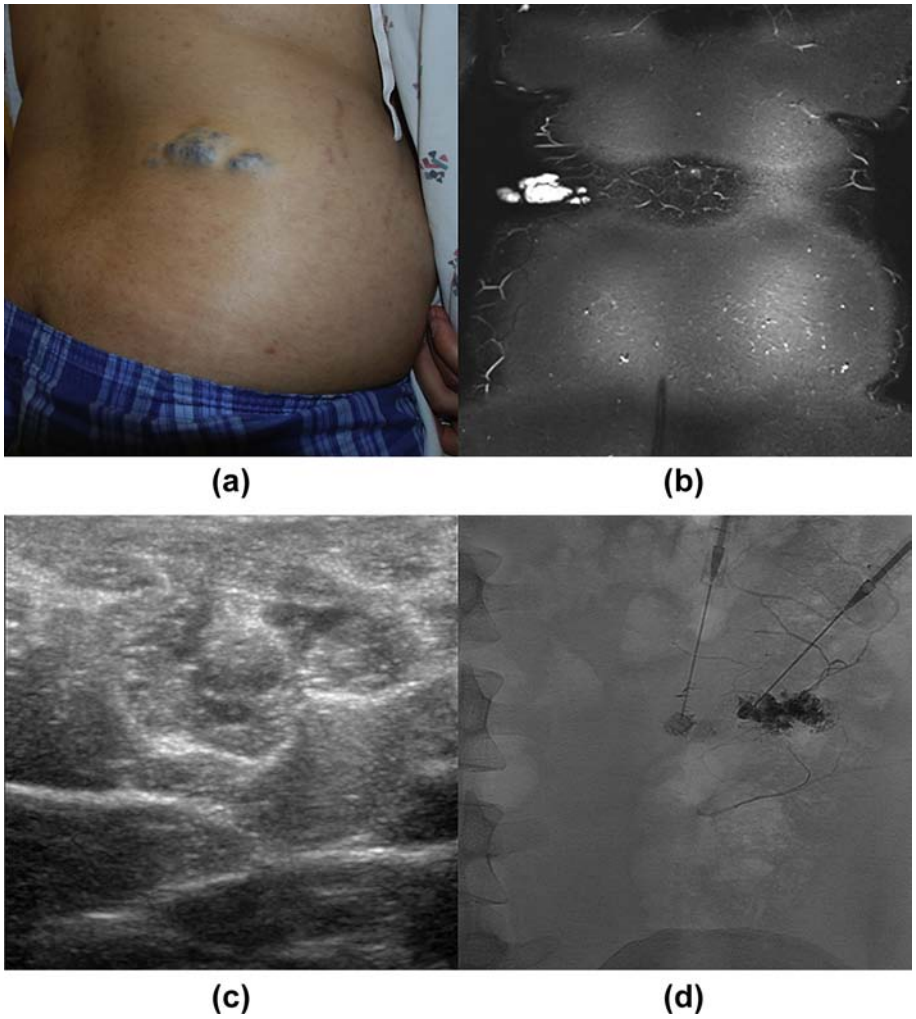

Figure 14 (a) A 20-year-old man with bluish lesion in left lower flank since birth. Similar lesions were also noted on the buttocks, right and left thighs, left wrist, and right forearm (not shown). These were painful when pushed on. His father had similar lesion on his left forearm. Note they are cutaneous and subcutaneous, raised lesions with some firmness, yet compressible. (b) Coronal T2 weighted image shows lobular T2-bright lesion in the subcutaneous fat. (c) Ultrasound during needle access for sclerotherapy. Lesion had firm borders but extensive venous spaces. No flow seen on power Doppler (not shown). (d) Percutaneous venogram of lesion during sclerotherapy treatment. Based on MRI only, diagnosis of glomuvenous malformation is very difficult as imaging features overlap with that of a VM. Presence of similar lesions in the patient's father along with superficial location and painful nature are very helpful in establishing the diagnosis of a glomuvenous malformation.

example, midline posterior CMs may be associated with tethered spinal cord. Facial CMs may be associated with Sturge–Weber syndrome, particularly in the V1 distribution (Fig 8). Patients with V1 distribution CMs should undergo early neurological and ophthalmological evaluation. Patients with V2 and V3 involvement are generally not at risk. Other conditions associated with CMs include Klippel–Trénaunay (KT), Parkes–Weber syndrome. CMs may be associated with underlying arteriovenous malformations (AVMs) as part of the RASA1 mutation.[20]

CMs associated with Sturge–Weber have a tendency to become thickened and lobulate with age. Early intervention with pulsed dye laser to the CM may prevent progression towards more nodular growth.[35,36] These are very difficult to treat once hypertrophy has occurred and may require difficult and repeated plastic surgical procedures to keep the enlargement under control. Angiography rarely demonstrates enough visible hypervascularity to render embolization an alternative to controlling this growth. In addition, there may be bony overgrowth that cannot be controlled. MRI demonstrates the superficial thickening.[37]

Fast-flow malformations

Arteriovenous malformation

AVMs and arteriovenous fistulas are pulsatile lesions without a mass and without the capillary transition between artery and vein, typically with associated bruit or murmur (Figs 1 and 9). They present in early childhood and grow with the child. They may also undergo periods of more rapid growth, associated with growth spurts and puberty as well as occurring after trauma, pregnancy, or surgery. They can be complicated by arterial steal in affected extremities. Venous congestion from AVMs can

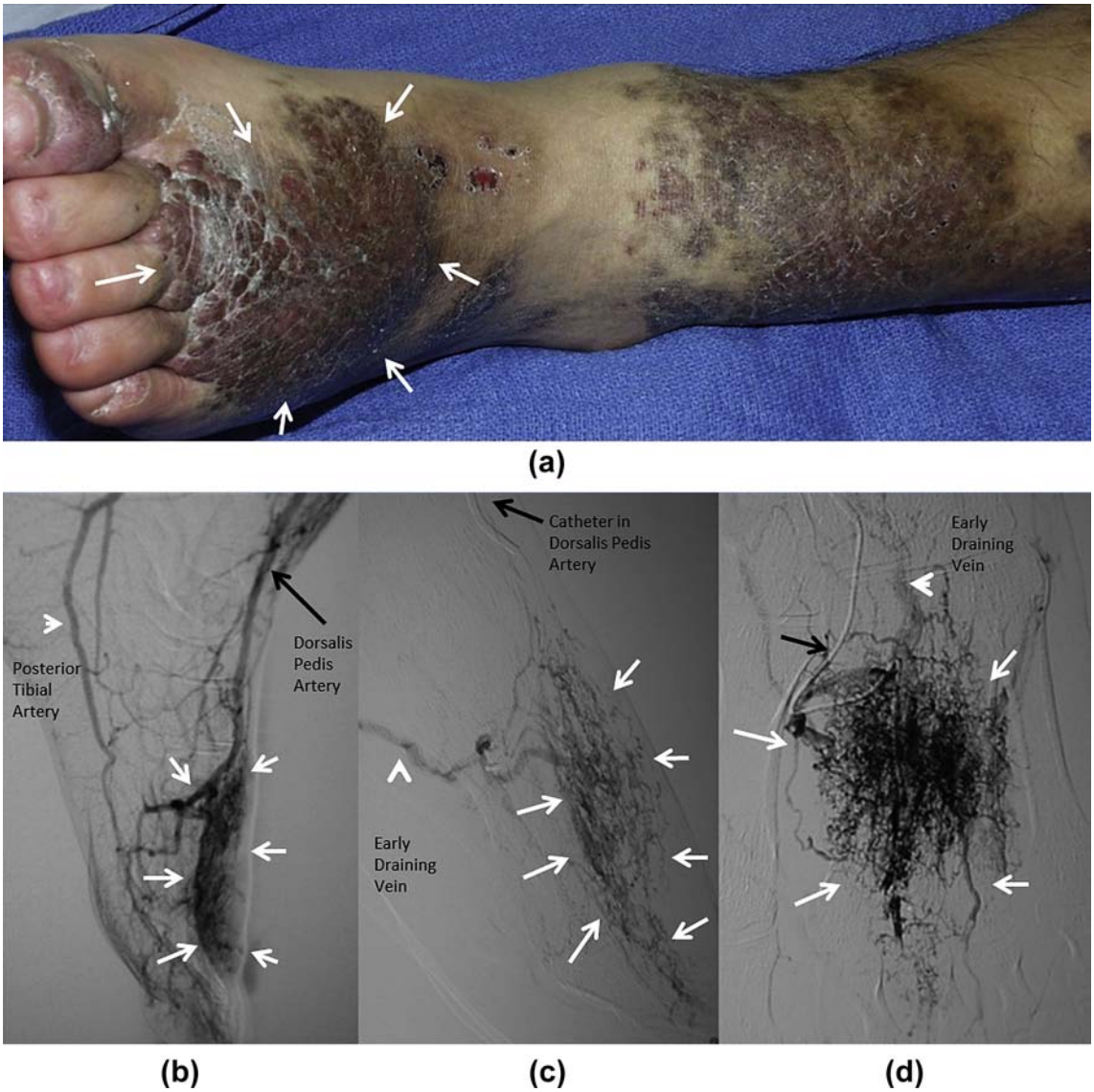

Figure 15 (a) Foot and lower leg of 24-year-old man with Parkes–Weber. Note thickened skin lesions as outlined by white arrows. Similar changes are also noted in the anterior lower shin. (b) Lateral arteriogram of foot from popliteal injection. Note hypervascularity of AVM nidus (white arrows) underneath the thickened skin lesions on photo (a). Note that the dorsalis pedis artery is the feeding artery (black arrow). The posterior tibial artery (arrowhead) is marked for orientation purposes. (c) Selective arterial phase on dorsum of foot on lateral view. Note the catheter in the dorsalis pedis artery (black arrow). The AVM nidus (white arrows) demonstrates early arterial enhancement with an early draining vein (arrowhead). (d) Selective arterial phase on dorsum of foot on anteroposterior view. Note microcatheter in the distal part of the feeding artery (black arrow) supplying the nidus of the AVM (white arrows). The draining vein is marked with the arrowhead.

lead to pain, bleeding, and skin breakdown. In some cases, they can result in high-output cardiac failure. Diagnosis can be made by MRI or CT angiography. Biopsy should be avoided because of the high risk of bleeding. Treatment typically involves transcatheter embolization, with or without additional modalities.[38,39] Digital subtraction angiography is useful in precise demonstration of the arterial feeders and venous drainage pathways for pre-embolization planning.

AVMs are clinically classified by the Schobinger scale of AVM severity (Table 3).[40] Grey-scale evaluation of AVMs demonstrates a tangle of vessels with no associated mass. Doppler evaluation shows arterial flow within the vessels, with prominent draining vessels with high flow as well. MRI reflects this high flow state by prominent flow-related signal voids, as well as easier visualization of feeding and draining vessels. MRA/MRV is frequently helpful in pre-procedural planning for these lesions.

Pathology demonstrates beds of venules and arterioles, intermixed with numerous larger-calibre arteries and thick-walled veins.

Complex malformations

Lymphaticovenous malformation

Lymphaticovenous malformations (LVMs) are slow-flow lesions that contain both lymphatic and venous elements.[41] In the authors' experience, these lesions are rare,

and often times seen in the setting of syndromes such as KT. Even in those patients with KT, LM and VM are seen separately (Figs 1 and 10). Mixed LVMs are generally found as superficial lesions infiltrating the skin or tongue (Fig 11).

Cavernous malformation-arteriovenous malformation

CM-AVM is an autosomal dominant condition that consists of cutaneous CMs and high-flow arteriovascular malformations. These lesions are also formed due to a RASA1 mutation. On physical examination, the CMs, previously described as port-wine stain, are flat reddish lesions.[42] In contrast to typical CMs, those associated with CM-AVM are usually smaller, multiple, and associated with an encircling pale halo.[43] Treatment usually involves embolization of the underlying AVM.

Syndromes associated with vascular malformations

VaMs can also be associated with syndromes (Table 4). In contrast to isolated VaM, limb overgrowth is more common in the syndromal VaM. KT, blue rubber bleb nevus syndrome (BRBNS), unilateral limb VM, mucocutaneous VMs, Sturge–Weber, Proteus, Congenital Lipomatous Overgrowth, Vascular Malformations, and Epidermal Nevi (CLOVE) syndrome, Maffucci, and Gorham–Stout syndromes are all associated with low flow-VaM. Parkes–Weber, Rendu–Osler–Weber, Cobb and Wyburn–Mason syndromes are associated with high-flow VaM. PTEN mutations in syndromes such as Bannayan–Riley–Ruvalcaba and Cowden syndromes also result in high-flow VaM.[44,45] We will discuss some of the more commonly encountered syndromes associated with VaM.

Syndromes associated with venous malformations

Klippel–Trenaunay syndrome

KT is characterized by hypertrophy of the affected limb with slow-flow VaMs, including CMs of the skin with underlying extensive VMs and/or LMs (Figs 1 and 11). Dysplastic/anomalous veins or persistent embryonic veins can be observed. The deep venous system may be atretic, hypoplastic, or abnormal in approximately 50% of patients with KT and must be confirmed patent prior to ablation of the superficial abnormal veins. These patients can vary from a mild form, to a more severe form with extensive involvement of the pelvis and viscera as well as the legs. Some may have more LMs, others may have more VMs, and some may have enlarged ectatic pelvic and leg veins. KT patients may also be at higher risk for pulmonary embolus and need to be evaluated for potential long-term anticoagulation.[46]

Blue rubber bleb nevous syndrome

BRBNS is characterized by multiple cutaneous VMs as well as internal VMs, typically involving subcutaneous tissues and muscles in numerous locations (Figs 1 and 12). Cutaneous lesions are often present shortly after birth and increase in size and number with growth of the child. Physical examination findings demonstrate small, bluish raised lesions, which can often be painful. These patients must be followed due to multiple small bowel lesions that frequently bleed, presenting in early adulthood as slow, chronic gastrointestinal bleeding and chronic iron-deficiency anaemia.[47,48]

Unilateral limb venous malformation

Some patients with diffuse VMs in an extremity do not have KT (no hypertrophy, no LM, no port-wine stain) and are classified as having unilateral limb VM[49] (Figs 1 and 13). The skin may appear bluish due to the VM in the subcutaneous region. They typically have numerous deeper VMs within muscles from the pelvis to the feet.

Mucocutaneous venous malformation

This is an autosomal dominant inherited VM with multiple bluish spots that are usually small and punctuate and painful to touch, but may be larger in size.[32]

Glomuvenous malformation

This is also an autosomal dominant inherited VM in which there are multiple small bluish to purple skin lesions[32] (Figs 1 and 14).

Syndromes associated with arteriovenous malformations

Parkes–Weber syndrome

Parkes–Weber syndrome (previously called Klippel–Trénaunay–Weber syndrome) is not a VM syndrome, but is characterized by hemihypertrophy of usually the lower limb, CM, and diffuse multiple tiny superficial arteriovenous shunts[50] (Figs 1 and 15). Unlike KT, Parkes–Weber is a fast-flow malformation due to the presence of arteriovenous fistulas. Pathogenesis is due to a RASA1 gene mutation on chromosome 5q13.1. RASA1 gene encodes for p120-RasGAP protein that promotes signalling of several growth factor receptors involved in proliferation, migration, and survival of vascular endothelial cells. On physical examination, the lesion is usually pinkish to red with diffuse areas of involvement.[51] MRI is helpful in classifying the malformation as a fast flow arterial or AVM, which helps differentiate from KT. Treatment usually involves multistaged embolizations to improve high-output cardiac failure and help save the limb.

Conclusion

ISSVA classification not only provides accurate diagnosis, but also provides a common language for clinicians involved the care of the vascular anomalies. SEMVAFC incorporates the ISSVA classification to provide a clear visual pathway and a practical multidisciplinary approach to accurate classification of highly complex VA.

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