



TECHNICAL REPORT

Evidence for the Diagnosis and Treatment of Acute Uncomplicated Sinusitis in Children: A Systematic Review

abstract

FREE

In 2001, the American Academy of Pediatrics published clinical practice guidelines for the management of acute bacterial sinusitis (ABS) in children. The technical report accompanying those guidelines included 21 studies that assessed the diagnosis and management of ABS in children. This update to that report incorporates studies of pediatric ABS that have been performed since 2001. Overall, 17 randomized controlled trials of the treatment of sinusitis in children were identified and analyzed. Four randomized, double-blind, placebo-controlled trials of antimicrobial therapy have been published. The results of these studies varied, likely due to differences in inclusion and exclusion criteria. Because of this heterogeneity, formal meta-analyses were not performed. However, qualitative analysis of these studies suggests that children with greater severity of illness at presentation are more likely to benefit from antimicrobial therapy. An additional 5 trials compared different antimicrobial therapies but did not include placebo groups. Six trials assessed a variety of ancillary treatments for ABS in children, and 3 focused on subacute sinusitis. Although the number of pediatric trials has increased since 2001, there are still limited data to guide the diagnosis and management of ABS in children. Diagnostic and treatment guidelines focusing on severity of illness at the time of presentation have the potential to identify those children most likely to benefit from antimicrobial therapy and at the same time minimize unnecessary use of antibiotics. *Pediatrics* 2013;132:e284–e296

INTRODUCTION

Acute bacterial sinusitis is reported as a complication of 5% to 10% of upper respiratory tract infections in children^{1,2} and is 1 of the more common indications for antibiotic use in the United States. In 2001, the American Academy of Pediatrics (AAP) published clinical practice guidelines for the management of sinusitis in children.³ The 2001 technical report that accompanied those guidelines included an analysis of 21 studies published from January 1966 through March 1999 which assessed the diagnosis and therapeutic management of acute sinusitis in children.⁴ These included 5 randomized controlled trials involving 255 children and 8 case series involving 418 children. The primary goal of the current analysis was to update the 2001

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KEY WORDS

acute bacterial sinusitis, antibiotics, ancillary treatment, diagnosis, systematic review

ABBREVIATIONS

AAP—American Academy of Pediatrics

CT—computed tomography

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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technical report by identifying and reviewing additional studies of pediatric acute sinusitis that have been performed in the last decade to aid the revision of the AAP practice guidelines.

This technical report revisits the same questions as the original report: (1) What is the efficacy of various types of antimicrobial therapy in children with acute sinusitis? (2) What is the efficacy of nonantimicrobial ancillary treatments in children with acute sinusitis? (3) What is the concordance of various clinical, laboratory, and radiographic findings in the diagnosis of acute sinusitis? In addition, the Subcommittee on Management of Sinusitis met before the initial literature search for the current report and raised additional questions:

1. What is the incidence of adverse events in the treatment of sinusitis?
2. Are there data to support the clinical definitions of acute, subacute, and recurrent acute sinusitis?
3. Are there data to recommend a specific duration of symptoms that distinguishes bacterial from viral sinusitis?
4. How have the epidemiology and bacteriology of acute sinusitis changed in the pneumococcal conjugate vaccine era?
5. Is there evidence to support antimicrobial prophylaxis in children with recurrent sinusitis?
6. What other guidelines for the management of acute sinusitis in children exist?

METHODS

Searches of PubMed were performed by using the same search term as in the 2001 report ("sinusitis"). All searches were limited to English language and human studies. Three separate searches were performed to

maximize retrieval of the most recent and highest-quality evidence for pediatric sinusitis. The first search limited results to all randomized controlled trials from 1966 to 2009, the second to all meta-analyses from 1966 to 2009, and the third to all pediatric studies (age limit <18 years) published since the last technical report (1999–2009). In addition, Web of Science was used to search for additional studies that cited the 2001 technical report and guidelines as well as citations of each double-blind, randomized controlled pediatric trial identified. The Cochrane Database of Systematic Reviews was also reviewed. Finally, ClinicalTrials.gov was searched to identify results of unpublished and ongoing studies. The Jadad scale (Table 1) was used to assess the quality of randomized trials included in this analysis.⁵ Additional literature updates using the same search strategies were performed in July 2010 and November 2012.

Whenever possible, data from randomized controlled trials (preferably placebo controlled) were used to answer the questions raised by the committee. When no such data were available, separate literature searches were performed.

TABLE 1 Criteria for Assessing Randomized Trials

Give 1 point for each of the following:

- a. The study is described as randomized
- b. The study is described as double-blind
- c. There was a description of withdrawals and dropouts

Given 1 additional point if:

- a. For randomized studies, the method of randomization was described and is appropriate
- b. For double-blind studies, the method of blinding was described and is appropriate

Deduct 1 point if:

- c. For randomized studies, the method of randomization was described and is inappropriate
- d. For double-blind studies, the method of blinding was described and is inappropriate

Adapted from Jadad et al.⁵

RESULTS

In the initial search, 183 randomized trials were identified, 98 of which were published since 1998. Of these 98, a total of 62 were eliminated on the basis of titles indicating a focus on adults, chronic sinusitis, or post-surgical management. Inclusion criteria and results of the remaining 36 studies were reviewed. Seven studies included adolescents as young as 12 years, but they represented <2% of the study population, and no age-specific results were reported. Twenty-one additional studies included teenagers but did not report how many were included; average ages for these studies were in the third to fourth decade of life. The updated literature search in July 2010 identified 2 additional randomized controlled trials that focused on ancillary treatment of sinusitis in children. A final search performed in November 2012 did not identify any additional controlled trials.

Overall, 17 randomized studies of sinusitis in children were identified and included in the current analysis. The meta-analysis search identified 1 study that focused exclusively on children and 2 others that focused primarily on adults but also assessed and separately reported results of pediatric studies. A review of ClinicalTrials.gov identified 28 sinusitis studies including children aged <18 years, only 3 of which were limited exclusively to children. One of these (Wald et al⁶) has recently been published and is included in the analysis; the other 2 studies are not yet recruiting patients.

TREATMENT

Efficacy of Antimicrobial Therapy

Randomized Placebo-Controlled Trials

Four randomized, double-blind, placebo-controlled trials involving 392 children were identified (Table 2).^{6–9} An

additional study¹⁰ that was included in the previous technical report was excluded because it included patients with chronic and subacute sinusitis. The results of these 4 studies varied. Two studies favored treatment, and the other 2 found no significant difference in clinical cure between the treatment and control groups.

Clinical improvement in children receiving placebo ranged from 14% to 79% across the 4 studies, suggesting significant heterogeneity. The outcomes in the treatment groups were less varied, ranging from 50% to 81%. However, the efficacies of specific treatments are difficult to compare directly because the studies were performed over a 25-year period, during which a universal conjugate pneumococcal vaccination program was introduced and the prevalence of penicillin-resistant *Streptococcus pneumoniae* and β -lactamase-producing *Moraxella* and *Haemophilus* species increased.

The disparity in outcomes in the placebo groups is likely explained by the different methods used in each study. Notably, the inclusion criteria differed between each of the 4 studies. For instance, the minimal duration of symptoms required for entry into the study by Kristo et al⁹ was not specified and averaged between 8 and 9 days for the treatment and control groups, respectively. Furthermore, only 32% of subjects had symptoms lasting at least 10 days. Therefore, the results of this study are not generalizable to the AAP definition of sinusitis, which is 10 days of symptoms, and should not be considered in the revised guidelines. Inclusion criteria for persistent symptoms in the other 3 studies were similar. Each specified respiratory symptoms that persisted for at least 10 days but <30 days. Only the 1986 study by Wald et al⁷ required an abnormal radiograph for study entry.

Another study by Wald et al (in 2009)⁶ was the only trial to include a subgroup of children who met criteria for worsening (on or after day 6 with fever or increase in symptoms) or severe (temperature $\geq 102^\circ\text{F}$ with purulent discharge for at least 3 consecutive days) symptoms of sinusitis.

Exclusion criteria for each of these 3 studies had some similarities. Allergy to study drug, recent receipt of antibiotics, and concurrent bacterial infection requiring treatment were exclusion criteria in all of the studies. Complications of sinusitis were also listed as exclusion criteria, although the definitions of this factor differed between the studies. For instance, Garbutt et al⁸ excluded children with “fulminant sinusitis,” including children with fever $\geq 39^\circ\text{C}$ (102.2°F); this condition was a specific inclusion criterion for the severe group in the 2009 study by Wald et al.⁶ In addition, underlying medical conditions were used to exclude children, but the specific diagnoses differed in the 3 studies. Wald et al⁷ excluded children with a variety of underlying medical conditions, including history of asthma and allergic rhinitis. Garbutt et al⁸ only excluded children with cystic fibrosis; children with asthma and allergic rhinitis were included. Wald et al⁶ only excluded children with immunodeficiency or anatomic abnormality of the upper respiratory tract.

The 3 studies used similar randomization schemes: patients were stratified according to age group and clinical severity before randomization. However, the metrics of clinical severity differed. The 2 studies by Wald et al^{6,7} used a 10-point questionnaire (Table 3), and the study by Garbutt et al⁸ used the S5 score (Table 4), previously validated by the same author.¹¹ Although each of these 3 studies stratified patients according to clinical severity before randomization,

separate results stratified by severity are not reported. This information may be helpful in the identification of patients (on the basis of clinical grounds) who might benefit from antimicrobial therapy.

Another key methodologic difference is that the study by Wald et al (1986)⁷ did not use intention-to-treat analysis. Fifteen (14%) of 108 children were excluded because of lack of compliance or drug toxicity, which may have introduced bias.

Because of these significant differences in study design, formal meta-analyses were not performed. However, qualitative analysis of these results suggests that there may be certain clinical characteristics that identify patients who benefit from antimicrobial therapy.

Randomized Controlled Comparison Trials

In addition to the 4 placebo-controlled studies described previously, there have been other randomized studies of acute sinusitis in children comparing different antimicrobial treatment courses (Table 5).^{12–16} Three of these were included in the previous report, and 2 additional studies have been published since 1998. None of these studies demonstrated a clear advantage of 1 therapy over another, and rates of cure or improvement were well above 80%. Although these studies offer some insight into the relative efficacies of different treatments, they do not include a placebo group. This factor is important given that many of the children included in these studies may have improved spontaneously without any specific antimicrobial therapy. In addition, none of these studies was designed as noninferiority or equivalence studies and, therefore, may have been underpowered to detect true differences between competing treatments.

TABLE 2 Randomized, Placebo-Controlled Trials of Antimicrobial Treatment of Acute Sinusitis in Children

Variable	Wald et al ⁷	Garbutt et al ⁸	Kristo et al ⁹	Wald et al ⁶
Inclusion criteria	Nasal discharge of any quality	"Persistent upper respiratory symptoms"	Acute respiratory symptoms suggestive of sinusitis that were "not improving"	Persistent: nasal discharge of any quality and/or daytime cough persisting for >10 d without improvement
	and/or		Nasal discharge and obstruction, sneezing, cough	Worsening: worsening on or after day 6 with fever or increase in symptoms
	Cough			Severe: temperature $\geq 102^{\circ}\text{F}$ with purulent nasal discharge for at least 3 consecutive days
	Symptoms present for 10–30 d	Symptoms present for 10–28 d	Symptoms present <3 wk, no lower bound	Symptoms present <30 d, lower bound per definitions above
Age: 2–16 y	Age: 1–18 y	Age: 4–10 y	Age: 1–10 y	
Abnormal radiograph results	NA	Abnormal US	NA	
Exclusion criteria	Penicillin allergy	Allergy	Allergy	Allergy
	Previous Rx within 3 d	Previous Rx within 2 wk	Previous Rx within 4 wk	Previous Rx within 15 d
	Underlying conditions (asthma, allergic rhinitis, CF, sickle cell anemia, congenital heart disease, immunodeficiency)	CF only	Previous sinus surgery	Underlying conditions (immunodeficiency or anatomic abnormality of upper respiratory tract)
	Otitis media, pneumonia, GAS pharyngitis (throat/NP culture performed at study enrollment)	"Fulminant sinusitis"	Current antimicrobial Rx	Concurrent bacterial infection
	Severe headache or periorbital swelling	(fever $>39^{\circ}\text{C}$, facial swelling, facial pain)	"Complications of sinus disease"	Complication of sinusitis requiring hospitalization, IV antibiotics, or subspecialty evaluation.
	Normal radiograph of paranasal sinuses	NA	NA	NA
	Source of patients	Primary or secondary care patients at an academic children's hospital	3 suburban primary care practices	1 private health care center
Randomization			Block randomization	Assigned to persistent or nonpersistent group then stratified by age: (<6 and ≥ 6 y) And clinical severity Then randomized
	Stratified by age: (<6 and ≥ 6 y) And clinical severity Then randomized	Stratified by age: (<7 and ≥ 7 y) And clinical severity Then randomized		Stratified by age: (<6 and ≥ 6 y) And clinical severity Then randomized
Metric for severity	Clinical severity score: <8 is mild and ≥ 8 is severe	Clinical severity score using S5 score	8 acute symptoms, rated 0–4	Same as Wald et al ⁷
Telephone follow-up	1, 2, 3, 5, and 7 d	3, 7, 10, 14, 21, 28, and 60 d	NA	1, 2, 3, 5, 7, 10, 20, and 30 d
Clinical visit	Day 10	Day 14	Day 14	Day 14
Primary outcome	Clinical outcome at 3 and 10 d	Change in sinus symptoms at day 14	% complete cure at 2 wk	Cure at day 14
Secondary outcomes	Not specified	Adverse events	Adverse effects	Adverse events
		Relapse	Improvement without complications	Proportion with treatment failure
		Change in functional status	Days when analgesics, nasal decongestants or cough mixtures were given	
		Parental satisfaction with treatment		
N placebo	35	55	41	28
N treatment group	30 amoxicillin (40 mg/kg per day) divided 3 times/d for 10 d	58 amoxicillin (40 mg/kg per day) divided 3 times/d for 14 d	41 cefuroxime 125 mg 2 times/d for 10 d	28 amoxicillin/clavulanate (90 mg/kg amoxicillin + 6.4 mg clavulanate) divided 2 times/d for 14 days
	28 amoxicillin/clavulanate	48 amoxicillin/clavulanate (45 mg/kg per day amoxicillin) divided 2 times/d for 14 d		
Adjuvant therapy	None were prescribed. Not formally studied	Prescription or over-the-counter symptomatic treatments allowed. Use recorded	Analgesics, nose drops, and cough mixtures allowed. Use recorded in diary	Use "discouraged"—not formally studied
Compliance	History and remaining medications at follow-up visit	Self-report at day 14	Residual drugs collected at day 14	History and remaining medications at follow-up visit

TABLE 2 Continued

Variable	Wald et al ⁷	Garbutt et al ⁸	Kristo et al ⁹	Wald et al ⁶
Adverse events	Children who developed rash and diarrhea were excluded from analysis	Assessed at day 14	Assessed at day 14	Assessed at day 14
Loss to follow-up	15 children excluded because of adverse events (8) and noncompliance (7)	None (typographic error in original manuscript)	3 children (2 placebo, 1 treatment) lost to follow-up	6 lost to follow-up in treatment group
Primary outcome	Cure at 10 d: Amoxicillin: 20/30 (67%); Amoxicillin/clavulanate: 18/28 (64%); Placebo: 15/35 (43%) Total: Antibiotic: 38/58; Placebo: 15/35 (66% vs 43%; $P < .05$) Failure at 10 d: Amoxicillin: 5/30; Amoxicillin/clavulanate: 7/28; Placebo: 14/35 Total: Antibiotic: 12/58; Placebo: 15/35 (21% vs 43%; $P < .05$)	Improvement at 14 d: Amoxicillin: 79% (46/58); Amoxicillin/clavulanate: 81% (39/48); Placebo: 79% (43/55)	Cure at 14 d: 22/35 in experimental group vs 21/37 in placebo (63% vs 57%; $P = .64$)	Cure at 14 d: 14/28 in experimental group vs 4/28 in placebo (50% vs 14%; $P = .01$) Failure at 14 d: 4/28 in experimental group vs 19/28 in placebo (14% vs 68%; $P < .001$) If all subjects lost to follow-up were considered failures, therapy is still effective (35% vs 68%; $P = .032$)
Jadad score	3	5	4	4

CF, cystic fibrosis; GAS, group A streptococcal; IV, intravenous; NA, not applicable; NP, nasopharyngeal; Rx, prescription; US, ultrasonography.

In addition to these randomized comparator studies, Garbutt et al⁸ and Wald et al⁷ used amoxicillin and amoxicillin/clavulanic acid treatments arms in

their placebo-controlled studies. No significant differences between these 2 treatments were detected.

TABLE 3 Scale Used in Studies by Wald et al^{6,7}

Symptoms or Signs	Points
Abnormal nasal or postnasal discharge	
Minimal	1
Severe	2
Nasal congestion	1
Cough	2
Malodorous breath	1
Facial tenderness	3
Erythematous nasal mucosa	1
Fever	
<38.5°C	1
≥38.5°C	2
Headache (retro-orbital)	
Severe	3
Mild	1

Interpretation: <8 = mild, ≥8 = severe.

TABLE 4 Scale Used by Garbutt et al¹¹

Symptom	Points			
	1	2	3	0
Blocked up or stuffy nose	Small	Medium	Large	Not a problem or do not know
Headaches or face pain	Small	Medium	Large	Not a problem or do not know
Coughing during the day	Small	Medium	Large	Not a problem or do not know
Coughing at night	Small	Medium	Large	Not a problem or do not know
Color of child's mucus			Yellow or green	None or clear

S5 score is obtained by averaging the scores for each symptom. In the clinical trial,⁸ children were stratified into 2 groups before randomization: S5 score <2 or S5 score ≥2.

Adverse Events Associated With Antimicrobial Therapy

Randomized Placebo-Controlled Trials

Adverse effects of treatment were described in all 3 studies. In the first study by Wald et al,⁷ rash developed in 1 child in the amoxicillin group and 1 in the placebo group. Diarrhea, requiring cessation of therapy, developed in 6 children in the amoxicillin/clavulanic acid group and 1 child in the placebo group. In the study by Garbutt et al,⁸ one-half of all study participants reported an adverse effect; these events were equally distributed across the

study groups. Diarrhea was reported by 20% to 22% of participants ($P = .97$ between the 3 groups). The only reported adverse effect that reached statistical significance was abdominal pain, which occurred in 29% of children in the amoxicillin group but only 15% and 9% of children in the amoxicillin/clavulanate and placebo groups, respectively ($P = .02$). In the most recent study by Wald et al,⁶ 44% of children in the experimental group experienced an adverse event compared with 14% in the control group ($P = .014$). The incidences of specific adverse events were not described, but diarrhea was reportedly the most common. Although efficacy data from the study by Kristo et al⁹ should not be considered in the guidelines, data can be used to compare adverse events associated with antimicrobial therapy compared with placebo. In this study, 3 children developed self-limited diarrhea (1 in the cefuroxime group and 2 in the placebo group).

Randomized Controlled Comparison Trials

Adverse events were reported in 4 of these studies.^{12,14–16} The incidence of

TABLE 5 Randomized Controlled Trials Comparing Different Antimicrobial Treatments for Acute Sinusitis

Author (Year)	Age (y)	Antimicrobial Agents	Duration	N	Cured (%)	Improved (%)	Failed (%)	Relapsed (%)	Recurred (%)	Jadad Score
Poachanukoon and Kitcharoensakkul (2008) ¹²	1–15	Amoxicillin-clavulanate (80–90 mg/kg per day)	14 d	72	ND	85	ND	11	6	3
		Cefditoren (4–6 mg/kg) 2 times/d	14 d	66	ND	79	ND	9	3	
Simon (1999) ¹³	0.5–17	Erythromycin (40 mg/kg per day)	14 d	50	96	ND	4	ND	10	1
		Ceftibuten (9 mg/kg per day)	10 d	50	92	ND	8	ND	12	
		Ceftibuten (9 mg/kg per day)	15 d	50	92	ND	8	ND	8	
		Ceftibuten (9 mg/kg per day)	20 d	50	100	ND	0	ND	8	
Ficnar et al (1997) ¹⁴	0.5–12	Azithromycin (10 mg/kg per day)	3 d	27	96	ND	0	4	ND	1
		Azithromycin (10 mg/kg on day 1, then 5 mg/kg on days 2–5)	5 d	18	100	ND	0	0	ND	
Careddu et al (1993) ¹⁵	2–14	Brodinoprim (10 mg/kg on day 1, then 5 mg/kg per day)	8 d	25	96	ND	4	ND	ND	1
		Amoxicillin-clavulanate (50 mg/kg per day)	NS	27	85	ND	15	ND	ND	
Wald et al (1984) ¹⁶	1–16	Amoxicillin (40 mg/kg per day)	10 d	27	81	4	11	4	4	3
		Cefaclor (40 mg/kg per day)	10 d	23	78	9	4	11	17	

ND, not determined; NS, not specified.

adverse events did not differ between study groups for 3 of these studies. Poachanukoon and Kitcharoensakkul¹² reported a higher rate of diarrhea (18.1%) in children receiving amoxicillin/clavulanate compared with those receiving cefditoren (4.5% [$P = .02$]). However, diarrhea was self-limited and did not require termination of medication or study withdrawal.

ANCILLARY TREATMENTS

Six randomized-controlled trials have assessed a variety of ancillary treatments for acute sinusitis (Table 6)^{17–20} and are summarized here.

Steroids

The 2001 technical report described 1 study that assessed the efficacy of intranasal steroids in children.¹⁷ In that study, 89 children received amoxicillin/clavulanate (40 mg/kg per day) and were randomized to receive either budesonide nasal spray ($n = 43$) or placebo ($n = 46$) for 3 weeks. Although no difference in symptom improvement was noted between the groups at the end of therapy (3 weeks), children in the budesonide group had improved cough and nasal discharge at 2 weeks,

whereas children in the placebo group did not, suggesting that corticosteroids may lead to more rapid resolution of symptoms. Since then, there has been 1 other randomized controlled trial in children studying the efficacy of intranasal budesonide.¹⁸ In this study, 52 children (mean age: 8 years; age range: 6–16 years) with acute maxillary sinusitis received cefaclor (40 mg/kg) for 10 days with either pseudoephedrine (2×30 mg daily) or intranasal budesonide (2×100 µg daily) for 10 days. There was no placebo group. Children with underlying allergy were excluded. Children in the budesonide group had statistically significantly better resolution of headache, cough, nasal stuffiness, and nasal drainage. There were no adverse events reported. However, these authors defined acute sinusitis as an infection that could take up to 12 weeks for complete resolution, and the results may therefore not be generalizable to AAP guidelines.

Decongestant-Antihistamine

No randomized controlled studies have been performed since a study cited in the 2001 report.¹⁹ All children in that

study received 14 days of amoxicillin (37.5–50 mg/kg per day, divided 3 times per day). They were then randomized to receive either placebo or the combination of oxymetazoline nasal spray and an oral decongestant-antihistamine. Both groups had marked clinical improvement in symptoms 3 days into treatment. In addition, there were no significant differences in clinical or radiographic findings between the 2 groups at the end of treatment.

Nasal Spray

One randomized controlled trial compared the use of 14 days of treatment with Ems mineral salts versus xylometazoline (0.05% solution) nasal spray in children with acute sinusitis.²⁰ There was no placebo group, and antibiotic use was not permitted. The primary outcome was mucosal inflammation (rubescence, swelling, and discharge) at baseline, day 7, and day 14. There were no significant differences between the 2 groups at day 14. However, at day 7, the mineral salt group had less nasal discharge than the xylometazoline group ($P = .0163$), suggesting that the spray may lead to more

TABLE 6 Randomized Controlled Trials of Ancillary Therapies for Acute Sinusitis

Author (Year)	Age (y)	Inclusion Criteria	Primary Therapy	LOT	Other Treatments	N	Main Outcome	Jadad Score
Barlan et al (1997) ¹⁷	1–15	2 major, or 1 major and 2 minor criteria. Duration >7 d; Major criteria: purulent nasal discharge, purulent pharyngeal drainage, cough; Minor criteria: periorbital edema, facial pain, tooth pain, earache, sore throat, wheeze, headache, foul breath, fever	Intranasal budesonide (50 µg each nostril) 2 times/day; Intranasal placebo bid	21 21	All received amoxicillin/clavulanate (40 mg/kg per day)	43 46	No difference in cough or nasal discharge scores at weeks 1 or 3. Budesonide scores statistically lower (less symptomatic) at week 2 for both outcomes	2
Yilmaz et al (2000) ¹⁸	6–16	Specific symptoms not specified Duration: infection that could take up to 12 wk to resolve	Intranasal budesonide (2 × 100 µg) Oral pseudoephedrine (2 × 30 mg)	10 10	All received cefaclor (40 mg/kg per day)	26 26	Budesonide group statistically better improvement in headache, cough, nasal stuffiness, and nasal drainage at day 10	1
McCormick et al (1996) ¹⁹	1–18	8–29 d of sinusitis symptoms	Oxymetazoline nasal spray (0.05%) plus syrup with decongestant-antihistamine Placebo nasal spray and syrup	14 14	All children received amoxicillin by age/weight: 10–12 kg, 150 mg tid; 12.1–15 kg, 200 mg tid; >15 kg, 250 mg tid Teenagers: 40 mg/kg per day (maximum: 500 tid)	34 34	No difference between groups in mean symptom score at enrollment, day 3, or day 14	4
Michel et al (2005) ²⁰	2–6	"Definition give[n] by the AAP"	Intranasal isotonic Ems mineral salts Intranasal xylometazoline (0.05%)	14 14	No additional treatment (including antibiotics) allowed	66 ^a	No difference in symptoms at day 14. Ems group had statistically significant less inflammation at day 7	2
Wang et al (2009) ²¹	3–12	(1) URI with purulent nasal discharge and/or cough >7 d (2) Abnormal findings of 1 or both maxillary sinuses by Water's projection	Standard therapy plus normal saline nasal irrigation, 15–20 mL per nostril 1–3 times/day Standard therapy alone	21 21	"Standard therapy" defined as systemic antibiotics, mucolytics, and nasal decongestants	30 39	Saline group had better scores for daytime rhinorrhea and nighttime nasal congestion. No statistically significant differences in quality of life score, nasal smear, or Water's projection	1
Unuvar et al (2010) ²²	3–12	(1) 10–30 d of URTI symptoms (2) Presence of severe symptoms of rhinosinusitis	Erdosteine syrup (5–8 mg/kg/day orally divided bid) Placebo	14 14	None	49 43	No significant difference in clinical improvement at 14 d between the 2 groups	4

bid, 2 times per day; LOT, length of therapy; tid, 3 times per day; URTI, upper respiratory tract infection.

^a Sixty-six patients in trial; numbers in each treatment arm not specified.

rapid resolution of symptoms. Wang et al²¹ randomized 69 children to receive standard therapy (systemic antibiotics, mucolytic agents, and nasal decongestants) or standard therapy plus nasal irrigation (15–20 mL of normal saline administered via syringe to each nostril 1–3 times per day). Outcomes included a daily nasal symptom score (summarized weekly), pediatric rhinoconjunctivitis quality of

life questionnaire (at baseline and 3 weeks), weekly nasal peak expiratory flow rate, weekly nasal smear, and Water's projection (baseline and 3 weeks). The irrigation group had significantly better symptom scores for daytime (but not nighttime) rhinorrhea at weeks 1, 2, and 3 and nighttime (but not daytime) nasal congestion at weeks 1, 2, and 3. Children in the irrigation group also had better nasal

peak expiratory flow rates and slightly better quality of life scores at 3 weeks. There were no statistically significant differences in nasal smear or Water's projections between the 2 groups after 3 weeks of treatment.

Mucolytic Agents

One randomized controlled trial assessed S5 scores in 49 children receiving the mucolytic erdosteine

compared with 43 children who received placebo.²² After 14 days of treatment, there was no significant difference in S5 scores between the 2 groups.

In addition to these studies, which were specifically designed to assess the efficacy of nonantimicrobial therapy, use of ancillary measures was measured and reported for 2 of the randomized trials of antimicrobial use. In the study by Garbutt et al,⁸ there were no significant differences in the overall use of ancillary therapies between the treatment and placebo groups (52% vs 48% vs 49%; $P = .92$). Although individual-level data were not presented, this finding makes it unlikely that unbalanced use of adjuvant therapies contributed to the study outcomes. Among individual therapies, only use of combination products was reported more frequently in 1 group (10% of amoxicillin/clavulanate vs 0% and 2% of amoxicillin and placebo, respectively; $P = .01$). In the study by Poachanukoon and Kitcharoensakkul,¹² use of concomitant intranasal corticosteroids (52%) and oral decongestants (22%) was common but did not differ between the study groups.

DIAGNOSIS

Although sinus aspiration remains the gold standard for diagnosis of acute sinusitis, it is rarely practiced outside of the research setting. Furthermore, few recent studies have used aspiration as a criterion for study entry or used bacteriologic cure as an outcome. Despite these microbiologic limitations, evidence from the trials summarized previously can answer a slightly different question: which (if any) clinical, laboratory, and/or radiologic findings are able to discriminate between children who are likely to benefit from antimicrobial therapy and those who are not?

CLINICAL FINDINGS

Duration of Symptoms

The most commonly used diagnostic criterion for acute bacterial sinusitis is persistent or prolonged duration of symptoms for 10 to 14 days.²³ This criterion is based on the observation that most viral upper respiratory tract infections last 5 to 7 days.³ However, the study by Garbutt et al⁸ demonstrated that duration of symptoms alone was not sufficient to warrant antimicrobial therapy. A minimum of 10 days of symptoms was required for study entry, and all 3 groups had a mean duration of symptoms greater than 2 weeks (amoxicillin: 15.8 days; amoxicillin/clavulanate: 18.5 days; placebo: 15.4 days).

Signs and Symptoms

Purulent rhinorrhea, nasal congestion, and headache are other common findings used to diagnose sinusitis.²³ The various clinical trials used different combinations of these findings in their inclusion criteria. The 3 placebo-controlled studies limited to children with at least 10 days of symptoms also used clinical severity scores based on these signs and symptoms. Tables 2 and 3 stratify study participants before randomization. Because this stratification occurred before randomization, severity-specific results might help clarify which children are likely to benefit from antimicrobial therapy.

Imaging Studies

The 2001 guidelines recommended that radiologic studies should not be used to diagnose sinusitis in children 6 years or younger and that computed tomography (CT) should be considered only for children requiring surgery.³ Ultrasonography has also been suggested as a potential diagnostic tool for acute sinusitis. The 2001 technical

report cited 1 study that demonstrated good concordance between ultrasonographic findings and retrieval of fluid on sinus aspiration.²⁴ On the basis of that study, ultrasonographic findings (either mucosal thickening of ≥ 5 mm or fluid in at least 1 maxillary sinus) were used as entry criteria in the study by Kristo et al.⁹ In that study, children also underwent occipitontal radiography, and the film results were defined as positive for sinusitis if there was mucosal thickening of at least 4 mm, an air-fluid level, or total opacification of at least 1 maxillary sinus. Eighty-nine percent of children in the treatment group and 92% of those in the placebo group met this criterion, suggesting good concordance between plain films and ultrasonography. However, these findings were not predictive of which children would benefit from antimicrobial therapy. Radiographic studies were not used in the other 2 recent placebo-controlled studies.^{6,8}

Laboratory Studies

None of the studies required routine laboratory studies for study entry. Microbiologic samples were only obtained in 2 placebo-controlled studies and did not include direct sinus sampling. Wald et al⁷ used results of throat and nasopharyngeal cultures to exclude patients with group A streptococcal pharyngitis from their study. Kristo et al⁹ obtained nasopharyngeal cultures on all patients but only reported those with results positive for *Streptococcus pneumoniae* and *Haemophilus influenzae*, which occurred in 12.5% of study participants.

SUBACUTE SINUSITIS

Subacute sinusitis has been defined as infection that lasts between 30 and 90 days.³ Three small randomized

controlled trials assessing the efficacy of different treatment strategies for subacute sinusitis were identified (Table 7).^{25–27} None of these studies included a placebo group. One compared empirical amoxicillin/clavulanate with culture-based (from nasal mucosa) antimicrobial treatment.²⁵ Culture of nasal specimens was not performed on the children in the empirical antibiotic group. Five (18.5%) of 27 culture results in the experimental group were positive for amoxicillin/clavulanate-resistant organisms (1 *Pseudomonas* species, 2 resistant to *S pneumoniae*, and 2 anaerobic streptococci), and appropriate therapy was initiated. Nasal obstruction at day 14 was unchanged or worse for 9 children (36%) in the empirical arm but only 4 children (15%) in the culture-based arm ($P = .037$, per authors). Another study compared azithromycin versus amoxicillin/clavulanate.²⁶ The third compared amoxicillin, amoxicillin/clavulanic acid, trimethoprim/sulfamethoxazole, and no antimicrobial therapy.²⁷ In these 2 studies, no advantage was detected in

any treatment arm compared with others. However, the studies were small and were likely not powered to detect true differences.

CLINICAL QUESTIONS FOR WHICH HIGH-QUALITY DATA ARE LACKING

Definitions of Acute, Subacute, and Recurrent Acute Sinusitis

The definitions of acute, subacute, and recurrent acute sinusitis are outlined in the 2001 AAP guidelines.³ Although logical and based on the presumed pathogenesis of these distinct clinical entities, there are few clinical or laboratory data to confirm these definitions in children. One study of subacute sinusitis included 52 sinus aspirations of 40 children with subacute (30–120 days of symptoms) sinusitis and found similar pathogens as in acute sinusitis.²⁸ The definition of subacute sinusitis used in this study and in the study by Ng et al²⁶ were derived from an expert consensus panel.²⁹ The study by El-Hennawi et al²⁵ cites the 2001 AAP guidelines,

and the study by Dohlman et al²⁵ does not provide a reference for the study definition of subacute sinusitis.

Epidemiology of Sinusitis in the Pneumococcal Conjugate Vaccine Era

A separate literature search was performed to identify studies of sinusitis in the era of the pneumococcal conjugate vaccine. Although there are substantial data regarding the epidemiology of invasive pneumococcal disease and acute otitis media since implementation of pneumococcal immunization, no recent pediatric sinusitis studies that included microbiologic data were identified. Brook et al³⁰ compared culture results from sinuses of adults before and after introduction of the pneumococcal conjugate vaccine. There was a statistically significant decrease in the prevalence of *S pneumoniae* and a significant increase in the prevalence of *H influenzae*. In addition, there was a 12% decrease in penicillin resistance observed in pneumococcal

TABLE 7 Randomized Controlled Trials of Antimicrobial Therapy for Subacute Sinusitis

Author (Year)	Age (y)	Inclusion Criteria	Antimicrobial Agents	Length	Other Treatments	N	Better (%)	Worse or Same (%)	Jadad Score
El-Hennawi et al (2006) ²⁵	<2	Persistent nasal discharge and nasal obstruction for 30–90 d	Amoxicillin-clavulanate (40 mg/kg per day)	14 d	All had therapeutic nasal suction every third day	30	64	36	2
			Culture-based (nasal suction)			30			
			Amoxicillin/clavulanate (40 mg/kg per day)			12	83	17	
			Amoxicillin/clavulanate (90 mg/kg per day)	14 d		6	100	0	
			Other antibiotics			5	100	0	
		No antibiotics (negative culture result)		4	50	50			
Ng et al (2000) ²⁶	5–16	Nasal discharge or blockage for 30–120 d and abnormal sinus radiograph	Azithromycin (10 mg/kg per day)	3 d	All received budesonide nasal spray 50 µg/nostriil 2 times/day for 91 d	20	ND ^a	30	3
			Amoxicillin/clavulanate (312 mg 3 times/day if aged ≤12 y or 375 mg 3 times/day if aged >12 y)	14 d		21	ND ^a	24	
Dohlman et al (1993) ²⁷	2–16	Mucoid nasal drainage, cough, or poorly controlled asthma for 3 wk–3 mo and abnormal sinus radiograph	Amoxicillin (30–40 mg/kg per day)	21 d	All received oral phenylephrine, phenylpropranolamine, and guaifenesin; all received saline nasal spray	25	72	28	3
			Amoxicillin-clavulanate (30–40 mg/kg per day)	21 d		26	73	27	
			TMP/SMX (8 mg/kg per day)	21 d		26	69	31	
			None			19	63	37	

ND, not determined; TMP/SMX, trimethoprim/sulfamethoxazole.

^a This study only reported “failures.”

isolates and a 6% increase in β -lactamase-producing *H influenzae*, but these findings did not reach statistical significance. The same authors also compared nasopharyngeal (but not sinus) cultures in children before and after licensure of the pneumococcal conjugate vaccine and found similar results.³¹

Antimicrobial Prophylaxis

One small, nonrandomized study of antimicrobial prophylaxis in children with chronic sinusitis was identified.³² Twenty-six of 86 children with chronic sinusitis received prophylaxis for 1 year. There was a 50% reduction in the number of episodes of sinusitis in 19 (73%) subjects. Nearly 25% of the children in the cohort had an underlying immunologic defect, but this discovery did not predict efficacy of prophylaxis. A randomized controlled study of azithromycin prophylaxis for acute recurrent sinusitis in children was identified on ClinicalTrials.gov and began recruiting patients in August 2009.

Duration of Symptoms

As presented previously, data from randomized trials suggest that duration of symptoms alone is not predictive of necessity of antimicrobial therapy. A small case series of complications of rhinosinusitis (almost exclusively orbital cellulitis) in children was recently published.³³ The authors noted that only 3 of 20 children admitted to a single institution over a 10-year period had symptoms of sinusitis for >10 days before hospitalization. On the basis of these data, they concluded that prevention of complications should not be a justification for initiating treatment after 10 days of symptoms.

Imaging

Since publication of the guidelines, there have been additional studies of

children undergoing CT of the head that have confirmed the poor specificity of CT for acute sinusitis.^{34,35} In addition, several small observational studies have assessed the use of MRI to diagnose acute sinusitis.^{36–38} In the first, MRI was performed on a group of children 4 to 7 years of age presenting to a primary care center with any sign of respiratory infection.³⁶ Forty-one (68%) of 60 children had a major abnormality on imaging. Twenty-six children underwent follow-up 2 weeks later. Of these, 18 (69%) still had abnormal MRI findings, although this finding did not correlate with clinical symptoms. Another study by the same authors compared MRI findings in a convenience sample of children without respiratory complaints. Eight of 19 asymptomatic children had abnormal MRI findings.³⁷ A similar study found abnormal sinuses in 14 (31%) of 45 asymptomatic children.³⁸

OTHER PEDIATRIC SINUSITIS GUIDELINES

Published guidelines were identified during the primary literature search. In addition, the Guidelines International Network (www.g-i-n.net) database was searched but yielded no results. Recently published pediatric guidelines for acute bacterial sinusitis are presented in Table 8.^{39–42} These include English-language, pediatric-specific guidelines and other English-language guidelines that included separate recommendations for children. These guidelines were in near-complete concordance with the 2001 AAP guidelines in terms of clinical diagnosis, choice of antimicrobial agents, avoidance of radiographic studies, and avoidance of adjuvant therapies. One exception was that the European position paper recommended topical corticosteroids (in addition to oral antibiotics) as a grade A recommendation.³⁹

The American College of Radiology Appropriateness Criteria, last updated in 2009, are another set of professional recommendations relevant to the diagnosis of sinusitis in children.⁴³ In summary, no radiologic studies are recommended by the American College of Radiology for acute uncomplicated sinusitis. Coronal CT of the paranasal sinuses is recommended for children with symptoms that persist after 10 days of appropriate therapy. Cranial CT with contrast, including the sinuses and orbits, is recommended for suspected complications of sinusitis.

DISCUSSION

The 2001 technical report noted a paucity of high-quality evidence for establishing the diagnosis and management of acute sinusitis in children. Nearly a decade later, data are still limited. Overall, 17 randomized controlled trials of pediatric acute sinusitis were identified. Of these, only 10 studies scored 3 points or higher on the Jadad scale, which is considered indicative of good study design.⁵ These findings are consistent with other recent systematic reviews of pediatric acute sinusitis. A 2002 Cochrane review included data from 6 randomized controlled trials involving 562 children.⁴⁴ However, 2 studies focused on chronic sinusitis and 1 focused on subacute sinusitis. In addition, a recently published meta-analysis of studies comparing antimicrobial therapy versus placebo in all age groups identified only 3 studies that included children, all of which were included in the current review.⁴⁵ The publication of another placebo-controlled trial in 2009 is a significant contribution; however, only 310 children with acute sinusitis (392 if the Kristo study is included) have been studied in placebo-controlled fashion, with inconsistent results. Although meta-analysis techniques are designed to increase sample size and power,

TABLE 8 Summary of Other Published Guidelines for the Management of Acute Sinusitis in Children

Guideline	Antimicrobial Guidelines for Acute Bacterial Sinusitis (Sinus and Allergy Health Partnership, 2004) ³⁹	Cincinnati Children's Hospital Evidence-Based Guideline (2006) ⁴⁰	European Position Paper on Primary Care Diagnosis and Management of Rhinosinusitis and Nasal Polyps (2007) ⁴¹	Guidelines for Treatment of Acute and Subacute Rhinosinusitis in Children (Italy, 2008) ⁴²
Diagnosis	No resolution after 10 d or worsens after 5–7 d with any of the following: nasal drainage, nasal congestion, facial pressure/pain, postnasal drainage, hyposmia/anosmia, fever, cough, fatigue, maxillary dental pain, and ear pressure/fullness	Clinical: at least 10 d without improvement Specific note: character of nasal discharge is not useful	(1) Cold with nasal discharge, daytime cough worsening at night >10 d (2) Cold that seems more severe than usual (3) Cold that was improving but suddenly worsens	(1) URTI without improvement within 10 d (2) URTI with severe symptoms (high fever, purulent rhinorrhea, headache, facial pain) (3) URTI that completely recedes within 3–4 d but recurs within 10 d
Imaging	Not recommended routinely	Not routinely recommended For children with persistent findings or complications, imaging decisions should be made in consultation with consulting subspecialists	Not recommended	Not recommended CT when surgery being considered
Antimicrobials	Mild disease, no recent antibiotics: amoxicillin/clavulanate, amoxicillin, cefpodoxime, cefuroxime, cefdinir For allergies: TMP/SMX, macrolides Moderate disease or mild disease with recent antibiotics: amoxicillin/clavulanate (high-dose), ceftriaxone For allergies, same as above, plus clindamycin	First-line: high-dose amoxicillin or amoxicillin/clavulanate for 10–14 d Second-line: cefuroxime, cefpodoxime, cefdinir For allergies: second-line antibiotics if non-type I reaction Clarithromycin or azithromycin for type I reaction	Recommended: specific agents not discussed	Amoxicillin 50 mg/kg per day If recent antibiotic exposure, school-attendance, or suspicion of antibiotic-resistant pathogens: Amoxicillin/clavulanate (80-90 mg/kg per day), cefuroxime (30 mg/kg per day), or cefaclor (50 mg/kg per day)
Adjuvant therapies	NA	Not recommended (antitussives, mucolytics, inhaled steroids, β_2 -agonists, antihistamines, decongestants)	Topical steroids (in addition to systemic antibiotics) listed as a level Ib recommendation (from at least 1 RCT)	Antihistamines, corticosteroids, decongestants, expectorants, mucolytics, and vasoconstrictors not recommended Antibiotic prophylaxis not recommended
Complications	NA	Consult otolaryngologist and/or ophthalmologist	Immediate referral/hospitalization	Prompt, aggressive, multidisciplinary intervention

This table incorporates pediatric-specific guidelines (Cincinnati, Italy) as well as general guidelines with pediatric-specific recommendations (Sinus and Allergy Health Partnership, European Position Paper). CT, computed tomography; NA, not applicable; RCT, randomized controlled trial; TMP/SMX, trimethoprim/sulfamethoxazole; URTI, upper respiratory tract infection.

these were not pursued given the significant heterogeneity between the studies.

There are no reliable diagnostic criteria to distinguish between children with acute viral and bacterial sinusitis. However, the inclusion and exclusion criteria used in the 2 randomized studies that demonstrated a benefit of antimicrobial therapy compared with placebo offer insight into criteria that may identify children who are likely to benefit from antimicrobial therapy. Qualitatively, greater severity of illness at the time of presentation seems to be

associated with increased likelihood of antimicrobial efficacy.

No studies of the microbiology of acute sinusitis in children have been published since the introduction of the conjugate pneumococcal vaccine. It is reasonable to assume that the same pathogen shifts observed in acute otitis media are found in acute bacterial sinusitis. However, this assumption would not necessarily imply that the treatment outcomes for otitis and sinusitis are the same.

Although the need for and choice of antimicrobial therapy remains controversial,

the short-term adverse effect profiles for common antibacterial agents used in the management of sinusitis seem to be fairly benign. Two studies found no significant differences in adverse events between placebo and antimicrobial therapy.^{8,9} A third reported that, although adverse effects were more common in the treatment group, those events occurring in children who received high-dose amoxicillin/clavulanate were mostly mild and self-limited.⁶ However, the long-term effects of antimicrobial use on resistance patterns at the population level remain unmeasured

and need to be considered in the revised guidelines.

Evidence to support the use of ancillary measures in the management of acute sinusitis in children is limited. Two small, randomized controlled studies demonstrated that children treated with intranasal steroids had better outcomes compared with children treated with systemic decongestants plus antibiotics¹⁸ or antibiotics alone.¹⁷ One of these studies demonstrated that corticosteroids hastened resolution of symptoms, but cure at the end of the study was equivalent. The other

defined acute sinusitis as an infection lasting up to 12 weeks, which may not be applicable to the definition of acute sinusitis used in the AAP guidelines. The efficacy of decongestants and antihistamines for sinusitis has not been proven. Given recent concerns regarding their safety profile in young children, the use of these agents should be avoided.

CONCLUSIONS

There are limited data to guide the diagnosis and management of acute

bacterial sinusitis in children. Although there have been 4 placebo-controlled studies of antimicrobial therapy in children with acute sinusitis, the results of these studies varied. It is clear that some children with sinusitis benefit from antibiotic use and some do not. Diagnostic and treatment guidelines focusing on severity of illness at the time of presentation have the potential to identify children who will benefit from therapy and at the same time minimize unnecessary use of antibiotics.

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