Published in final edited form as:

J Pediatr. 2014 March ; 164(3): 536–541. doi:10.1016/j.jpeds.2013.11.021.

Predicting response to antimicrobial therapy in children with acute sinusitis

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Abstract

Objective—To determine prognostic factors that independently predict response to antimicrobial therapy in children with acute sinusitis.

Study design—206 children meeting *a priori* clinical criteria for acute sinusitis who were given antimicrobial therapy by their primary care provider were included. The severity of symptoms in the 8 to 12 days after treatment was initiated was followed using a validated scale. We examined the univariate and multivariate association between factors present at the time of diagnosis (symptoms, signs, nasopharyngeal culture result, radiograph results) and time to resolution of symptoms. This study was conducted 8 to 10 years after 7-valent pneumococcal conjugate vaccination was introduced, but before introduction of the 13-valent pneumococcal conjugate vaccination.

Results—Children with proven nasopharyngeal colonization with *Streptococcus pneumoniae* improved more rapidly (6.5 vs. 8.5 median days to symptom resolution) than those who were not colonized with *S. pneumoniae*. Age and radiograph findings did not predict time to symptom resolution.

Conclusions—In children with acute sinusitis, proven nasopharyngeal colonization with *S. pneumoniae* at presentation independently predicted time to symptom resolution. Future randomized, placebo-controlled trials could investigate the usefulness of testing for the presence of nasopharyngeal pathogens as a predictor of response to treatment.

Keywords

Pediatrics; nasopharyngeal; flora; colonization; symptoms

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The authors declare no conflicts of interest.

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Knowledge of prognostic factors that may predict duration of symptoms in children treated for presumed acute bacterial sinusitis would allow physicians to counsel parents appropriately regarding the expected course of illness. In addition, if strong predictive factors are identified, these factors could be used as stratification variables in future clinical trials. This would allow researchers to ensure that groups are comparable with respect to known affecting outcome factors.¹

In adults with acute sinusitis, age,² clinical severity,² and growth of pathogenic bacteria from nasopharyngeal culture³ appear to be helpful in predicting the response to therapy. No published studies to date have investigated which factors predict resolution of symptoms in children with acute sinusitis.

The objective of this study was to identify factors that independently predict response to antimicrobial therapy in children with acute sinusitis.

METHODS

We prospectively enrolled consecutive children aged 2 to 12 years of age with clinically-diagnosed acute sinusitis presenting to one of 6 general ambulatory pediatric clinics in Pittsburgh during two consecutive respiratory seasons. Most (90%) children were enrolled during the winter months (October to March of 2008–2009 and 2009–2010). The diagnosis of acute sinusitis was made according to stringently defined *a priori* clinical criteria consistent with the American Academy of Pediatrics most recent guidelines.⁴ Children with: (1) persistent upper respiratory tract symptoms [i.e., 10–29 days of cough (not exclusively nocturnal) and/or nasal symptoms (rhinorrhea of any quality)] who were not improving; or (2) worsening symptoms [substantial worsening of nasal symptoms and/or fever after a period of improvement] were eligible. We excluded children who: (1) had received antimicrobial treatment within 7 days before presentation; (2) had evidence of another infection (ie, acute otitis media or pneumonia); or (3) had underlying immune deficiency, cystic fibrosis, ciliary dyskinesia, or major developmental delay. We excluded children meeting clinical criteria for sinusitis for whom antimicrobial agents were not prescribed by their primary care physician because of the mild nature of their illness. Children with asthma who were otherwise eligible were included only if they were not wheezing on exam and if they had nasal symptoms that were worsening or persistent (ie, no child with asthma was enrolled based on prolonged cough alone). Children with a history of allergic rhinitis who met the entry criteria were included only if their respiratory symptoms had worsened acutely. This study was conducted 8 to 10 years after 7-valent pneumococcal conjugate vaccination (PCV7) was introduced, but was completed before introduction of the 13-valent pneumococcal conjugate vaccination (PCV13). The Institutional Review Board at the University of Pittsburgh approved this study before patient enrollment.

At the time of diagnosis, one of the study investigators interviewed parents regarding their child's symptoms and performed a detailed physical examination. The same investigator also obtained a nasopharyngeal specimen at the baseline visit using a sterile, flexible, thin, polyester/rayon-tipped moistened swab. In some cases, a nasopharyngeal culture was not performed (mostly due to parental refusal). The swab was placed into Amies transport media (without charcoal), refrigerated, transported to the lab for culturing, and inoculated onto a trypticase soy 5% sheep blood agar and a chocolate plate. Cultures were incubated overnight at 37°C with 5% CO₂. If no growth was present after overnight incubation, the culture was re-incubated for another 24 hours. Growth of pathogenic bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*) was assessed using standard semiquantitative techniques (growth in 0, 1, 2, 3, or 4 quadrants); 3+ and 4+ growth was considered heavy growth. Pneumococcal isolates that were resistant to oxacillin

by disk diffusion were further tested with an E-test to determine their minimum inhibitory concentration (MIC) to penicillin. Isolates for which the penicillin MIC was between 0.1 and 1 µg/mL were defined as penicillin intermediate, and those for which the penicillin MIC was >1 µg/mL were defined as penicillin resistant. The decision to begin antimicrobial therapy and the agent used was at the discretion of the treating clinician. In all cases, the nasopharyngeal swab was collected before therapy was begun.

We obtained anteroposterior and occipitomeatal (Water view) radiographs on all children in the study on the day of diagnosis. For children ≥ 6 years of age, we also obtained lateral views to permit assessment of the frontal and sphenoid sinuses (usually not well-developed in children < 6 years of age). Sinus radiographs were independently reviewed, at the end of the study, by two reference radiologists (LF, AB) who were unaware of any clinical data. Each sinus was rated as normal or abnormal. Although previous studies have classified children with > 4mm of mucosal thickening as having an abnormal radiograph consistent with a diagnosis of sinusitis. It is now clear that no degree of thickening is sufficient to rule in sinusitis. Additionally, superimposition of ethmoidal air cells precludes reliable delineation of degree of mucosal thickening. Thus, instead of using the threshold of 4 mm (that was developed to rule in disease), we used the absence of any mucosal thickening to indicate absence of significant sinus disease (ie, children in whom all sinuses were found to be clear were considered as having a normal radiograph; all others were considered as abnormal). Disagreements between the two radiologists were resolved by discussion.

We used the Pediatric Rhinosinusitis Symptom (PRSS-P) score as the main measure of outcome. The PRSS-P asks parents to rate the severity of 8 symptoms (daytime cough, nighttime cough, runny nose, stuffy nose, irritability, green or yellow mucus from the nose, trouble sleeping, feeling tired) over the preceding 24 hours. Parents were asked to complete the scale every evening until the follow-up appointment (days 8–12). Each symptom was scored on a 3-point Likert scale (none = 0, a little = 1, a lot = 2). The total score was obtained by summing the scores on these 8 equally-weighted items. Completed diaries were collected at the time of the follow-up visit on Days 8 to 12.

Statistical Analyses

We compared median time with resolution of symptoms (defined as reaching a score of ≤ 2 on the PRSS-P on two successive occasions) according to the levels of the potential prognostic factors (variables measured at baseline: signs, symptoms, nasopharyngeal culture results, and radiograph findings) using a proportional-hazards model. To assess the independent contributions of each factor, we formed a cox multivariate model using variables significantly ($p < 0.15$) associated with the outcome on univariate analysis while adjusting for symptom score at the time of diagnosis. We also evaluated whether the type and/or dosage of antimicrobial used could have confounded our results.

RESULTS

Of 258 children with a clinical diagnosis of acute sinusitis, 206 who were given antimicrobial therapy by their primary care providers and were considered for this analysis. Of these, 198 (96%) returned completed diaries. Demographic and clinical characteristics of these 198 children are shown in Table I. A total of 38 (19%) children, all of whom had worsening symptoms, had had symptoms for 6 to 9 days. A total of 106 (54%) children had symptoms for 10–19 days, and 54 (27%) had symptoms for 20–30 days. The mean age (standard deviation) of children enrolled was 76.6 (35.3) months; 26 (14%) of 190 patients had normal radiographs. Most children (87%) were treated with either amoxicillin or amoxicillin/clavulanate; 43% of prescribed antibiotics were considered as high-dose (ie, 80 mg/kg/day amoxicillin).

Of the 150 children with nasopharyngeal cultures, 73 (49%) had at least one pathogen recovered. *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* were isolated from 44 (29%), 23 (15%), and 22 (15%) children, respectively (Table I). Of the 44 isolates of *S. pneumoniae*, 8 (18%) exhibited intermediate resistance to penicillin and 2 (5%) were fully resistant to penicillin. In children carrying *S. pneumoniae*, 57% (25) were colonized with serotypes not included in either PCV7 or PCV13, 25% (11) were colonized with serotypes only in PCV13 (4 serotype 3, 3 serotype 6A, and 4 serotype 19A), and 11% (5) were colonized with PCV7-related serotypes (23A or B). Beta-lactamase production was present in 48% and 100% of the *H. influenzae* and *M. catarrhalis* isolates, respectively. Younger children were significantly more likely to be colonized with *S. pneumoniae* (40% of children < 6 years vs. 17% of children ≥ 6, $p=0.005$). Colonization with *H. influenzae* and *M. catarrhalis* did not differ significantly by age.

Nasopharyngeal specimens were not collected in 48 children (mostly because of parental refusal). Parents in the suburban clinics were significantly more likely to refuse the nasopharyngeal swab than parents in the inner-city urban clinics. As such, children with missing cultures (who are not included in the study) were more likely to be Caucasian; there were no differences in age or sex between children with and without nasopharyngeal cultures.

The 11 variables that were significantly ($p<0.15$; Table II) associated with time to symptom resolution (severity of symptoms at enrollment, age at entry, growth of *S. pneumoniae*, growth of *M. catarrhalis*, history of allergic rhinitis, history of asthma or wheezing, headache, face pain, measured temperature $> 38^{\circ}\text{C}$, transverse nasal crease, and tenderness of either frontal sinus to pressure) on univariate analysis were considered for inclusion into the multivariate model. We did not include tenderness to pressure over the frontal sinuses in our multivariate model as it was assessed only for a subgroup of children (children < 72 months of age), and thus was absent in more than half the children. Neither the type of antimicrobial agent, nor the dose used (high dose amoxicillin or amoxicillin/clavulanate vs. all others) was associated with time to resolution ($p=0.74$ and 0.62 , respectively), and thus are not included in the multivariable models. The only variable that remained independently associated with time to resolution after adjustment for baseline severity of symptoms was nasopharyngeal colonization with *S. pneumoniae* at baseline. Median time to symptom resolution in children with and without nasopharyngeal colonization with *S. pneumoniae* was 6.5 and 8.5 days, respectively ($p=0.002$; Figure).

DISCUSSION

In children with a clinical diagnosis of acute sinusitis who are being treated with antimicrobial therapy, those with proven nasopharyngeal colonization with *S. pneumoniae* resolved more rapidly than children who were not colonized with *S. pneumoniae*. A difference of 2 days in the time to resolution of symptoms is clinically meaningful. The association between nasopharyngeal colonization with *S. pneumoniae* and time to resolution of symptoms was robust; it remained significant after controlling for other potential confounding variables (ie, severity of symptoms at baseline and type and dosage of antimicrobial agent used). Because the nasopharynx is the reservoir from which pathogens enter the sinuses, it stands to reason that children with pathogens in their nasopharynx appear to benefit more from antimicrobial therapy. This hypothesis is consistent with randomized, placebo-controlled trials of adults with acute sinusitis or upper respiratory tract infection that have shown antimicrobial therapy to be more effective in the subset of patients with nasopharyngeal colonization with respiratory pathogens.^{3,5}

Colonization with pathogens other than *S. pneumoniae* did not independently predict response to therapy. The reasons for this remain unclear. Perhaps antimicrobial agents are less effective in children with *H. influenzae* and *M. catarrhalis* because these organisms are better able to produce biofilm.⁶ Or perhaps, the host's immune response to infection due to *S. pneumoniae* is different from that due to *H. influenzae* and *M. catarrhalis*.⁷ Future work regarding the nasal microbiome may shed some light on this question.

The overall rate of nasopharyngeal colonization with respiratory pathogens observed in this study (48%) was generally consistent with rates from the only previous study that reported nasopharyngeal colonization data in children with acute sinusitis since the introduction of PCV7.⁸ The proportion of penicillin-susceptible *S. pneumoniae* isolates (77%) was similar in both studies. In contrast, we found relatively lower rates of colonization with *H. influenzae* (15%), and lower rates of beta-lactamase producing *H. influenzae* (25%) than previously reported.⁸ These differences may be related to the different demographic and clinical characteristics of children enrolled in the two studies.

This study, conducted after introduction of PCV7, reports the distribution of serotypes of *S. pneumoniae* in the nasopharynx of children diagnosed with acute sinusitis. We found that the 57% of *S. pneumoniae* isolates were non-vaccine serotypes (serotypes not found in PCV-7 or PCV-13), a finding which is consistent with a previous study of nasopharyngeal colonization in children with acute otitis media conducted during the same time period in France.⁹ In contrast with the French study, however, we found lower rates of colonization with serotype 19A (24% vs. 9%). Selection for resistant serotypes, specifically serotype 19A, has been linked to high antibiotic pressure.¹⁰ Compared with the French study, children in our study were older, less likely to be in daycare, and less likely to have received antibiotics recently. Accordingly, the observed differences in the proportion of children carrying serotype 19A is likely due to differences in the demographic and clinical characteristics of the samples.

Based on our results, we recommend that future randomized trials comparing antimicrobial therapy with placebo in children with acute sinusitis consider testing for respiratory pathogens (either through nasopharyngeal culture or by polymerase chain reaction testing) at the time of randomization. In this way, the efficacy of antimicrobial testing in these subgroups could be compared. If substantial differences in efficacy are found, perhaps point-of-care tests for *S. pneumoniae*,^{11,12} could serve as a method of reducing prescription of antimicrobial testing.

This study has several limitations. First, we did not obtain nasopharyngeal samples on all children enrolled. Although performance of the nasopharyngeal culture was related to the child's race, it is unlikely that it would have biased our results (because race was not associated with either colonization with *S. pneumoniae* or with time to resolution of symptoms). Second, because this study was not placebo-controlled, our data cannot be used to make decisions about subgroups of children with acute sinusitis who should or should not be treated with antimicrobial therapy. Third, inclusion of children with atopic diatheses may bias results. However, we tried to ensure that episodes of respiratory disease did not represent merely allergic rhinitis or an exacerbation of asthma by enrolling most patients during the winter months, by excluding children with wheezing on examination, and by excluding patients presenting with nocturnal cough as their sole symptom. Furthermore, the presence of atopic disease was not significantly associated with time-to-resolution of symptoms in the multivariate model. Finally, based on data collected after introduction of the PCV7,¹³⁻¹⁷ we expect that with the introduction of the PCV13, the proportion of disease caused by *S. pneumoniae* will decrease, by eliminating disease caused by serotypes included in the vaccine at least temporarily. However, this reduction is likely to be modest because

slightly more than one-half of cases were colonized with non-PCV13 serotypes. Accordingly, colonization with *S. pneumoniae* will likely remain an important prognostic factor.

Acknowledgments

Supported by NIH/NCRR/CTSA (UL1 RR024153-University of Pittsburgh CTSI). N.S. was supported by NIAID (1R21AI076677).

We thank D. Kathleen Colborn, BS, for serving as the data manager., and Diana H. Kearney, RN, CCRC, for serving as the study coordinator (both at the University of Pittsburgh)

Abbreviations

PRSS Pediatric Rhinosinusitis Symptom Scale

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Figure 1.
Resolution of symptoms in children with acute sinusitis according to nasopharyngeal colonization with *S. pneumoniae* at baseline

Table 1

Selected demographic and clinical characteristics of 198 children with acute sinusitis

	<u>No. of children (%)</u>
Age at entry, months	
24–71	104 (52.5)
72–155	94 (47.5)
Mean (SD) ^a	76.6 (35.3)
Male	94 (47.5)
History of asthma or wheezing	73 (36.9)
History of allergic rhinitis	48 (24.2)
Duration of symptoms	
6 to 9 days	38 (19.2)
10 to 14 days	91 (46.0)
15 to 19 days	15 (7.6)
20 to 30 days	54 (27.3)
Mean (SD) ^a	14.7 (5.7)
Chief complaint	
Cough	113 (57.1)
Runny/stuffy nose	55 (27.8)
Other	30 (15.1)
Nasopharyngeal cultures	
No pathogens	77 (51.3)
Pathogen(s), at least one	73 (48.7)
Not collected	48 (24.2)
<i>S. pneumoniae</i> ^b	44 (29.3)
Penicillin susceptibility	
Susceptible (<0.1 µg/mL)	34 (22.7)
Intermediate (0.1–1 µg/mL)	8 (5.3)
Resistant (>1 µg/mL)	2 (1.3)
Serotypes present	
PC7 ^c serotypes	0 (0)
PC7-related ^d serotypes	5 (2.5)
PCV13 ^e serotypes	11 (5.6)
Non-PCV7 or -PCV13 serotypes	25 (12.6)
Nontypeable	3 (1.5)
<i>H. influenzae</i> ^b	23 (15.3)
Beta-lactamase producing	11 (7.3)
<i>M. catarrhalis</i> ^b	22 (14.8)
Beta-lactamase producing	22 (14.8)
Antibiotic used	
Amoxicillin	76 (38.4)

	<u>No. of children (%)</u>
Amoxicillin/Clavulanate	97 (49.0)
Cefdinir	18 (9.1)
Azithromycin	7 (3.5)

^a Mean and standard deviation (SD), not number of children, presented

^b Pathogen alone or in combination with other pathogen(s)

^d Vaccine-related serotypes include serotypes 9A, 19B, 23A, and 23B

Table 2Time to resolution of symptoms according to selected baseline characteristics^a

Characteristic	N	Median days to resolution	p
Age at entry, months			
24–71	104	7.5	.13
72–155	94	8.5	
History of asthma or wheezing			
Yes	73	8.5	.14
No	125	7.5	
History of allergic rhinitis			
Yes	48	8.5	.15
No	150	7.5	
Exposed to other children ^b			
Yes	164	8.5	.33
No	33	7.5	
Duration of symptoms			
6 to 9 days	38	8.5	.38
10 to 19 days	106	8.5	
20 to 30 days	54	7.5	
Type of presentation			
Persistent	161	8.5	.96
Worsening	37	8.5	
Radiograph findings			
Normal	26	8.5	.45
Mucosal thickening	97	8.5	
Complete opacification	67	7.5	
Severity of cough ^c			
Severity ≤50	96	7.5	.38
Severity >50	74	8.5	
Severity of congestion ^c			
Severity ≤50	81	8.5	.95
Severity >50	89	8.5	
Nasopharyngeal culture			
Growth of at least 1 pathogen	73	7.5	.03
No growth	77	8.5	
Growth of <i>S. pneumoniae</i>			
Yes	44	6.5	.02
No	106	8.5	
Growth of <i>H. influenzae</i>			
Yes	23	8.5	.46
No	127	8.5	
Growth of <i>M. catarrhalis</i>			

Characteristic	N	Median days to resolution	p
Yes	22	7.5	.09
No	127	8.5	
Compliance with antibiotic administration			
Yes (took 80% of doses)	171	7.5	.39
No	27	8.5	
Type of antimicrobial agent used			
Amoxicillin	76	7.5	
Amoxicillin/clavulanate	97	8.5	0.74
Other	25	8.8	
Dose of antibiotic used ^d			
High-dose amox or amox/clav (80 mg/kg/day)	80	8.5	0.62
Low dose amox or amox/clav or other antibiotic	105	8.5	
Fever in the past 48 hours			
Yes	52	8.5	
No	144	7.5	.77
Headache since the onset of illness			
Yes	95	8.5	.04
No	95	7.5	
Facial swelling since the onset of illness			
Yes	56	7.5	.76
No	142	8.5	
Face pain since the onset of illness			
Yes	41	<i>f</i>	.10
No	149	8.5	
Asymmetric face pain since the onset of illness ^e			
Yes	13	<i>f</i>	.90
No	20	<i>f</i>	
Measured temperature > 38° C			
Yes	8	<i>f</i>	.08
No	188	7.5	
Transverse nasal crease			
Yes	29	9.5	.12
No	169	7.5	
Facial swelling (either side)			
Yes	53	7.5	.86
No	145	8.5	
Either maxillary sinus tender to pressure			
Yes	49	9.5	.52
No	149	7.5	
Either frontal sinus tender to pressure ^e			
Yes	28	11.5	.03

Characteristic	N	Median days to resolution	p
No	66	8.5	
Either inferior turbinate swollen			
Yes	130	7.5	.32
No	68	8.5	
Pus in middle meatus			
Yes	44	7.5	.26
No	154	8.5	

^a Only variables felt to be important *a priori* or which were found to be significant are included in this table

^b Defined as exposure to 3 or more children for 10 or more hours per week at home, daycare or school

^c As assessed by the examining physician on a 100 point visual analog scale (0 = not severe, 100 = severe)

^d In 13 children, the dose was not recorded. Amox = amoxicillin, amox/clav = amoxicillin/clavulanate

^e Not all 198 children provided data for these findings

^f Median time to resolution could not be calculated because <50% of children had symptom resolution