Frequency of recovery of pathogens causing acute maxillary sinusitis in adults before and after introduction of vaccination of children with the 7-valent pneumococcal vaccine

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The objective of the study was to compare the proportions of the recovery of pathogens of acute maxillary sinusitis in adults in the 4-year period prior to the 5-year period that followed the introduction of vaccination of children with the 7-valent pneumococcal vaccine (PCV7). Cultures were obtained through endoscopy from 385 adults with acute maxillary sinusitis, 156 between 1997 and 2000, and 229 between 2001 and 2005. One hundred and seventeen potentially pathogenic organisms were isolated from the cultures obtained between 1997 and 2000. The predominant organisms were *Streptococcus pneumoniae* (54 or 46 % of all isolates), *Haemophilus influenzae* non-type b (42 or 36 %), *Moraxella catarrhalis* (7 or 6 %), *Streptococcus pyogenes* (8 or 7 %) and *Staphylococcus aureus* (6 or 5 %). One hundred and sixty-seven potentially pathogenic organisms were isolated from the cultures obtained between 2001 and 2005. The most predominant organisms were *H. influenzae* non-type b (71 or 43 % of all isolates), *Strep. pneumoniae* (58 or 35 %), *M. catarrhalis* (13 or 8 %), *Strep. pyogenes* (12 or 7 %) and *Staph. aureus* (13 or 8 %). Significant statistical differences were noted in the rates of recovery of *H. influenzae* non-type b ($P < 0.05$) and *Strep. pneumoniae* ($P < 0.05$). A decrease occurred in the recovery of *Strep. pneumoniae* resistant to penicillin from 41 to 29 %, and an increase was noted in the isolation of beta-lactamase-producing *H. influenzae* from 33 to 39 %; however, neither change was statistically significant. These data illustrate that a significant shift occurred in the causative pathogens of acute maxillary sinusitis in adults in the 5 years after the introduction of vaccination of children with the PCV7 compared to the previous 4 years.

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INTRODUCTION

The growing resistance to antimicrobial agents of all respiratory tract bacterial pathogens has made the management of bacterial sinusitis more difficult. Failure of antimicrobials to clear the infection can be due to persistence of the pathogen(s) because of inadequate pharmacokinetic and pharmacodynamic qualities of the antimicrobials, and the development of resistance to the antimicrobial used (Brook & Gober, 2004; Brook, 2005; Pichichero & Pichichero, 1995; Craig & Andes, 1996).

The Sinus and Allergy Partnership recently published guidelines for the diagnosis and optimal treatment of acute bacterial rhinosinusitis (Sinus and Allergy Health Partnership, 2004). They based their recommendations on predicted bacterial efficacy rates from mathematical modelling of

acute sinusitis based on pathogen distribution, resolution rates without treatment, and *in vitro* microbiological efficacy. Since the above recommendations are based on the frequency of recovery of the pathogenic organisms, awareness of the effect of the recent introduction of the *Streptococcus pneumoniae* conjugated vaccine (in April 2000) on the frequency of recovery of pathogens is of great practical use. A shift in the frequency of recovery of causative pathogens was recently demonstrated in children with acute otitis media (AOM) who were vaccinated with the 7-valent pneumococcal vaccine (PCV7) (Casey & Pichichero, 2004; Block *et al.*, 2004); however, no evaluation of the effect on the introduction of the vaccine on the recovery of respiratory pathogens was done in adults.

This study compared the proportion of recovery of pathogens of acute maxillary sinusitis in the 4 years before and the 5 years after the introduction of vaccination of children with the PCV7.

Abbreviations: AOM, acute otitis media; PCV7, 7-valent pneumococcal vaccine.

METHODS

Patients. The population studied was middle class, residing in suburban locations in the vicinity of Washington, DC. The patients were consecutively seen in the outpatient clinic between 1997 and 2005 and were diagnosed as suffering from acute bacterial maxillary sinusitis. They each had symptoms lasting between 10 and 30 days. None had had ear or sinus infection for at least 3 months before their initial visit, and they had not received antimicrobial therapy for at least 2 months.

Patients' complaints included facial pain, frontal headache, purulent nasal discharge, fever and malaise. Occipitontal (Waters' view), lateral, oblique and verticomental views or computed tomography were obtained. Sinusitis was defined radiographically as complete sinus opacity, an air-fluid level, or mucous-membrane thickening of at least 6 mm in the maxillary sinus. For the Waters' view, mucosal thickening of the maxillary sinuses was measured as the shortest distance from the air-mucosal interface to the most lateral part of the maxillary sinus wall. Specimens were obtained through endoscopy and the sinus secretions were collected with calcium-alginate-tipped micro-swabs. The study was granted an Institutional Review Board approval.

Microbiology. Cultures were obtained using endoscopic aspiration before therapy using calcium alginate swabs that were immediately plated into media supportive of the growth of aerobic bacteria. The method of specimen collection has been described previously (Brook *et al.*, 1996). The collectors of cultures and the microbiologist were blinded to the patients' therapy. Specimens were processed semi-quantitatively, and organisms were identified using standard methods (Murray *et al.*, 1995). All isolates of *Strep. pneumoniae* were screened for penicillin susceptibility with a 1 µg oxacillin disc by the Kirby-Bauer disc-diffusion method. Intermediate resistance to penicillin was defined as a MIC of 0.1–1.0 µg ml⁻¹ and high resistance to penicillin was defined as MIC ≥2.0 µg ml⁻¹.

MIC values of all antimicrobials were determined by the broth microdilution methodology following the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) with cation-adjusted Mueller–Hinton broth (Difco Laboratories) supplemented with 5% lysed horse blood for *Strep. pneumoniae* and *Streptococcus pyogenes*. MIC values of amoxycillin and amoxycillin/clavulanate were determined by using *Haemophilus* test medium for *Haemophilus* species and *Moraxella catarrhalis* (National Committee for Clinical Laboratory Standards, 1995). MIC values were interpreted according to the NCCLS M100-S10 MIC testing supplemental tables (National Committee for Clinical Laboratory Standards, 2000). Beta-lactamase production was determined by the chromogenic cephalosporin methodology, by using nitrocefin as the substrate (O'Callaghan *et al.*, 1972). Statistical significance was calculated by Fishers exact test (two-sided) unadjusted.

RESULTS

Three hundred and eighty five patients with acute maxillary sinusitis were studied, 156 in the 4 years between 1997 and 2000, and 229 in the 5 years between 2001 and 2005. Their ages ranged from 19 to 73 years; 218 were males. No differences were noted in the age distribution and gender of the patients in the two study periods.

One hundred and seventeen potentially pathogenic organisms were isolated from the cultures obtained between 1997 and 2000. Organisms were isolated in 89 patients (57%). A single isolate was recovered from 64 patients, two were found in 22, and three in three individuals. The predominant organisms were *Strep. pneumoniae* (54 or 46% of all isolates), *Haemophilus influenzae* non-type b (42 or 36%), *M. catarrhalis* (7 or 6%), *Streptococcus pyogenes* (8 or 7%) and *Staphylococcus aureus* (6 or 5%) (Table 1).

One hundred and sixty seven potentially pathogenic organisms were isolated from the cultures obtained between 2001 and 2005. Organisms were isolated in 134 patients (59%). A single isolate was recovered from 105 patients, two were found in 25, and three in four. The most predominant organisms were *H. influenzae* non-type b (71 or 43% of all isolates), *Strep. pneumoniae* (58 or 35%), *M. catarrhalis* (13 or 8%), *Strep. pyogenes* (12 or 7%), and *Staph. aureus* (13 or 8%). Significant statistical differences were noted in the rates of recovery of *H. influenzae* non-type b ($P<0.05$) and *Strep. pneumoniae* ($P<0.05$).

A decrease occurred in the recovery of *Strep. pneumoniae* resistant to penicillin (total number of penicillin-intermediate-susceptible and penicillin-resistant strains) from 41% between 1997 and 2000 to 29% between 2000 and 2005 (Table 2). An increase was noted in the isolation of beta-lactamase-producing *H. influenzae* from 33% between 1997 and 2000 to 39% (Table 3). However, neither of these changes was statistically significant.

DISCUSSION

These data illustrate that a statistically significant shift occurred in the causative pathogens of acute maxillary sinusitis in adults in the 5 years following the introduction

Table 1. Recovery of acute maxillary sinusitis pathogens in 156 patients between 1997 and 2000, and 229 patients between 2001 and 2005

Period (number of patients)	Number of isolates									
	<i>Strep. pneumoniae</i>		<i>H. influenzae</i>		<i>M. catarrhalis</i>		<i>Strep. pyogenes</i>		<i>Staph. aureus</i>	
	<i>n</i>	%*	<i>n</i>	%*	<i>n</i>	%*	<i>n</i>	%*	<i>n</i>	%*
1997–2000 (<i>n</i> =156)	54	46	42	36	7	6	8	7	6	5
2001–2005 (<i>n</i> =229)	58	35	71	42	13	8	12	7	13	8

*Percentage of total number of isolates.

Table 2. Susceptibility to penicillin of *Strep. pneumoniae* recovered in 156 patients with acute maxillary sinusitis between 1997 and 2000, and 229 patients between 2001 and 2005

Period (number of patients)	Penicillin susceptible		Penicillin intermediate susceptible		Penicillin non-susceptible		Total isolates
	<i>n</i>	%*	<i>n</i>	%*	<i>n</i>	%*	
1997–2000 (<i>n</i> = 156)	32	59	6	11	16	30	54
2001–2005 (<i>n</i> = 229)	41	71	7	12	10	17	58

*Percentage of all *Strep. pneumoniae*.

of vaccination of children with the PCV7 compared to the previous 4 years. While the proportion of *Strep. pneumoniae* declined by 11 %, the proportion of *H. influenzae* increased by 6 %. A small (not statistically significant) increase also took place in the isolation of other pathogens (*M. catarrhalis*, *Strep. pyogenes* and *Staph. aureus*), which accounted for 18 % of the isolates between 1997 and 2000, and increased to 23 % between 2001 and 2005. Although there was a 12 % decrease in the resistance of *Strep. pneumoniae* to penicillin and a 6 % increase in the recovery of beta-lactamase-producing *H. influenzae*, these changes were not statistically significant.

The significant changes in the recovery of sinusitis pathogens in adults as a result of the introduction of the *Strep. pneumoniae* conjugated vaccine to children younger than 2 years may be due to indirect or herd immunity in adults. Our findings are in concordance with previous studies in Israel that observed an overall reduction in colonization by vaccine-type *Strep. pneumoniae* in the community due to herd immunity (Dagan, 2004). The use of PCV7 was found to reduce nasopharyngeal acquisition of vaccine-specific serotypes of *Strep. pneumoniae*, which in turn reduced the incidence of pneumococcal disease among vaccinated as well as non-vaccinated individuals. Since most antibiotic resistance in *Strep. pneumoniae* is confined to vaccine-type serotypes, vaccine use also reduces antibiotic resistance (Givon-Lavi *et al.*, 2003; O'Brien & Dagan, 2003). Since we did not identify the serotypes of the *Strep. pneumoniae* isolates, we could not determine whether there was a change in the recovery of these serotypes after 2001.

A shift in the frequency of recovery of causative pathogens was recently demonstrated in children with AOM (Casey & Pichichero, 2004; Block *et al.*, 2004). Casey & Pichichero (2004) determined whether a change occurred in the frequency and distribution of the causative pathogens in persistent AOM after the introduction of the pneumococcal conjugate vaccine in 2000. In a 9-year period between 1995 to 2003 they evaluated 551 children with AOM who had not responded to or failed amoxicillin treatment. The rate of recovery of *Strep. pneumoniae* declined from 44 % prior to 2001 to 31 % after that time, while the isolation of *H. influenzae* increased from 43 to 57 %. Fewer *Strep. pneumoniae* isolates were penicillin resistant and more *H. influenzae* isolates became beta-lactamase producing.

Block *et al.* (2004) determined the changes in the microbiology of AOM before and after community-wide implementation of PCV7. They compared 336 AOM isolates from 1992 to 1998 with 83 AOM isolates from 2000 to 2003 in children who had received three or four doses of PCV7. The proportion of *Strep. pneumoniae* decreased from 48 to 31 % ($P=0.009$), and nontypable *H. influenzae* increased from 41 to 56 % ($P=0.01$); the increase in beta-lactamase-positive *H. influenzae*, 56 versus 64 %, was not significant. The proportions of intermediate penicillin non-susceptible pneumococci (PNSP) and resistant PNSP were 16 and 9 % versus 13 and 6 % pre- and post-PCV7, respectively. Post-PCV7, Gram-negative bacteria and beta-lactamase-producing organisms accounted for two-thirds and one-half of all AOM isolates, respectively.

Table 3. Beta-lactamase production by *H. influenzae* recovered in 156 patients with acute maxillary sinusitis between 1997 and 2000, and 229 patients between 2001 and 2005

Period (number of patients)	Beta-lactamase positive		Beta-lactamase negative		Total isolates
	<i>n</i>	%*	<i>n</i>	%*	
1997–2000 (<i>n</i> = 156)	14	33	28	67	42
2001–2005 (<i>n</i> = 229)	27	39	42	61	69

*Percentage of *H. influenzae*.

Further studies are needed to ascertain the continuous effects of PCV7 on the bacterial causes of acute sinusitis. It is important to carefully monitor the bacterial causes of sinusitis and whether replacement with potential virulent organisms and development of antibiotic resistance in non-vaccine-type pneumococci will occur over time.

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