Otolaryngology–Head and Neck Surgery (2008) 138, 274-278

LITERATURE REVIEW

Acute bacterial rhinosinusitis and otitis media: Changes in pathogenicity following widespread use of pneumococcal conjugate vaccine

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OBJECTIVE: Acute bacterial rhinosinusitis and acute otitis media are two of the most common respiratory tract infections. The common pathogenic bacteria associated with these infections are *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*, and *Staphylococcus aureus*. With the recent widespread use of pneumococcal conjugate vaccine, there is evidence that there is a shift of both the pneumococcal serotypes and the distribution of pathogenic bacteria. The purpose of this article was to investigate whether the literature supports changes in pathogenicity of acute bacterial rhinosinusitis and otitis media after widespread use of conjugate pneumococcal vaccine.

DATA SOURCES: MEDLINE search of the literature was performed between 1995 and 2007.

REVIEW METHODS: Literature review of changes in distribution of pathogens, resistance rates, and pneumococcal serotype changes before and after widespread use of conjugate pneumococcal vaccine.

RESULTS: There is evidence that the distribution of pneumococcal serotypes has changed after the widespread use of conjugate pneumococcal vaccine. There appears to be both less invasive and noninvasive pneumococcal disease and with childhood immunization there also appears to be a protective effect on adults (herd immunity). Increases in nonvaccine serotypes, some with high levels of resistance are being identified in some communities. There is also growing evidence that there may be an increasing prevalence of *Haemophilus influenzae* in these infections.

CONCLUSIONS: Widespread use of conjugate pneumococcal vaccine has led to decreasing incidence of pneumococcal otitis media and likely also acute bacterial rhinosinusitis, which may have implications for treatment recommendations for these infections.

Acute bacterial rhinosinusitis (ABRS) is a common upper respiratory infection with inflammation of the mucosa of the nose and paranasal sinuses.[1] Because viruses tend to cause most cases of rhinosinusitis, it has been recommended that ABRS be identified in patients who have worsening symptoms after 5 to 7 days following the onset of symptoms or persistent symptoms for 7 to 10 days.[2] Acute bacterial rhinosinusitis has been estimated to effect three in every 1000 people in the United States each year; some individuals have multiple episodes.[3] It also appears that the incidence of ABRS is increasing.[4,5]

Streptococcus pneumoniae (20% to 45%) and *Haemophilus influenzae* (22% to 35%) are the predominant organisms in acute bacterial rhinosinusitis in adults while *Streptococcus pneumoniae* (30% to 43%), *Haemophilus influenzae* (20% to 28%) and *Moraxella catarrhalis* (20% to 28%) are the predominant organisms as traditionally reported in acute bacterial rhinosinusitis in children.[5] Although *Staphylococcus aureus* has been identified as being cultured in many prospective clinical trials, it was often considered a contaminant. A recent meta-analysis suggests that *S aureus* is a real pathogen in approximately 10% of cases of ABRS.[6]

Acute otitis media (AOM) is also a very common respiratory tract infection that is more commonly reported in children than adults. Although ABRS can occur in both adults and children, it is more commonly reported in adults. In fact, AOM is one of the most common infections in children.[7] The pathogenicity of AOM is similar to ABRS with *S pneumoniae, H influenzae,* and *M catarrhalis* as the common organisms.[8]

One of the concerns with antibiotic therapy has been growing antibiotic resistance to commonly used respiratory antibiotics.[9] Rapidly increasing resistance rates were identified in the 1990s and an emergence of multidrug resistant strains has become a significant concern.[9] Forty percent of *S pneumoniae* isolates have been found to be resistant to two or more of the antibiotics tested and over 28% were resistant to three or more antibiotics.[9]

In 1990, conjugate *H influenzae* type b (Hib) vaccines were initiated as a routine part of childhood immunizations. This vaccine is nearly universally effective against the typable *H influenzae* strains that were responsible for a number of aggressive diseases such as meningitis and supraglottitis. Although nontypable strains of *H influenzae* are still major pathogens in ABRS, AOM, and lower respiratory

Received July 20, 2007; revised October 12, 2007; accepted November 14, 2007.

0194-5998/$34.00
doi:10.1016/j.otohns.2007.11.011

tract infections, Hib vaccinations have nearly eliminated the incidence of *H influenzae* meningitis in widely vaccinated populations.[10]

Unlike *H influenzae* where one subtype accounted for almost all of the invasive disease and where a single vaccine was effective in dramatically reducing these invasive diseases, over 90 serotypes of *S pneumoniae* have been isolated, many of which can cause disease in human beings.[10] A 23-valent pneumococcal polysaccharide vaccine has been available for many years although it is not effective in children younger than 2 years of age where invasive pneumococcal disease often occurs.[10] In the United States, seven serotypes are responsible for over 80% of the invasive disease caused by *S pneumoniae* in young children.[10] Heptavalent conjugate pneumococcal vaccine (PCNV7) was found to be 100% effective in preventing invasive pneumococcal disease[10] and was approved for use in children in February 2000.[11] Follow-up studies have supported this efficacy in the prevention of invasive pneumococcal disease[12-14] while the effect has been seen to have been extended to the adult community, or herd immunity.[13,15] In a population-based study that evaluated invasive pneumococcal disease in a continuously participating area for conjugate pneumococcal vaccines in children, the disease rates for invasive pneumococcal was noted to not only dramatically drop in children, but in adults as well.[12] The rates of disease decreased by 32% in adults 20 to 39 years of age, 8% for those 40 to 64 years of age, and 18% in those 65 years and older.[12] Another study in seven hospitals in a health system showed an even more dramatic reduction of invasive pneumococcal disease in adults, with a reduction of 68% to 70% in children, 42% in adults 18 to 49 years, and 30% in adults older than 64 years of age.[13]

The impact of routine vaccination on more common diseases such as ABRS and AOM is now becoming more clear. This article will depict the changes in pathogenicity of ABRS and AOM after the widespread use of conjugate pneumococcal vaccine and will describe how such changes may impact decisions with respect to treatment.

METHODS

A MEDLINE search of the literature was performed between 1995 and 2007. The search terms used were, "acute sinusitis, acute rhinosinusitis, acute otitis media, Prevnar, conjugate pneumococcal vaccine, pneumococcal vaccination." Articles that detailed changes in pathogenic organisms in ABRS or AOM, those that describe the effectiveness or impact of conjugate pneumococcal vaccines or those that propose changes in treatment after the widespread use of the vaccine were identified and reviewed and served as the source of this review. The references from articles used were also reviewed to identify significant additional information. Although a thorough search was undertaken, a formal systematic review was not performed and selective articles serve as the source of this review.

RESULTS

Pathogen Shift

One of the dramatic results of the widespread use of conjugate pneumococcal vaccine has been a significant shift in the pathogenic organisms found in both ABRS and AOM. In a study performed by Brook et al,[16] the proportions of the recovery of pathogens obtained by endoscopic directed cultures in adults with acute maxillary sinusitis were compared between the 4 years prior to and the 5 years after the introduction of the conjugate pneumococcal vaccine. *S pneumoniae* was found to decrease from the most common pathogen at 46% of isolates to 35% after the use of the vaccine; *H influenzae* increased from 36% to become the most common pathogen at 43%. There also was an increase in the cases caused by *M catarrhalis* and *S aureus*. In a similar study,[17] nasopharyngeal cultures were obtained in children with acute maxillary sinusitis before and after widespread use of conjugate pneumococcal vaccination. *S pneumoniae* decreased from 43% of isolates to 25%, whereas *H influenzae* increased from 35% to 41%, *M catarrhalis* remained stable (13% to 14%). *S pyogenes* increased from 7% to 12% and *S aureus* increased from 4% to 8%.

The data that show a pathogen shift are even more robust in AOM. Casey and Pichichero[18] looked at three intervals (1995-1997, 1998-2000, 2001-2003) during the transition to widespread conjugate pneumococcal vaccination and found sequential decreases in *S pneumoniae* cultured from middle ear aspirates (48%, 44%, and 31%) with a corresponding increase in *H influenzae* isolates (38%, 43%, and 57%).

Along with this shift in pathogens, there has been a change in the serotypes of *S pneumoniae* responsible for both AOM and ABRS with an increase in serotypes not found in the vaccine.[19-21] In one study,[20] the number of episodes of AOM that were attributable to serotypes contained in the vaccine has decreased by 51% whereas the number of episodes attributable to other serotypes has increased by 33%. Because the serotypes found in the vaccine are associated with more significant and invasive disease, it might be expected that the reduction in these serotypes might have an impact on disease severity in ABRS and AOM, although evidence to this potential benefit is lacking to date. There has, however, been some speculation that this serotype replacement may reduce the long-term efficacy of the 7-valent conjugate pneumococcal vaccine against AOM.[21]

One of the more significant concerns is that the replacement of invasive pneumococcal serotypes with those not covered in the vaccine may lead to reoccurrence of invasive disease from these newer serotypes. A recent review[22] of the impact of 7-valent pneumococcal vaccine in Alaskan children has shown that there has been a 96% decrease in the serotypes contained in the vaccine, but since 2004 there has been a 140% increase in the invasive pneumococcal disease by seroptypes not contained in the vaccine. Serotype 19A accounted for 28.3% of those invasive cases in children

younger than 2 years of age.[22] In another study,[23] nasopharyngeal carriage rates in children who undergo pressure equalization tubes has revealed the identification of nonvaccine serotypes that account for 50.7% of all strains isolated. Serotypes 19A and 35B account for 7% and 12%, respectively, of all pneumococcal isolates; 19A was found resistant to all oral agents tested and 35B was resistant to penicillin and cefuroxime.

Pneumococcal Resistance

Multiple studies have shown that there has been a reduction in both the nonsusceptible and high level resistant strains of *S pneumoniae* cultured in AOM and to a lesser extent in ABRS.[11,12,18,24,25] Whitney et al[12] showed that there was a reduction of 35% in strains nonsusceptible to penicillin. High level resistance of *S pneumoniae* to penicillin also appears to have dropped; reports[11] show it to have decreased from 15% to 5%. There has been an associated increase in the β-lactamase–producing strains of *H influenzae*.[18]

Effectiveness of Conjugate Pneumococcal Vaccine in ABRS and AOM

Most of the studies[8,11,18-20] that evaluated the effectiveness of the vaccine in ABRS and AOM were performed in children; a great majority assessed the impact on AOM. In a randomized double-blind efficacy trial that compared conjugate pneumococcal vaccine to hepatitis B vaccine as a placebo, the number of AOM events by any cause decreased by 6% whereas culture confirmed episodes of pneumococcal otitis media decreased by 34% and the number of episodes in the serotypes contained in the vaccine decreased by 57%.[20] It has been estimated that with universal use in the United States, 1.2 million of the 20 million cases of otitis media could be prevented.[20] Episodes of recurrent otitis media may be decreased by as much as 26%, and there is evidence that this may also reduce tympanostomy tube placement by 24%.[26,27]

The impact on the incidence of episodes of ABRS is more difficult to assess as acute sinusitis, particularly in children, can be caused by a number of pathogens and is often viral.[4,5] There has been a clear shift in the pathogens associated with both ABRS and AOM, and this shift is parallel between the two groups. This is not unexpected because the pathogenic organisms are similar for ABRS and AOM, and the shift in the microbiology of ABRS has been suggested to have occurred because of the involvement of the same pathogens in AOM and ABRS.[28] Even though there has not been strong evidence related to a decrease in the incidence of ABRS after widespread use of conjugate pneumococcal vaccination, the pathogen shift might have an important effect on the severity of disease. Benninger et al[29] have shown that ABRS patients infected with *S pneumoniae* have more significant symptoms and worse radiographic findings than those infected with *H influenzae*. Another interesting phenomenon has been the apparent increase in the culture rates of *S aureus*.[16] Although there has been some speculation that *S aureus* in ABRS might be a contaminant, a recent meta-analysis of randomized clinical trials of antibiotic therapy in ABRS strongly suggests that *S aureus* is a real pathogen and should be considered in the treatment of ABRS.[6] If there is an increase in culture rates for *S aureus* in ABRS in adults and children,[16] then this may have some impact on treatment decisions.

It is reasonable to expect that the incidence of ABRS will decrease in a similar fashion to what has occurred in AOM, because of the similar importance of *S pneumoniae* as a pathogen in both infections along with the relative decrease in frequency of ABRS attributable to *S pneumoniae* and increase of those attributable to *H influenzae*.[16,17] Of interest is that in one study[13] during a 4-year period where the impact of conjugate pneumococcal vaccine was investigated, there were significantly fewer episodes of influenza-like illnesses, which might suggest that part of the reduction in AOM may be related to milder respiratory seasons. There does appear to be a strong association between the development of ABRS with upper respiratory tract infections[5] and reduction in these episodes could theoretically reduce the incidence of ABRS.

Bacterial Interference

The increasing rate of isolation of *S aureus* in isolates of ABRS and AOM in the era of postpneumococcal vaccinations has raised the question of bacterial interference. Bacterial interference is a dynamic antagonistic interaction between at least two organisms that affects the life cycle of each. It has been suggested by Bogaert et al[30] that bacterial interference may be a contributing factor to the increase in the incidence of AOM caused by *S aureus* since the introduction of conjugate pneumococcal vaccine. They had evaluated nasopharyngeal carriage in a large group of healthy children and they found that there was a negative correlation between the colonization of the nasopharynx with serotypes of *S pneumoniae* found in the pneumococcal vaccine and the colonization with *S aureus*. No negative correlation was seen in the cultures where the serotypes of *S pneumoniae* were not found in the vaccine. In another study,[31] the rates of *S aureus* carriage were found to be much lower in carriers of *S pneumoniae* than in those who did not colonize with it. The opposite was also true.

The reduction of *S pneumoniae* after the widespread use of conjugate pneumococcal vaccine may play a role in the increasing incidence of ABRS and AOM caused by *S aureus*. Brook et al[16,17] have shown in two separate studies that the incidence of positive cultures for *S aureus* from both the maxillary sinuses in adults and the nasopharynxes of children with ABRS has increased from 5% and 4%, respectively, to 8%. The impact of these potential interactions is not as yet well understood, but the concept of bacterial interference is becoming more important and the impact of pneumococcal vaccination on the flora of the upper airway is not fully understood.

DISCUSSION

Conjugate pneumococcal vaccinations have led to a dramatic decrease in the rates of invasive pneumococcal disease in children and have resulted in an associated decrease in invasive diseases in adults. There is the potential, however, that the benefit that has occurred may reduce over time as the serotypes contained in the vaccine are replaced by other serotypes that may lead to invasive disease.[22] It may be reasonable to continue to consider adding additional serotypes to future vaccines.

The vaccine has played a significant role in a reduction in the overall incidence of AOM and a reduction in the incidence of *S pneumoniae* associated AOM and ABRS. With the reduction of *S pneumoniae,* there has appeared to be a shift to other pathogens, with the most significant increase in *H influenzae*. There has also been an apparent increase in both the colonization of the nasopharynx with *S aureus* as well as the incidence of *S aureus* in ABRS and AOM. The frequency of both *S pneumoniae* overall resistance and high level resistance have decreased in ABRS and AOM, and there may also have been a proportional increase in β-lactamase–producing *H influenzae*. All of these changes would seem to have significant implications on the recommendations for treatment for ABRS and AOM.

Recent guidelines for the treatment of ABRS have focused on growing antibiotic resistance.[5] With the increasing penicillin resistance and β-lactamase producing strains of *H influenzae* and *M catarrhalis*, consideration for the use of antibiotics that are effective against these resistant strains have grown. Multidrug resistance has also become more prevalent in resistant strains.[9] Because pneumococcal disease may result in more severe symptoms in both ABRS and AOM[29] and is also associated with significant morbidity in lower respiratory tract infections, many guidelines have prioritized the treatment of *S pneumoniae*.

Acute bacterial rhinosinusitis, although similar to AOM pathogenically, is more commonly diagnosed in adults. Although this is also self-limited in many occasions,[4] antibiotics are recommended for treatment.[5] With evidence to support the reduction in the incidence of *S pneumoniae* associated ABRS, and the increase of *H influenzae* associated ABRS, consideration needs to be made for the use of an antibiotic that is effective for both *S pneumoniae* and *H influenzae*, particularly in the face of increasing β-lactamase–producing organisms. Because amoxicillin is relatively ineffective against such strains and since the macrolides similarly may not have good coverage against these organisms,[5] consideration should be made for the use of an antibiotic that is effective against both *S pneumoniae* and *H influenzae*. These would include amoxicillin augmented with clavulonic acid or one of the newer generation cephalosporins.[25]

The emergence of *S aureus* as a recognized pathogen[6] and one which may be increasing[16] in upper respiratory tract infections may result in changes in consideration of therapy in the future. Although the prevalence of *S aureus* remains relatively small, it is important that this organism be watched closely. This is particularly true in the era of increasing rates of community-acquired methicillin-resistant *S aureus*.

CONCLUSION

The widespread use of conjugate pneumococcal vaccine has resulted in a significant reduction in invasive pneumococcal disease. It has also resulted in a reduction in the overall incidence of AOM and a change in pathogens in both ABRS and AOM, with a reduction in *S pneumoniae* and an increase in *H influenzae*. Resistant strains of *S pneumoniae* appear to be decreasing, whereas there may be an increase in β-lactamase–producing *H influenzae*. Nonvaccine pneumococcal serotypes appear to be increasing both in nasopharyngeal cultures and in some cases have been associated with invasive disease. Antibiotic resistance rates for selected serotypes such as 19A may be high. These changes in patterns of pathogenicity may require a reconsideration of antibiotic therapy to assure coverage for nonvaccine pneumococcal serotypes and for *H influenzae*. Future vaccine development will likely require consideration of the emergence of serotypes currently not included in the 7-valent vaccine.

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FINANCIAL DISCLOSURES

Michael S. Benninger is a consultant to Bayer, Abbott, Ortho-McNeill, and Sanofi-Aventis; speaker for Abbott. He received funding from Abbott to partially offset the cost of this review. They did not participate in any aspect of the writing of this article.

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