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Putting the Brakes on Multi-Drug Resistant Pneumococci in Pediatrics

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The rising incidence of multi-drug resistant strains of *Streptococcus pneumoniae* throughout the world provokes concerns about the continued availability of effective antimicrobial agents. Because resistance has been linked to prior use of antimicrobial agents in the patient and extensive use of these drugs in the community, the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) have issued guidelines for judicious use of antimicrobial agents (1). How extensive is the problem and how effective are the public health initiatives in reducing the volume of prescriptions for antimicrobial agents in pediatric patients? Is the pneumococcal conjugate vaccine likely to reduce the incidence of invasive disease sufficiently to reduce the amount of antimicrobials prescribed for febrile children? If these efforts succeed in reducing the quantity of antimicrobial agents used in infants and children, will the incidence of multi-drug resistant pneumococci diminish? These questions are the subject matter for this brief review.

THE PROBLEM

Development of bacterial resistance to antimicrobial agents has been a constant feature of drug therapy since the introduction of the sulfonamides in the mid-1930s. Each decade has identified a problem with one or more resistant pathogens: the pandemic of penicillinase-producing *Staphylococcus aureus* in the 1950s and 1960s; the emergence of multi-drug resistant gram-negative enteric bacteria in the 1960s and 1970s; the identification of beta-lactamase producing *Haemophilus influenzae* and *Moraxella catarrhalis* in the

1980s; and since the 1990s concern for multi-drug resistant pneumococci. The prevalence of multi-drug resistant pneumococcal strains has been increasing in the United States since the mid-1980s; the incidence of non-susceptible strains of pneumococci is now in excess of 25% in most regions of the country. For unknown reasons, the highest incidence of multi-drug resistant strains is in the Southwestern states; in Dallas the incidence of penicillin non-susceptible strains is approximately 60%, and half of these strains are fully resistant (personal communication, George H. McCracken, Jr.).

Factors that enhance risk for colonization and infection with resistant pneumococci include prior exposure to antimicrobial agents, age less than 2 years, day care attendance and hospitalization. Isolates from mucosal surfaces, such as the nasopharynx or throat, yield higher rates of resistance than do invasive isolates from usually sterile body fluids such as blood and CSF. No clinical features distinguish infection with resistant versus susceptible strains of *S. pneumoniae* and there is no correlation between virulence and antimicrobial susceptibility or lack thereof.

EDUCATION OF PROVIDERS AND CONSUMERS

Because of the association between multi-drug resistance and quantity of antimicrobial usage in the individual and the community, authoritative groups have developed educational programs for health care workers. The CDC and the AAP guidelines "Judicious Use of Antimicrobial Agents" emphasize the need to distinguish

appropriate and inappropriate usage of antimicrobial agents in infants and children (1). Since otitis media is the single most frequent diagnosis that leads to prescribing of antibiotics in infants and children, educational efforts have focused on increasing the accuracy of diagnosis by pneumatic otoscopy and ancillary techniques, such as tympanometry (many console and portable models available) and acoustic reflectometry (Ear Check, MDI Instruments Chester, NJ). In addition, educational efforts directed at parents have made them aware of the potential that antimicrobial agents have for fostering bacterial resistance.

Antimicrobial Use for Pediatric Patients is Down - A Lot!

The results of surveys regarding the amount of antimicrobial use in children living in different regions of the United States and using different data bases indicate a substantial decrease over the past 10 years. In northern Wisconsin, a community program to promote judicious antibiotic use resulted in a decline of 19% in prescriptions per clinician in the intervention region and 8% in the control region (2). In Knox County, Kentucky, antimicrobial prescription rates for children declined 19% after a community-wide campaign; a decline of 8% was identified in the control group (3). In rural Alaska, antibiotic courses per person decreased by 31% after a controlled intervention trial (4).

McCaig and colleagues compared rates of antimicrobial prescribing for children by office-based physicians

during two 2-year periods, 1989-1990 and 1999-2000, using data from the National Ambulatory Medical Care Survey (5). The average population-based annual rate of overall antimicrobial prescriptions per 1000 children and adolescents younger than 15 years decreased from 838 in 1989-1990 to 503 in 1999 – 2000, or a 40% decrease. Data on visit-based rates are presented in **Table 1**, and indicate an overall decrease of 29%. This decrease did not occur in the heavy volume use of antimicrobial agents for otitis media or sinusitis, but did occur when the diagnosis was upper respiratory tract infection (URI). The results of a survey of antibiotic usage in children who received care from organizations in the HMO Research Network provide corroboration of the National Ambulatory Medical Care Survey (6). Antibiotic prescriptions decreased in the 5-year period 1995 to 2000 in each pediatric age category (**Table 2**).

Although the reasons for this extraordinary decrease in the number of prescriptions for children are uncertain, some comments should be noted. First, the decrease occurred before the introduction of the pneumococcal conjugate vaccine. Second, the intervention programs were effective but a decrease in prescriptions also occurred in the control groups. Finally, data are not yet available to indicate an effect, if indeed there will be one, of reduced antimicrobial use in pediatric patients on lowering the incidence of multi-drug resistant pneumococci.

TABLE 1
Trends in Antimicrobial Prescribing Rates for Children and Adolescents (5)

Outcome	1989-1990	1999-2000	% Change
Visit-based rate*	330	234	29
Otitis media [†]	809	802	1
Sinusitis [†]	819	766	6
Pharyngitis [†]	785	686	11
URI [†]	359	221	38

*Prescriptions per 1000 office visits.

[†] Prescriptions per 1000 office visits for a specific diagnosis.

TABLE 2
Decreasing Antibiotic Use in Children, 1995-2000 (6)

Age	1995	2000	%Reduction
3 months – 3 years	2.23*	1.73	22.5%
3 years – 7 years	1.29	0.96	25.6%
7 years – 18 years	0.78	0.65	16.5%

*Antibiotics / Person year

Role of Pneumococcal Conjugate Vaccine (PCV) in Multi-Drug Resistant *S. pneumoniae*

The results of clinical trials in Northern California and Finland evaluating the efficacy of the 7-valent pneumococcal conjugate vaccine (Prevnar, Wyeth-Lederle Vaccines) provide a profile of the efficacy of this vaccine for the various pneumococcal infections in infants and young children (Table 3) (7-10). This efficacy includes an 89% decrease in invasive disease (bacteremia, meningitis and bacteremic pneumonia), a 7% decrease in episodes of acute otitis media (AOM), and a 4.3% decrease in children under 5 years of age with a clinical diagnosis of pneumonia, but this increases to 20.5% if a radiological examination was performed and indicated consolidation, pleural empyema or parenchymal infiltrate (7-10).

These data reflect only a portion of the importance of the pneumococcal conjugate vaccine. In Northern California, there was a 24% reduction in surgical procedures for placement of tympanostomy tubes for chronic otitis media and an overall reduction in antibiotic prescriptions of 5.7% (9). Epidemiologic data suggest that on average young children have about one episode of AOM per year; if we assume that each child with an episode of AOM in each of the first two years of life receives an antibiotic prescription and there are approximately 3.8 million children in each annual birth cohort for the first two years of life, then the vaccine would be responsible for an annual reduction of more than 400,000 prescriptions in this infant age group. These reductions in antimicrobial usage in infants would be superimposed on the decrease already reflected in the surveys carried out prior to the introduction of the pneumococcal conjugate vaccine in 2000.

A potential "herd effect" from pneumococcal conjugate vaccine (PCV) was noted by Shinefield and colleagues in the Northern California Kaiser Permanente

Vaccine program (11). Comparing the rate of invasive pneumococcal disease in older children and adults before (April 1995 to March 2000) and after (April 2000 to March 2002) introduction of PCV, these investigators noted the following decrease in pneumococcal disease rates: 5 to 19 years = 18%; 20 to 39 years = 58%; 40 to 59 years = 15%; >60 years = 14%. Because there are annual fluctuations in the incidence of pneumococcal disease, these data must be viewed with caution and require corroboration over time. Nevertheless, the results suggest that the use of PCV in infants may have a substantial impact on invasive pneumococcal disease in older children and adults who have not received the vaccine.

Some restraints on the enthusiasm about the efficacy of PCV should be noted. First, about 20% of invasive pneumococcal disease is due to serotypes not included in the vaccine; invasive pneumococcal disease will continue to be a concern albeit at a much lower incidence. Second, serotype replacement is suggested by nasopharyngeal carriage studies that indicate a decrease in colonization due to vaccine serotypes and a replacement by non-vaccine serotypes, with the net result that the rates of pneumococcal carriage are unchanged. Third, concern for serotype replacement is heightened by the results of the microbiologic studies of ear aspirates of children with AOM in Finland; children who received PCV had an increase of AOM to non-vaccine serotypes (10). These results are parallel to the data indicating a decrease in pneumococcal carriage of vaccine serotypes. Fourth, the decrease in episodes of otitis media and pneumonia are relatively modest when contrasted with the substantial decrease in invasive disease. Fifth, the unanticipated shortage of PCV in most communities throughout the United States indicates the fragility of manufacture of this product. None of these concerns, however, should dampen enthusiasm for the introduction of this extraordinarily important vaccine for infants and children.

TABLE 3
Efficacy of 7-Valent Pneumococcal Vaccine in Infants

Endpoint	Vaccine Efficacy (Percent Decrease in Incidence)	Reference Number
Any acute otitis media	7	9,10
Placement of ventilating tubes	24	9
Antibiotic prescriptions	5.7	9
Clinical pneumonia to 5 years of age	4.3	8
plus consolidation, pleural empyema, or parenchymal infiltrate	20.5	8
All invasive pneumococcal disease	89	7

The Future

There are a number of issues relevant to multi-drug resistant pneumococci that will be answered only with the passage of time:

1. **The plasticity of the pneumococcus.** Changes in prevalent capsular polysaccharide type and virulence occur over time without apparent explanation. As early as the 1930s, investigators produced transformation of pneumococcal type *in vitro*. We may expect that pneumococcal serotypes not in the current vaccine may emerge with increased virulence requiring modification of the components in the PCV.

2. **The durability of the decreased antimicrobial usage in infants and children.** Without insight into the reasons for the marked decrease in the volume of antibiotics prescribed for children, one needs to be cautious about the sustained effect. We may assume that physicians are now more aware of appropriate use of antimicrobial agents. The role of parents in refusing or discouraging antibiotic prescribing for their children with uncertain diagnoses may be important in this observed phenomenon.

3. **Further decrease in amount of antimicrobial agents used in children.** The National Ambulatory Medical Survey identified the major decrease in antibiotic usage was for URI's. Nevertheless, 22% of patients with this diagnosis received an antimicrobial agent. Thus, further reduction in antimicrobial usage may be achieved by limiting or eliminating the usage of antibiotics for URI's. In addition, physicians may heed the advice of some experts who recommend initial observation for children with AOM; observation should be limited to those children who are older than 2 years of age, who have no or only low grade fever, who do not have severe inflammation of the tympanic membrane or who have uncertain diagnoses of AOM.

4. **New vaccines.** Possible changes in serotypes responsible for invasive disease as well as regional differences in invasive serotypes will likely lead to introduction of 9-, 11- or 13-valent PCV in the near future. Investigators will continue to seek a pneumococcal vaccine based on a common antigen so that ultimately a vaccine with coverage for all serotypes can be introduced. A common antigen vaccine also could be less expensive than the current vaccine which necessitates manufacture of 7 separate formulations. A less expensive vaccine might allow for its use in children living in areas with limited resources.

5. **Impact of changing antibiotic usage patterns on multi-drug resistant pneumococci.** Although the decrease in antimicrobial agent usage for children in the United States appears to be a real phenomenon, *no change in the incidence of multi-drug resistance* has yet been documented.

References

1. Dowell SF, Marcy SM, Phillips WR et al. Principles of judicious use of antimicrobial agents for pediatric upper respiratory infections. *Pediatrics* 1998; 101 (Suppl): 163-165.
2. Belongia EA, Sullivan BJ, Chyou P-H et al. A community intervention trial to promote judicious antibiotic use and reduce penicillin-resistant *Streptococcus pneumoniae* carriage in children. *Pediatrics* 2001; 108:575-583.
3. Perz JF, Craig AS, Coffey CS et al. Changes in antibiotic prescribing for children after a community-wide campaign. *JAMA* 2002; 287:3103-3109.
4. Hennessy TW, Petersen KM, Bruden D et al. Changes in antibiotic-prescribing practices and carriage of penicillin-resistant *Streptococcus pneumoniae*: a controlled intervention trial in rural Alaska. *Clin Infect Dis* 2002; 34:1543-50.
5. McCaig LF, Besser RE, and Hughes JM. Trends in antimicrobial prescribing rates for children and adolescents. *JAMA* 2002; 287: 3096-3102.
6. Finkelstein J, Stille C, Nordin J et al. Decreasing antibiotic use in US children: 1995-2000. *Pediatric Res* 2002; 51:213A.
7. Black S, Shinefield H, Fireman B et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J* 2000; 19:187-195.
8. Black SB, Shinefield HR, Ling S et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *Pediatr Infect Dis J* 2002; 21:810-815.
9. Fireman B, Black SB, Shinefield HR et al. Impact of the pneumococcal conjugate vaccine on otitis media. *Pediatr Infect Dis J* 2003; 22:1-7.
10. Eskola J, Kilpi T, Palmu A et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001; 344:403-409.
11. Shinefield HR. Effect of universal administration of pneumococcal vaccine in infancy on IPD in the community. Presented at a symposium on Pneumococcal Diseases in the Era of Pneumococcal Conjugate Vaccine. Boston, MA October 21, 2002.

Target Audience: General practitioners, family physicians, pediatricians, pediatric infectious diseases specialists, nurse practitioners, physician assistants, microbiologists, and others with an interest in antimicrobial resistance and antimicrobial usage.

Learning Objectives After reading this publication, the reader should be able to:

- Characterize the epidemiology of pneumococcal antibiotic resistance and enumerate risk factors for acquisition of antibiotic resistant pneumococci in the pediatric population.
- List and describe the results of at least two (2) studies which characterize temporal trends in antibiotic usage in the pediatric population.
- Discuss the impact and potential consequences of the widespread usage of pneumococcal conjugate vaccine.

CME Self Assessment Examination

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See instructions and pertinent information on the reverse before requesting credit.

1. Each of the following enhance risk for colonization and infection with resistant *Streptococcus pneumoniae* except:

- a) Prior exposure to antimicrobial agents
- b) Age less than 2 years
- c) Nutritional deficiency
- d) Day care attendance
- e) Hospitalization

Answer: _____

2. Which of the following statements about *S. pneumoniae* is true:

- a) Isolates from mucosal surfaces are more likely to yield resistant isolates than those from sterile body sites
- b) No clinical features distinguish infection with susceptible strains from those with resistant strains
- c) Upper respiratory infections are the single most frequent diagnosis leading to prescriptions for antibiotics in infants and children
- d) There is a strong correlation between virulence and antimicrobial susceptibility
- e) a, b, and c are true

Answer: _____

For questions 3-4, circle T if the statement is True and F if the statement is False:

- 3. In the past 10 years there has been a substantial decrease in the prescription rate for antibiotics in children T F
- 4. The decrease in the rate of antibiotic usage occurred only after the licensure of the 7-valent pneumococcal vaccine T F

5. Which of the following statements about the 7-valent pneumococcal conjugate vaccine are true:

- a) The vaccine has been associated with an 89% decrease in invasive disease among recipients
- b) The vaccine "covers" about 80% of the resistant serotypes of *S. pneumoniae*
- c) At least one study suggests a "herd effect" among older children and adults after the introduction of pneumococcal conjugate vaccine.
- d) Only a and c are true
- e) a, b, and c are true

Answer: _____

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