Patterns of Antibiotic-Resistant *Streptococcus pneumoniae* in Children in a Day-care Setting

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BACKGROUND. *Streptococcus pneumoniae* is one of the primary causes of illness and death among young children, and evidence suggests that the prevalence of antibiotic-resistant *S pneumoniae* is increasing. The purpose of this study was to investigate the prevalence of antibiotic-resistant *S pneumoniae* in a sample of children in day-care facilities in a region that includes both rural and urban communities.

METHODS. Nasopharyngeal cultures were obtained from 104 children in eight day-care centers located in rural and urban central Kentucky in April and May, 1997. Thirty-five of the children produced isolates positive for *S pneumoniae*. Each isolate was tested for susceptibility to penicillin, trimethoprim-sulfamethoxazole, erythromycin, tetracycline, vancomycin, and cefotaxime.

RESULTS. Of the children with *S pneumoniae* isolates, 54% had isolates that were resistant to penicillin and 40% that were resistant to trimethoprim-sulfamethoxazole. Twenty-one (60%) of the isolates had resistance to at least one of the six tested antimicrobials, with 15 (43%) having resistance to more than one of the antimicrobials. The mean age of children with isolates resistant to penicillin was significantly less (2.7+1.6) than those with penicillin-susceptible isolates (3.7 + 1.1, $P = .02$). There was no relation between resistance and rural or urban day-care location.

CONCLUSIONS. A substantial proportion of *S pneumoniae* isolates in young children are resistant to antibiotics. Limiting the effect of *S pneumoniae* drug resistance may require a reexamination of outpatient treatment strategies for childhood respiratory tract infections.

KEY WORDS. *Streptococcus pneumoniae*; antibiotic resistance; child day-care centers; respiratory tract infections. *(J Fam Pract 1998; 46:142-146.)*

Streptococcus pneumoniae is one of the primary causes of illness and death among young children.[1] It is the most common cause of acute otitis media,[2] as well as bacteremia in childhood.[3] In one recent series, pneumococcal bacteremia and subsequent focal infections were 11 times more common than *Salmonella*, 15 times more common than *Haemophilus influenzae*, and 51 times more common than *Neisseria meningiditis* and *Streptococcus pyogenes* infections in children.[3]

Recently, an increasing percentage of *S pneumoniae* isolated in the United States have exhibited resistance to penicillin and other drugs.[4,5] Approximately 20% of pneumococci in some areas of the United States have been shown to express relative or high-level penicillin resistance.[6,7] Although there is some doubt that penicillin resistance will be a serious health threat to healthy individuals,[8] penicillin-resistant pneumococcus has become a worrisome pathogen in patients with serious health problems who have been hospitalized recently and treated with antibiotics.[9] In other areas of the world, penicillin resistance is even more common, prompting public health officials to focus on the emergence of this strain in the United States and examine strategies to deal with this new pathogen.[10]

Young children often harbor *S pneumoniae* in the upper respiratory tract. Nasopharyngeal swab specimens efficiently yield pneumococci. In several studies antibiotic-resistant *S pneumoniae* has been

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found in the general pediatric community at relatively high rates. Penicillin-resistant *S pneumoniae* was discovered in more than 50% of the children with nasopharyngeal carriage of pneumococcus at a child day-care center in rural western Kentucky.[11] Similarly, 53% of the children who were colonized by *S pneumoniae* at a child day-care center in Omaha, Nebraska, produced isolates that were highly resistant to penicillin.[12] Among children with *S pneumoniae* isolates in Memphis, Tennessee, 59% showed resistance to at least one class of antimicrobial agents, with 40% resistant to penicillin.[13]

Although these studies have identified high rates of antibiotic-resistant *S pneumoniae*, their research designs tend to focus on one day-care center or several day-care centers in one city, thereby providing a limited understanding of the prevalence of antibiotic-resistant *S pneumoniae*. The regionwide reservoir of antibiotic-resistant *S pneumoniae* and the differences in rural or urban residence have not previously been investigated. The purpose of this study was to investigate the prevalence of antibiotic-resistant *S pneumoniae* in a sample of children in day-care facilities in a region that includes both rural and urban communities.

METHODS

Study participants consisted of 104 children attending eight day-care centers in central Kentucky. The day-care centers were identified through the published listing of licensed day-care centers maintained by a state agency. The centers were located in the metropolitan statistical area counties of Fayette and Madison and the nonmetropolitan counties of Franklin and Rowan. Using Fayette County as the center of the region, none of the day-care centers was farther than 60 miles from Fayette County. The study was approved by the Medical Institutional Review Board at the University of Kentucky.

Children aged 2 to 72 months were eligible for participation. Day-care centers and parents were recruited through the following procedure: The day-care center director was contacted by telephone, informed of the study, and asked to participate. If interested, the director was sent information on the study including a sample informed consent sheet. Two weeks later, the day-care center director was contacted to confirm participation and asked to distribute consent sheets to their parents. Approximately 2 weeks later, cultures were obtained from children whose parents had signed informed consent sheets. Data were collected in April and May of 1997.

The nasopharyngeal cultures were obtained by introducing a sterile calcium alginate-tipped swab into the posterior nasopharynx. A public health nurse from the state department of public health obtained all nasopharyngeal samples. Following collection of the nasopharyngeal secretions, the material was inoculated directly onto sheep blood agar plates and incubated at 37°C for 24 to 48 hours under 5% CO_2. Isolates were identified as *S pneumoniae* on the basis of morphology, alpha-hemolysis, bile solubility, and susceptibility to ethylhydrocupreine. The potential for carriage of multiple populations of pneumococci, which may have different resistant patterns, was addressed by separately isolating and analyzing colonies that appeared on culture plates with different morphologies or hemolysis patterns.

Antimicrobial susceptibility testing was done using the E test (AB Biodisk North America, Inc, Culver City, Calif) according to manufacturer's instructions. This test correlates well with microtiter broth dilution minimal inhibitory concentrations and has the advantage of providing data on a continuous scale rather than the 2-fold dilution format of microtiter assays.[14,15] The susceptibility of each isolate to penicillin, trimethoprim-sulfamethoxazole, erythromycin, tetracycline, vancomycin, and cefotaxime was tested. Breakpoints for susceptible, intermediate resistance, and high resistance were those recommended by the National Committee on Clinical Laboratory Standards.[16] Each day, *S pneumoniae* ATCC 4619 was run concurrently with study isolates as a control.

Each child provided data on standard demographics (age, sex, and race, with race determined by the race of the child's mother). The child was also categorized according to whether he or she was currently a Medicaid recipient. Recent use of antibiotics was defined as use within 2 weeks prior to the culture.

The analysis consisted of descriptive and bivariate (chi-square, *t* test) statistics. It was felt that estimates from a multivariate analysis would suffer from a lack of stability because of limited sample size and therefore were not computed.

RESULTS

Cultures from 35 of the 105 children who participated in the study yielded pneumococci. The characteristics of the total sample and the children with positive isolates are shown in Table 1.

Table 2 shows that more than half of the pneumococcal isolates were resistant to penicillin and that 40% were resistant to trimethoprim-sulfamethoxazole. No resistance was found for vancomycin. Twenty-one (60%) isolates had resistance to at least one of the tested antimicrobials, with 15 (43%) having resistance to more than one of the antimicrobials.

In relation to patient characteristics, bivariate analyses suggested no difference in penicillin resistance between isolates collected in metropolitan and nonmetropolitan areas within the region (Table 3). An analysis of patient characteristics with resistance to any of the antimicrobials yielded similar results with no significant differences among all of the patient characteristics, except age. The mean age of children with isolates resistant to penicillin was significantly less (2.7 ± 1.6) than those with penicillin-susceptible isolates (3.7 ± 1.1, $P = .02$). Similarly, the mean age of children with isolates resistant to any of the tested antimicrobials was significantly less (2.7 ± 1.5) than those with isolates susceptible to all of the antimicrobials (3.9 ± 1.1, $P = .01$).

TABLE 1

Characteristics of Day-care Children Participating in Study of Antibiotic-Resistant Pneumococcus

	Pneumococcal-negative Children* No. (%) (n=69)	Pneumococcal-positive Children* No. (%) (n=35)	*P* Value
Mean age (y±SD)	3.42 ± 1.51	3.16 ± 1.48	.40
Gender			.68
Male	36 (52)	20 (57)	
Female	33 (48)	15 (43)	
Race			.22
White	55 (80)	31 (89)	
Black	12 (17)	3 (9)	
Other	2 (3)	1 (3)	
MSA residence			.83
Yes	46 (67)	22 (63)	
No	23 (33)	13 (37)	
Medicaid recipient			.92
Yes	23 (33)	12 (34)	
No	46 (67)	23 (66)	
Taken antibiotics in past 2 weeks			.50
Yes	19 (28)	12 (34)	
No	50 (72)	23 (66)	

*Determined by nasopharyngeal cultures.
MSA denotes metropolitan statistical area; SD, standard deviation.

DISCUSSION

The results of this study add further support to the growing body of evidence showing substantial rates of drug-resistant pneumococci among young children.[11-13] These results expand on the previous work to indicate that a high prevalence of drug-resistant pneumococcus (eg, 54% resistant to penicillin) is not isolated to one day-care center, or even one city. Across multiple day-care centers in a region that includes both rural and urban areas, high rates of penicillin-resistant and multidrug-resistant pneumococcus was found. Importantly, there was no significant difference in the likelihood of resistance between isolates gathered in rural or urban areas in the region.

Streptococcus pneumoniae is a leading cause of morbidity and mortality, and emergence of drug-resistance will make these infections caused by these organisms more difficult to treat.[17] Increased use of more expensive antimicrobials and lengthened hospital stays have been estimated to increase the cost of treating *S pneumoniae* infections from between $100 million and $30 billion per year.[18]

The Centers for Disease Control and Prevention (CDC) recently convened a working group to define the public health impact of drug-resistant *S pneumoniae*.[10] Evidence suggests that antibiotics are widely used for many respiratory tract infections of probable viral origin.[19,20] Recent data from Iceland suggests that community-wide consumption of antimicrobials is positively related to the nasopharyngeal carriage of penicillin-resistant pneumococci.[21] One of the CDC's recommendations was to promote the judicious use of antimicrobials, particularly for outpatient respiratory tract infections.

In our study at least 40% of the pneumococcal isolates were resistant to penicillin or trimethoprim-sulfamethoxazole. These inexpensive and previously

TABLE 2

Proportions of Pneumococcal Isolates Resistant to Specific Antimicrobial Drugs (n=35)

Drug	Level of Resistance	MIC* No. (%)	No. (%) Resistant	Total No. (%) Resistant
Penicillin	Intermediate	0.12-1.2	14 (40.0)	
	High	≥2	5 (14.3)	19 (54.3)
Cefotaxime	Intermediate	1	2 (5.7)	
	High	≥2	3 (8.6)	5 (14.3)
Erythromycin	Intermediate	8-16	7 (20.0)	
	High	>16	2 (5.7)	9 (25.7)
Tetracycline	Intermediate	4	0 (0.0)	
	High	≥8	3 (8.6)	3 (8.6)
Trimethoprim-sulfamethoxazole	Intermediate	1-2	7 (20.0)	14 (40.0)
	High	≥4	7 (20.0)	14 (40.0)
Vancomycin	None†			

MIC denotes minimal inhibitory concentration.
*National Committee for Clinical Laboratory Standards breakpoints.
†No isolates were resistant to vancomycin.

efficacious agents thus cannot always be relied upon for cure. Unfortunately, few alternatives exist. Tetracycline cannot be used in young children because of problems with accumulation in growing bone and tooth enamel.[22] Third-generation cefalosporins such as cefotaxime are expensive, painful to give intraveneously, and should be reserved for serious infections such as meningitis. This leaves the macrolides and older agents such as cholramphenicol. Undoubtedly overuse of these agents will also lead to the emergence of resistance.

Our results demonstrated that younger children were more likely to be colonized with pencillin-resistant pneumococci, a finding that has been previously demonstrated.[23] With the rise in antibiotic-resistant *S pneumoniae*, a pneumococcal vaccine for young children may be a particularly important public health measure for managing pneumococcal disease through prevention.[10] Although a pneumococcal conjugate vaccine is in development and would be applicable for young children, it is not currently available. The CDC states this conundrum quite clearly: "An effective pneumococcal protein-conjugate vaccine prescribed at least for all children <2 years of age would be the most effective means of preventing pneumococcal illness in children; however, conjugate vaccines are still being developed and evaluated."[10]

Antibiotic resistance rates in day-care centers rather than hospital laboratories were studied for several reasons. The day-care center sampling allows for examination of colonization in asymptomatic individuals, whereas hospital resistance rates are based on cultures performed only on symptomatic individuals. Furthermore, focusing on day-care centers provides the study with a better understanding of the regionwide reservoir of antibiotic-resistant *S pneumoniae*. We chose to focus on both intermediate and high resistance as indicative of antibiotic-resistant *S pneumoniae*. Although the absolute level of the minimal

TABLE 3

Bivariate Analysis of 35 Pneumococcal-Positive Patients Resistant to Penicillin, by Patient Characteristics

	Resistant to Penicillin No. (%)	*P* Value
Sex		.92
Male	11 (55.0)	
Female	8 (53.3)	
Race		.85
White	17 (54.8)	
Nonwhite	2 (50.0)	
MSA residence		.51
Yes	11 (50.0)	
No	8 (61.5)	
Medicaid recipient		.28
Yes	5 (42.0)	
No	14 (61.0)	
Taken antibiotics in past 2 weeks		.08
Yes	9 (75.0)	
No	10 (43.5)	

inhibitory concentration provides the most useful information for patient management, categorizing isolates as nonsusceptible (ie, intermediately resistant or highly resistant) does have significant implications for patient care and is a common way of presenting pneumococcal resistance data.[17,24]

The relatively small sample size in this study limits the power that the analysis had to examine risk factors for carriage of drug-resistant pneumococcus. Thus, although the proportion of children who had been given antibiotics within 2 weeks of the culture had penicillin-resistant isolates was 32% higher than those without antibiotics (75% vs 43%), the difference was statistically significant at only .08. To detect a statistically significant difference of 75% and 43% at .05 with a power of 80%, 86 individuals with *S pneumoniae* isolates would be required. The present study obtained samples from more than 100 children in four counties, but a larger statewide or national study might provide a particularly useful picture of the prevalence of drug-resistant *S pneumoniae*.

As drug-resistant *S pneumoniae* continues to emerge, treatment and prevention of pneumococcal infections becomes increasingly difficult. Limiting the effect of pneumococcal drug resistance may require a reexamination of outpatient treatment strategies for childhood respiratory tract infections.

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