

Original Article

Pneumococcal Infections in Trinidad: Patterns of Antimicrobial Susceptibility: 1994 - 2002

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SUMMARY: Antimicrobial susceptibilities of 156 *Streptococcus pneumoniae* strains isolated from 1994 through 2002 were studied. Of this total, 38.7, 26.3, 16.7, 8.9, and 9.6% were recovered from patients with bacteremia, pneumonia, otitis media, sinusitis, and meningitis, respectively. All *S. pneumoniae* strains were fully susceptible to amoxicillin-clavulanic acid and ampicillin, with 9.0 and 2.6% being resistant to penicillin and ceftriaxone, respectively. The ratios of resistant strains to tetracycline, co-trimoxazole, and chloramphenicol were 73.7, 69.3, and 63.5%, respectively. Approximately 90% of strains remain sensitive to erythromycin. A high prevalence of resistance to the penicillins and cephalosporins does not exist in Trinidad, although a trend toward such a pattern appears to be developing. The most frequent serotype was 14 (37.8%), followed by 6B (20.0%), 23F (10.3%), and 4 (6.4%), and all were recovered from children. The other serotypes accounted for <6% of the total isolates. All penicillin- and ceftriaxone-resistant strains belonged to serotype 14 (MIC ≥ 2 $\mu\text{g/ml}$ and ≥ 4 $\mu\text{g/ml}$), respectively. Identifiable risk factors for resistant isolates included the prevalence of otitis media and sinusitis among children treated inadequately with oral cephalosporins; the ease of obtaining antibiotics without a prescription at many pharmacies; and the indiscriminate prescribing of antibiotics by general practitioners.

INTRODUCTION

Streptococcus pneumoniae (Pneumococcus) remains a common pathogen and a leading cause of morbidity and mortality (1,2). These organisms are the most common etiologic agents of otitis media and sepsis in children under the age of 2 years, and the predominant cause of bacterial pneumonia and meningitis (3,4). Penicillin is considered the drug of choice in the treatment of such infections, and most developing countries still rely heavily on these drugs. For the past 50 years, *S. pneumoniae* has been among the organisms most highly susceptible to penicillin, but resistance to penicillin has by now emerged. Penicillin resistance was first reported from Australia in 1967 (5) and in New Guinea in 1969 (6). Since then, resistance to these drugs in many countries of Asia, Africa, Europe, and North America (7-9,28, 32) has been reported.

In recent times, pneumococcal strains with high level resistance to penicillin have emerged, and these strains have shown resistance to other antibiotics such as the cephalosporins, tetracyclines, sulfonamides, erythromycin, chloramphenicol, and clindamycin (10-12,22). Resistance rates vary geographically (13-17), which implies a growing need to monitor their prevalence in various localities. Certain serotypes of *S. pneumoniae* appear to be more virulent than other serotypes, and have been associated with the majority of invasive infections (18,29). Serotype distribution varies with time, geographical location, and the age of the patient (18-21). Serotype 5 is among the least common types in North America, but is common in West Africa (22). Among children, serotypes 6, 14, 9, and 23 account for the majority of infections in India, the United Kingdom, and the USA

(23,24,28). Although resistance to one or more antibiotics has been reported in representative isolates of all the common serotypes, serotypes 6, 14, 19, and 23 appear to be most resistant to multiple antibiotics worldwide (21,22,25).

In Trinidad, published data on the prevalence of pneumococcal infections are scanty. Even scantier is the resistance profile of these organisms. Most microbiological diagnoses of pneumococcal otitis media or sinusitis are reached erratically because the sites are usually not accessible for routine specimen collection, and patients with pneumococcal pneumonia maybe too sick to produce quality sputum for detection of the organism. Also, interpretations of cultures of sputum are often complicated by the fact that the pneumococci also occur as upper respiratory tract commensals.

The present study was undertaken to assess the baseline prevalence of pneumococci at the Eric Williams Medical Sciences Complex (EWMSC); to ascertain whether multi-drug resistant strains do exist in Trinidad; and to evaluate the risk factors for carriage and the implications for such resistance profiles for the country.

MATERIALS AND METHODS

For the period 1994 through 2002, a survey was conducted of the prevalence and antibiotic sensitivity pattern of all *S. pneumoniae* isolated at the diagnostic laboratory of the EWMSC. The EWMSC is a 560-bed medical complex located in the northwestern part of Trinidad.

Isolation and identification: All isolates were recognized by their colonial morphology and alpha hemolysis displayed on sheep blood agar plates. The isolates were further identified by their gram stain characteristics, sensitivity to optochin (5 μg), and bile solubility. Pneumococcal isolates recovered from the same patient more than once were considered to be one isolate. The Caribbean Epidemiological Center (CAREC), located in Trinidad, performed capsular

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typing. Isolates were serotyped by the capsular swelling method using commercially available antisera (Statens Seruminstitut, Copenhagen, Denmark).

Antibiotic susceptibility testing (disc diffusion): Antimicrobial susceptibility testing was done via the disc diffusion method (except for penicillin and ceftriaxone) on Mueller-Hinton agar supplemented with 5% defibrinated sheep blood using an inoculum of several colonies suspended in Mueller-Hinton broth and adjusted to a 0.5 McFarland standard conforming to guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) (26). The following antibiotic discs and concentrations (in brackets) were used: penicillin G (10 U), ampicillin (10 μ g), augmentin (amoxicillin-clavulanic acid) (20/10 μ g), chloramphenicol (30 μ g), erythromycin (10 μ g), trimethoprim-sulfamethoxazole (1.25/23.75 μ g), tetracycline (30 μ g), ceftriaxone (30 μ g), and oxacillin (1 μ g). All these antibiotics were obtained from Oxoid Ltd., Basingstoke, Hampshire, UK. Plates were incubated in 5% CO₂ at 35-37°C for 20 to 24 h. Isolates were considered sensitive if zones of inhibition were comparable to those of the control organisms, and resistant if only very small or no zones were observed (26).

Antibiotic susceptibility testing (micro broth dilution): MIC determinations for penicillin and ceftriaxone were performed by CAREC using standard micro broth dilution with Mueller-Hinton media supplemented with 5% lysed horse blood. Susceptibility categories were determined by the NCCLS (27). Guidelines for breakpoints of penicillin, ≤ 0.06 μ g/ml = susceptible; 0.12-1.0 μ g/ml = intermediate; ≥ 2 μ g/ml = resistant; ceftriaxone, ≤ 0.05 μ g/ml = susceptible; 1.0 μ g/ml = intermediate; ≥ 4 μ g/ml = resistant. Isolates in the intermediate category were few and were considered as non-susceptible or resistant.

Statistical analysis: All data were retrieved from the record books compiled in the microbiology laboratory for the period 1994-2002. Data was manually typed, arranged, and analyzed. Other information extracted from the record books for each isolate included year and month of isolation, laboratory number, clinical diagnosis, site of isolation (e.g., blood, CSF), and susceptibility patterns. Reference control organisms were *Staphylococcus aureus* ATCC 25923 and *S. pneumoniae* ATCC 49619 supplied by CAREC.

RESULTS

During the 9-year period, a total of 156 *S. pneumoniae* isolates were recorded. Of this total, 38.7% were from patients with bacteremia, 26.5% from patients with lower respiratory tract infections, 16.8% from those with otitis media, 8.9% from those with sinusitis, and 9.6% from those with meningitis (Table 1). More than 60% of isolates were from the pediatric unit.

The distribution of the serotypes for the 9-year study period is shown in Table 2. Serotypes 14, 6B, 23F, 4, 6A, and 15C accounted for 85% of the isolates, of which serotypes 14, 6B, 23F, and 4 were recovered from children. All these serotypes are contained within the 23-valent pneumococcal polysaccharide vaccine.

The antibiotic susceptibility pattern of the pneumococcal isolates from clinical sources is shown in Table 3. Blood isolates were more resistant to penicillin (12 isolates with MIC ≥ 2 μ g/ml) than those isolated from CSF (2 isolates with MIC ≥ 4 μ g/ml). A *S. pneumoniae* strain recovered from blood with diminishing susceptibility to penicillin via

Table 1. Clinical source of 156 strains of *Streptococcus pneumoniae* isolated at the EWMSC, 1994-2002

Source	No. of isolates (%) *n = 156
Blood	60 (38.5)
LRT	41 (26.3)
Ear (swab)	26 (16.7)
URT (Sinus puncture)	14 (8.9)
CSF	15 (9.6)
Total	156 (100)

EWMSC, Eric Williams Medical Sciences Complex, LRT, lower respiratory tract; URT, upper respiratory tract; CSF, cerebrospinal fluid.

*n = total number isolated.

Table 2. Serotypes of 156 strains of *Streptococcus pneumoniae* isolated from clinical sources at the EWMSC, 1994-2002

Serotypes	No. of isolates (%)
14	59 (37.8)
6B	31 (20.0)
23F	16 (10.3)
4	10 (6.4)
6A	8 (5.1)
18	8 (5.1)
15C	7 (4.5)
6	3 (1.9)
11	3 (1.9)
19	3 (1.9)
19F	3 (1.9)
23A	3 (1.9)
NT	2 (1.3)
Total	156 (100)

NT, non typable.

Table 3. Comparison of antibiotic resistance percentage of 156 *Streptococcus pneumoniae* strains isolated from clinical sources at the EWMSC, 1994-2002

Antibiotic	Blood n = 60	LRT n = 41	Ear n = 26	CSF n = 15	Sinusitis n = 14
Penicillin					
MIC ≥ 2 μ g/ml	20	0	0	13.3	0
Ceftriaxone					
MIC ≥ 4 μ g/ml	6.7	0	0	0	0
Erythromycin	6.7	14.6	11.5	13.3	14.3
Tetracycline	25.0	26.8	26.9	26.7	28.6
Co-trimoxazole	38.3	43.9	11.5	13.3	14.3
Chloramphenicol	36.7	39.0	34.6	33.3	35.7
Augmentin	0	0	0	0	0
Ampicillin	0	0	0	0	0

Abbreviations are in Table 1.

Co-trimoxazole, trimethoprim-sulfamethoxazole; Augmentin, amoxicillin-clavulanic acid.

disc diffusion (MIC 1.0 μ g/ml) was first noticed in February 2000. By the end of March 2000, penicillin non-susceptible (resistant) strains were found (MIC 2.0 μ g/ml). Of the 12 blood isolates resistant to penicillin, only 4 were resistant to ceftriaxone with regard to the percentage of the 156 pneumococcal isolates resistant to the non- β -lactam drugs, resistances to erythromycin (10.9%), tetracycline (26.3%),

co-trimoxazole (trimethoprim-sulfamethoxazole) (30.7%) and chloramphenicol (36.5%) were higher among respiratory tract isolates than those from other sites. Also, the resistance patterns of isolates from the other sites did not differ significantly from each other when compared to the aforementioned non- β -lactam drugs.

DISCUSSION

This study did not suggest a high prevalence rate of resistance among pneumococcal isolates in Trinidad. Our rate of 9.0% resistance to penicillin is much lower than the 24.3% reported from Kenya (16), or that reported from Ghana (32%) (9), and Taiwan (33%) (21), but in agreement with rates of 7-10% reported elsewhere (10,42). In fact, the highest recorded incidences of penicillin-resistant pneumococci came from Hungary, South Africa, Spain, and France. South African isolates belonged predominantly to serotypes 6, 14, 19, and 23 (29). In Hungary, resistant isolates belonged to serotypes 19A, 6B, and 23F (14). In Spain, serotypes 6, 9, and 19 are the most common isolates from blood cultures; from CSF, resistant isolates are mainly of serotypes 6, 9, and 23, while from the lung, serotypes 6, 9, 14, 19, and 23 are often recovered (30). In France, penicillin-resistant isolates comprise serotypes 6, 14, 19, 23, and 23F (31). Isolates of pneumococci in our study comprised a wide variety of serotypes, the predominant ones of which were 14, 6B, 23F, 4, 6A, 18, and 15C, many of which have also been described as predominant in other parts of the world (12, 33, 34).

Differences in reported incidences appear to support geographical variation in the prevalence and serotypes of drug-resistant strains of pneumococci, and emphasize the importance of community-based monitoring of pneumococcal susceptibility to antimicrobial agents as a guide to therapy. The drugs commonly used to treat pneumococcal infections at our institution are still quite effective. However, recent surveys on antimicrobial susceptibility indicate that the prevalence of resistance among pneumococci resistant to non- β -lactam drugs is increasing. In a report from Taiwan, 82 and 87% of 200 pneumococci were resistant to erythromycin and trimethoprim-sulfamethoxazole, respectively (21). Similarly, Arnold et al. (13) reported that pneumococci shown to be resistant to penicillin also exhibited resistance to trimethoprim-sulfamethoxazole (95%), erythromycin (55%), and tetracycline (25%). The situation is further complicated by recent reports that describe the failure of extended spectrum cephalosporins, chloramphenicol, and vancomycin in the treatment of pneumococcal meningitis due to intermediate level and high-level resistance to β -lactams (10,35).

Several risk factors associated with the carriage of penicillin-resistant pneumococci have been identified. Arnold et al. (13) reported that ethnic origin, higher family income, day care center attendance, private medical insurance, use of the β -lactam antibiotics, and frequency of treatment of otitis media were recognized risk factors; while most of these factors have also been proposed by others (4,35), the report by Arnold et al. (13) did not adequately explain the roles private insurance and higher family income play in the carriage of these resistant organisms. They also failed to elaborate on age (prevalence of carriage is 3-4 times greater in patients over age 40), seasonal prevalence, and the fact that pneumococcal infections often parallel epidemics of influenza viral respiratory tract infections. Currently, although the prevalence of penicillin-resistant pneumococci is low, as

was found in this study, risk factors for their emergence are present. The prevalence of otitis media and sinusitis among children in our communities and kindergarten schools and the widespread use of other β -lactam drugs (e. g., cephalothin and cefuroxime) for the treatment of other respiratory tract and urinary tract infections have contributed to increased resistance of microorganisms (36,37).

One interesting observation made from this study was that although the prevalence of pneumococcal resistance to penicillin was found to be low, there is evidence from earlier reports from this country that the incidence of β -lactam resistance is increasing, particularly in the community (38,39). The detection of resistance to penicillin and other drugs is disturbing and has far reaching implications for antibiotic therapy, especially in a developing country that relies heavily on imported drugs. Because isolates from CSF relatively or fully resistant to penicillin may not respond to penicillin therapy (10,11,35), the presence of such strains in a community implies that empiric antibiotic therapy must include alternative drugs. The presence of ceftriaxone resistance, although low (four blood isolates), is a cause for further concern because ceftriaxone as well as cefotaxime is used to treat pneumococcal meningitis often resistant to penicillin.

Additionally, resistance to other drugs that can be given orally presents an additional problem for outpatient management of common infections such as otitis media and sinusitis often caused by pneumococci. Reports have shown that the ease of procuring antibiotics without a prescription at many pharmacies has resulted in uncontrolled distribution of medication and may complicate the problem of antibiotic resistance (40,41). This, along with indiscriminate prescribing by general practitioners in the community, the absence of antibiotic prescribing policies, and inadequate information on the patterns of bacterial resistance may all further contribute to the emergence of resistant microorganisms (21,33,37,40).

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