Streptococcus pneumoniae Blood Culture Isolates from Patients with and without Human Immunodeficiency Virus Infection: Alterations in Penicillin Susceptibilities and in Serogroups or Serotypes

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We performed a 3-year retrospective study of Streptococcus pneumoniae blood culture isolates recovered at Baragwanath Hospital, Soweto, South Africa, from 1993 to 1995. The study group comprised 457 patients, including 98 children, of known human immunodeficiency virus (HIV) serostatus. Of these patients, 70 (30 [8.4%] of 359 adults and 40 [40.8%] of the 98 children) were infected with penicillin-resistant S. pneumoniae strains (minimal inhibitory concentration, $\geq 0.12 \mu g/mL$); 56 of these strains were intermediately resistant to penicillin. HIV-positive patients had significantly more penicillin-resistant isolates than did HIV-negative patients (43 [29.7%] of 145 HIV-positive patients vs. 27 [8.6%] of 312 HIV-negative patients; $P < .001$); this difference was found for both adults (19% vs. 4.3%; $P < .001$) and children (53.3% vs. 30.2%; $P < .0343$). Multiple resistance occurred more frequently in HIV-positive children ($P = .02$). HIV-positive adults had a statistically significant increase in the percentage of serogroups and serotype usually found in children and commonly associated with antimicrobial resistance, i.e., serotype 14 and serogroups 6, 19, and 23 (48% vs. 28.6%; $P < .001$). The increased prevalence of serogroups or serotypes usually found in children was also found among penicillin-susceptible strains. These data suggest that HIV-infected adults may again become susceptible to the serogroups or serotypes found in children.

Penicillin resistance in a clinically significant isolate of Streptococcus pneumoniae was first observed in Australia in 1967; the isolate was recovered from the sputum of a patient with hypogammaglobulinemia [1]. In South Africa, penicillin-resistant S. pneumoniae strains were first detected in Durban in 1977, among patients with bacteremia, meningitis, pneumonia, and empyema [2]. In 1978, the occurrence of multiply and highly resistant strains was reported in Johannesburg and Soweto [3]. Since then, there has been a progressive increase in prevalence of penicillin-resistant strains causing systemic infection in South Africa, i.e., from 5% in 1979 to 14% in 1990 [4]. Worldwide spread of penicillin-resistant pneumococci has occurred [5, 6].

Bacterial pneumonia is more frequent in HIV-positive patients than in seronegative controls, and the rate of bacterial pneumonia increases with decreasing CD4 lymphocyte counts [7]. S. pneumoniae is the leading cause of community-acquired bacterial pneumonia [7] and associated bacteremia [8] in HIV-infected patients. Redd et al. [9] estimated that the increased incidence of pneumococcal bacteremia in patients with AIDS was 9.4 cases per 1,000 patients per year in San Francisco, up to 100 times greater than before the AIDS epidemic. In a study from East Africa, S. pneumoniae was found to be the earliest and most common pathogen to cause disease during HIV infection [10]. Invasive pneumococcal infection is the most common serious bacterial infection in HIV-infected children [8, 11].

Rates of HIV infection and AIDS are increasing progressively in South Africa. It was estimated that by the end of 1994, there were 1,100,000 HIV-infected people in South Africa, with a doubling time of 15.5 months [12].

At Baragwanath Hospital, Soweto, the HIV seropositivity rate increased from 7.5% to 23.5% among adults selectively tested in medical wards and from 7.1% to 36% among children selectively tested in pediatric wards between January 1993 and January 1996. The HIV seropositivity rate among patients attending an antenatal clinic at the hospital increased from 2.4% to 11.6% between 1993 and 1995 (authors’ unpublished data).

The purpose of the present study was to investigate whether there was an association between penicillin-resistant pneumococci in invasive bacteremic disease and HIV infection in our hospital and to evaluate the serogroups or serotypes involved.

Patients and Methods

Baragwanath Hospital is a large tertiary-care teaching institution with $\sim$3,300 beds, which serves the population of Soweto ($\sim$3 million persons). We performed a retrospective...
study at the hospital over a 3-year period, from January 1993 to December 1995, during which S. pneumoniae was isolated from blood cultures of 1,012 inpatients, including 750 adults and 262 children. The study group comprised 457 inpatients (45.2% of the total), 359 of whom were adults and 98 were children; HIV serostatus had been determined for all of these patients.

The BACTEC system (Becton Dickinson, Sparks, MD) was used to determine growth in blood cultures. All strains were initially screened for antimicrobial susceptibility by the disk diffusion method on 5% blood agar plates with use of disks containing 1 μg of oxacillin (Oxoid; Basingstoke, Hants, England) to detect strains with reduced susceptibility to penicillin. Oxacillin zone sizes of >20 mm were interpreted as indicating susceptibility, and those of ≤19 mm were interpreted as indicating resistance. Disks containing 30 μg of chloramphenicol, 30 μg of tetracycline, 15 μg of erythromycin, 2 μg of clindamycin, and 5 μg of rifampin were used [13]. Susceptibility to trimethoprim-sulfamethoxazole (TMP-SMZ) was tested by using a 1.25/23.75-μg disk on Mueller Hinton agar with laked blood.

MICs were determined for strains with reduced zones of inhibition by using the broth microdilution method with cation-adjusted Mueller-Hinton broth. Penicillin MICs of <0.06 μg/mL were regarded as indicating susceptibility, MICs of 0.12–1 μg/mL, as indicating intermediate susceptibility, and >1 μg/mL, as indicating resistance. The National Committee for Clinical Laboratory Standards MIC breakpoints were used for reporting antimicrobial resistance of pneumococci [14]. Cefotaxime and ceftriaxone MICs of ≤1 μg/mL were regarded as indicating intermediate susceptibility, and those of ≥2 μg/mL were regarded as indicating resistance.

The isolates were also serogrouped or serotyped on the basis of the Quellung reaction, as determined with specific pneumococcal antiserum (Statens Seruminstitut, Copenhagen).

Nosocomial bacteremia was defined as detection of pneumococci in blood culture >48 hours after admission to hospital. HIV testing was performed by using the recombinant HIV 1 and 2 third-generation EIA (Abbott Diagnostic Products, Wiesbaden, Germany), and the results were confirmed by western blot in 1993 and by a second EIA (Enzygnost HIV-1/2; Behring Diagnostics, Marburg, Germany) in 1994 and Wellcozyme HIV 1 + 2 (Murex Diagnostics, Dartford, UK) in 1995. Additional confirmatory tests for children <15 months of age were not performed in this study, and all HIV-positive children with invasive pneumococcal disease were assumed to be HIV infected.

Statistical analysis was performed with use of the χ² square test to evaluate differences between groups. Stratified analysis was carried out by using the Mantel-Haenszel χ² estimate. Odds ratios and 95% confidence intervals were calculated.

**Results**

Of the 457 patients in the group studied, 22 (6.1%) of the 359 adults and 9 (9.2%) of the 98 children had pneumococcal meningitis as well as bacteremia. The majority of patients had lower respiratory tract infection and bacteremia. The male-to-female ratio was 2.4:1 among adults, with a ratio of 3.6:1 among HIV-negative adults and 1:1 among HIV-positive adults. The male-to-female ratio was 2:1 among children, with a ratio of 1.6:1 among HIV-negative children and 2.5:1 among HIV-positive children.

Although the total number of medical patients and children admitted to Baragwanath Hospital annually did not increase over the study period, the number of patients with pneumococcal bacteremia increased from 321 in 1993 to 375 in 1995. Despite a slight decline in the percentage of patients tested annually for antibodies to HIV (from 47.4% in 1993 to 44.3% in 1995), the percentage of HIV-positive patients increased from 19.1% (29 of 152) in 1993 to 31.1% (42 of 135) in 1994 and 43.5% (74 of 170) in 1995.

S. pneumoniae isolates recovered from blood cultures performed for HIV-positive and HIV-negative patients are shown in table 1. Penicillin resistance was detected in a total of 70 (15.3%) of 457 isolates; 30 (8.4%) of 359 isolates were identified in adults, and 40 (40.8%) of 98 isolates were identified in children. Of these 70 isolates, 56 were intermediately resistant; nine were resistant; and MIC results were not obtained for five. A total of 29.7% were resistant in the HIV-positive group, as compared with 8.65% in the HIV-negative group. This result was statistically significant (P < .001; OR = 4.45; 95% CI = 2.53–7.84). A significant association between resistance and HIV seropositivity was found for the adult group, where 19% of resistant strains occurred in HIV-positive patients, and 4.25% occurred in HIV-negative patients (P < .001; OR = 5.29; 95% CI = 2.28–12.45). The association was also significant for the children, where 53.3% and 30.2% of strains were resistant in HIV-positive and HIV-negative children, respectively (P = .034; OR = 2.64; 95% CI = 1.07–6.61).

Antimicrobial susceptibility patterns are shown in table 2. Strains resistant to penicillin alone were most common. Multiple resistance (resistance to at least three different classes of antibiotics) also occurred, particularly among the children. Tetracycline resistance alone occurred more commonly in adults.

The penicillin MICs for resistant strains tested in adults and children are indicated in table 3. MICs varied from 0.12 μg/mL to 4 μg/mL, with the majority of strains in the intermediate category (MICs, 0.12–1 μg/mL) for both HIV-positive and HIV-negative patients. High-level resistance occurred in 3 (0.83%) of 359 adults and 6 (6.1%) of 98 children. The penicillin MICs were 2 μg/mL in all cases except one (a child with meningitis), where the MIC was 4 μg/mL.

The results of serogrouping or serotyping of S. pneumoniae strains in adults and children are summarized in figure 1. Fourteen of the strains (9 from adults and five from children) lost viability before testing. Twenty-one of 90 serogroups or serotypes were represented. The most common type was serotype 1 in HIV-negative adults (100 patients [38.6%]) followed by...
serotype 14 (10.8%) and serogroups 19 (9.3%), 6 (8.1%), and 3 (7.7%). Among HIV-positive adults, serotype 1 was also the most common type but only occurred in 20 patients (20%), followed by serogroup 19 (17%), serotype 14 (16%), and serogroup 6 (13%). The reduction in the incidence of serotype 1 was statistically significant (P = .0013; OR = 0.40; 95% CI = 0.22–0.71). Of HIV-positive adults, 48% were infected with serogroups common among children (i.e., 6, 19, 23 and serotype 14), whereas 28.6% of HIV-negative adults were infected with these serogroups (table 4). This finding was also significant (P < .001; OR = 2.31; 95% CI = 1.39–3.82).

In adults with penicillin-susceptible strains, a greater variety of serogroups or serotypes occurred in HIV-negative patients than in HIV-positive patients (figure 1). There was a trend towards an increase in the percentage of “pediatric” serotypes among HIV-positive patients (30 [37.0%] of 81 patients) vs. HIV-negative patients (63 [25.4%) of 248), and this difference was statistically significant (P = .04; OR = 1.73; 95% CI = 0.98–3.05). Among adults with penicillin-resistant strains, the serogroups recovered were similar (serogroups 6, 14, and 19) for HIV-negative and HIV-positive patients, although serogroup 6 was the most common serogroup in HIV-negative adults, and serogroup 19, followed by serotype 14, was most common in HIV-positive adults. Serogroups 9 and 23 were also represented among HIV-positive adults.

Serogroup 6 was the most common serogroup isolated among HIV-negative children, (35.8% of isolates), followed by 14 and 19 (11.3% of strains each; figure 1). In HIV-positive children, serogroups 6 and 23 and serotype 14 each accounted for 20% of strains. Although the percentage of “pediatric” serogroups increased from 62.2% to 73.3%, this increase was not statistically significant. Approximately the same percentage of these serogroups and serotype occurred among penicillin-susceptible strains, although serogroup 6 was less frequent in HIV-positive children. Among penicillin-resistant strains, serogroup 6 was most common in HIV-negative children (50% of isolates), while serogroup 23 was most common in HIV-positive children (33.3%). Of the penicillin-susceptible strains, serogroup 6 was still most common (29.7% of isolates) in HIV-negative children, while serotype 1 was most common (33.3%) in HIV-positive children; serogroups 6 and 19 and serotype 14 were equally represented (14.3% of isolates).

Rates of resistance to antibiotics other than penicillin were highest for tetracycline (43 [9.4%] of 457 isolates), followed by erythromycin (17 [3.7%] of 457), rifampin (14 [3.1%] of 457), and chloramphenicol (14 [3.1%] of 457). Erythromycin resistance was accompanied by clindamycin resistance in all cases except one. TMP-SMZ susceptibility testing of all isolates was begun in 1995, and 5.8% (7 of 120) were found to be resistant. Resistance to cefotaxime or ceftriaxone, based on MIC determinations, was less common; resistance to these drugs occurred in seven patients (1.5%; five children and two adults), all of whom except one child were HIV positive. The resistance was intermediate (MIC, 1 µg/mL) in the adults and in two children, and high-level (MIC, 2 µg/mL) in three children (two were infected with serogroup 23, and one was infected with serogroup 19).

Overall resistance to each of the antimicrobial agents tested was higher among children than among adults. This finding also applied to TMP-SMZ; 3 (3.2%) of 94 isolates in adults were resistant, and 4 (15.3%) of 26 isolates in children were resistant. The rates of resistance to all antimicrobials, except tetracycline and rifampin, were higher among HIV-positive children than among HIV-negative children. The increase in rates of resistance to erythromycin and chloramphenicol among HIV-positive children did not reach statistical significance.

Rates of resistance to erythromycin and rifampin were increased among HIV-positive adults vs. HIV-negative adults, but rates of resistance to tetracycline were not. Rates of resistance to chloramphenicol, cefotaxime, and ceftriaxone were very low among adults.

Multiple resistance, defined as resistance to at least three different classes of antibiotics, occurred in 12 (26.7%) of 45 HIV-positive children vs. 5 (9.4%) of 53 HIV-negative children. This difference was statistically significant (P = .02; OR = 3.42; 95% CI = 0.99–12.44). Multiple resistance included resistance to penicillin in 18 (78%) of 23 resistant isolates overall; however, this rate was 100% for isolates from children. Fifty percent (12 of 24) and 31.3% (5 of 16) of all isolates recovered from HIV-positive children and HIV-negative children, respectively, were multidrug resistant. The most common pattern was resistance to penicillin, chloramphenicol, and tetracycline. This pattern occurred with or without resistance to erythromycin and clindamycin, TMP-SMZ,
Table 2. Antimicrobial resistance patterns by serogroup or serotype for *Streptococcus pneumoniae* blood culture isolates, 1993–1995, in South Africa.

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>Adults</th>
<th></th>
<th>Children</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-positive</td>
<td>HIV-negative</td>
<td>HIV-positive</td>
<td>HIV-negative</td>
</tr>
<tr>
<td>Penicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (3)</td>
<td>6 (4)</td>
<td>6 (6)</td>
<td>6 (8)</td>
</tr>
<tr>
<td></td>
<td>9 (1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>14 (5)</td>
<td>14 (2)</td>
<td>14 (3)</td>
<td>14 (1)</td>
</tr>
<tr>
<td></td>
<td>19 (6)*</td>
<td>19 (4)</td>
<td>19 (2)</td>
<td>19 (1)</td>
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<tr>
<td></td>
<td>23 (1)*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Penicillin, chloramphenicol</td>
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<tr>
<td></td>
<td>19 (1)*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Penicillin, tetracycline</td>
<td>14 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin, erythromycin/lincosamide</td>
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</tr>
<tr>
<td>Penicillin, chloramphenicol, tetracycline</td>
<td>19 (1)</td>
<td></td>
<td>23 (3)*</td>
<td>14 (1)*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>19 (1)*</td>
<td></td>
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<tr>
<td>Penicillin, tetracycline, erythromycin/lincosamide</td>
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<tr>
<td>Penicillin, chloramphenicol, erythromycin/lincosamide</td>
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<tr>
<td>Penicillin, chloramphenicol, tetracycline, erythromycin/lincosamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1 (1)</td>
<td>1 (19)</td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin/lincosamide</td>
<td>6 (1)</td>
<td></td>
<td>14 (1)</td>
<td></td>
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<tr>
<td>Chloramphenicol, tetracycline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline, erythromycin/lincosamide</td>
<td>14 (2)</td>
<td>14 (2)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>6 (1)</td>
<td></td>
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</tbody>
</table>

NOTE. NS = not serotyped.

* With rifampin resistance in addition: HIV-positive adults, 19 (2); HIV-positive children, 23 (2); HIV-negative children, 23 (1) and 14 (1). With rifampin resistance alone: HIV-positive adults, 1 (2), 6 (2), and 1 (serotype unknown); HIV-positive children, 6 (1); and HIV-negative children, 6 (1) and 18 (1).

² With cefotaxime and ceftriaxone resistance in addition: HIV-positive adults, 23 (1) and 19 (1); HIV-positive children, 23 (5) and 19 (1); and HIV-negative children, 23 (1).

rifampin, and third-generation cephalosporins. Among multidrug-resistant isolates, serogroups 19 and 23 and serotype 14 were represented most often. Resistance to TMP-SMZ was associated with multiple resistance in three of seven cases (an HIV-positive adult infected with serogroup 19 and two HIV-positive children infected with serogroups 19 and 23). Multiple resistance seldom occurred in either HIV-positive or HIV-negative adults (table 2).

The majority of strains of *S. pneumoniae* in this study were community acquired. Nosocomial spread of pneumococci occurred in 15 patients (12 children and 3 adults). Ten penicillin-resistant pneumococcal bacteremic infections (nine of which were in children) were acquired in the hospital over the 3-year period. Four of these infections occurred in HIV-positive patients (one adult [serogroup 19] and three children [two with serogroup 23 and one with serotype 14]). Six of these infections occurred in HIV-negative children (three isolates of serogroup 6 and one each of serotype 14, serogroup 19, and serogroup 23). Only four of the strains were highly resistant, and all of these were detected in children: three of these were multiply resistant serogroup 23 (two of which were recovered from HIV-positive children) and one was multiply resistant serotype 14, recovered from an HIV-negative child. One of the children with serogroup 23 also developed meningitis. Five penicillin-susceptible pneumococcal bacteremic infections were acquired in the hospital during the same period: two in adults (one HIV-negative patient infected with serotype 1 and one HIV-positive patient infected with serogroup 6) and three in HIV-negative children (two infected with isolates of serotype 1 and one infected with serogroup 6).
Table 3. Penicillin MICs for resistant Streptococcus pneumoniae strains from HIV-positive or HIV-negative adults and children.

<table>
<thead>
<tr>
<th>MIC (μg/mL)</th>
<th>Adults</th>
<th>Children</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HIV-positive</td>
<td>HIV-negative</td>
</tr>
<tr>
<td>0.12</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>0.25</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>0.5</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18*</td>
<td>11</td>
</tr>
</tbody>
</table>

* MICs not available for strains from five patients (one HIV-positive adult, two HIV-positive children, and two HIV-negative children).

Discussion

We found a significant association between penicillin-resistant pneumococcal bacteremia and HIV seropositivity in the group of adults and children we evaluated. This finding is in keeping with findings for adults in Kenya [15] and for children in the United States with invasive pneumococcal infections [11].

Among HIV-infected adults, there was a significant trend towards a greater proportion of infections due to serogroups 6, 19, and 23 and serotype 14, which are commonly found in children. These strains are often associated with resistance and represent the majority of resistant pneumococci isolated worldwide [5] and in South Africa [4].

It has been shown that penicillin-resistant pneumococci occur more often in patients who have received prior β-lactam antibiotic therapy, have been hospitalized during the 3 months before the infection, or have had previous episodes of pneumonia [16]. It was not possible to obtain accurate information regarding these issues in our retrospective study. Selective pressure by penicillin may have occurred, since penicillin and amoxicillin are inexpensive and are the most commonly used antimicrobial agents in Soweto clinics. Penicillin may be used more frequently in HIV-infected patients who have multiple bacterial infections.

Selective pressure by other antibiotics, such as TMP-SMZ, could play a role in the emergence of resistant pneumococci. In a study on hospitalized HIV-infected adults in France, treatment with antibacterial agents, particularly TMP-SMZ, in the previous 3 months was found to be associated with an increased risk of isolation of pneumococci with reduced susceptibility to penicillin, suggesting that long-term therapy with TMP-SMZ might promote the selection of penicillin-resistant pneumococci [17]. A significant association between carriage of penicillin-resistant pneumococci and recent consumption of TMP-SMZ was shown in children [18]. In the 26% of our strains that were tested, TMP-SMZ resistance was found to be relatively low, and combined penicillin and TMP-SMZ resistance was very low among adults, although relatively higher rates occurred among children. In studies on children from more affluent suburbs in Johannesburg, where TMP-SMZ is prescribed more frequently, the rate of resistance in pneumococci was found to be higher than that in Soweto [4, 5]. TMP-SMZ is offered as prophylaxis to immunocompromised adults who have been admitted to our hospital, but relatively small numbers of patients in the community receive it, and compliance may be a problem. Prophylactic TMP-SMZ is also recommended for immunocompromised children.

Selective pressure by tetracycline possibly accounted for the tetracycline resistance seen in community-acquired isolates of serotype 1 (25 [18.9%] of 132 were resistant). In contrast to the investigators in Kenya [15], we did not find that tetracycline resistance was associated with HIV seropositivity. This finding may reflect local antibiotic usage in Nairobi.

Penicillin resistance was higher among children than among adults, as has been described previously [5]. This difference

Figure 1. Distribution of serogroups or serotypes of Streptococcus pneumoniae blood culture isolates among adults and children, by HIV status and penicillin susceptibility, for the period 1993–1995.
incidence of invasive resistant strains among HIV-positive cases of intermediate resistance [10, 27]. Clinicians should be

spread from infants and young children to HIV-infected isolates has not been adequately studied. Successful treatment

infection, they are likely to transmit one of the common sero- of intermediately penicillin-resistant pneumococci [26]. The

may be spread more frequently from child to immunocom- (i.e., parenteral penicillin or parenteral ampicillin), and these

resistant pneumococcal strains are spreading within HIV- immunocompetent patients. Our empirical therapy for commu-

been reported to be common, often occurring in association with intermediate resistance to penicillin are not thought to

serotype in 28.9% (132 of 457 strains) is in keeping with a those with accompanying bacteremia and an increased bacterial

was also found between children and adults who were HIV positive. Serogroups 6, 19, and 23 with serotype 14 account

two-thirds of all pneumococci carried during the first 2 years of life [19]. These pediatric serogroups colonize children
earlier than do other serogroups [5] and are carried for longer periods (mean period, 4.2 months vs. 2.7 months for all other

serogroups combined; \( P < .01 \)) [19]. These serogroups are poorly immunogenic in young children <2 years of age and

sometimes in those \( \leq 5 \) years of age [20]. Pneumococcal carriage has been correlated with the emergence of clinical dis-
ease: of new strains acquired by children, 15% were found to result in disease before the HIV epidemic [19]. A reduction in

risk of disease occurs after the first decade of life, in accordance with maturing antibody responses [21].

The significant shift towards an increase in the serogroups common in children (serogroups 6, 19, and 23 and serotype

14) in HIV-positive adults with penicillin-susceptible strains may be due to characteristics of these groups/types that are

unrelated to resistance determinants or additional antibiotic sele-
tion pressure (i.e., it may reflect a loss of immunity to these pneumococci that had been acquired in childhood). However,

this shift may also be influenced by strains with reduced zones of inhibition on disk susceptibility testing for which MICs are in

the susceptible range of 0.03–0.06 \( \mu \)g/mL [22].

Intrafamilial carriage of a single type of \( S. \) pneumoniae and spread of the organism to more than one family member have been reported to be common, often occurring in association with an upper respiratory tract infection [23]. It is likely that resistant pneumococcal strains are spreading within HIV-infected families, particularly between parent and child. They may be spread more frequently from child to immunocom-

promised parent than vice versa. If children are a source of infection, they are likely to transmit one of the common sero-
groups/serotypes (6, 14, 18, 22, or 25) carried in the nasopharynx. Spread from infants and young children to HIV-infected mothers during repeated close contact could explain the higher incidence of invasive resistant strains among HIV-positive women (male-to-female ratio = 1:1), than among HIV-negative women (male-to-female ratio = 3.6:1).

The finding of serotype 1 as the most common invasive serotype in 28.9% (132 of 457 strains) is in keeping with a previous report from South Africa [24]. This finding is also in agreement with reports from South America but differs from those from Europe and the United States, where serotype 14 and serogroups 19 and 23, associated with the highest rates of nasopharyngeal carriage, are relatively more common [21]. However, in contrast to data from South America, we found that serotype 5 was relatively unimportant (isolated from 1.5% of patients) but that serogroup 6 was the second most important overall (isolated from 19.6% [62 of 457] of patients).

The rapid falloff of relative risk of serotype 14 that has been described in the second decade of life [21] did not occur in our study. Serotype 14 constituted 12.9% (59 of 457) of the total percentage of isolates (12.3% in adults), and serogroups 19 and 23 became relatively more important, comprising 9% and 3%, respectively, of the total percentage of isolates. Overall, this represented a significant shift towards the serogroups commonly found in children.

The progressively increasing rate of pneumococcal bacter-

emia associated with HIV infection seen at our hospital has been observed elsewhere. An increase in the rate of bacteremic and nonbacteremic \( S. \) pneumoniae infections, which almost doubled during the period 1987–1992, was noted in a hospital in Madrid and was partially attributable to HIV infection [25].

The association of HIV seropositivity with penicillin-

resistant pneumococci and multidrug resistance may have ad-

verse consequences in terms of morbidity and mortality. Strains with intermediate resistance to penicillin are not thought to be of clinical significance, except in cases of meningitis in immunocompetent patients. Our empirical therapy for commu-

nity-acquired pneumonia is in keeping with local guidelines (i.e., parenteral penicillin or parenteral ampicillin), and these guidelines have not been influenced by the current prevalence of intermediately penicillin-resistant pneumococci [26]. The response in HIV-infected patients with resistant pneumococcal isolates has not been adequately studied. Successful treatment with conventional penicillin dosages has been achieved in some cases of intermediate resistance [10, 27]. Clinicians should be guided by individual patients’ clinical responses to therapy, and moderately increased dosages of penicillin may be required, particularly in patients who are immunocompromised and in those with accompanying bacteremia and an increased bacterial

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**Table 4.** Isolation of \( S. \) pneumoniae serogroups 6, 19, and 23 and serotype 14 from blood cultures of HIV-positive and HIV-


<table>
<thead>
<tr>
<th>Age group</th>
<th>HIV-positive patients ((n = 145))</th>
<th>HIV-negative patients ((n = 312))</th>
<th>Total ((n = 457))</th>
<th>OR</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>48/100 (48)</td>
<td>74/259 (28.6)</td>
<td>122/359 (34)</td>
<td>2.31</td>
<td>1.39–3.82</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Children</td>
<td>33/45 (73.3)</td>
<td>33/53 (62.3)</td>
<td>66/98 (67.3)</td>
<td>1.67</td>
<td>0.65–4.33</td>
<td>.3430</td>
</tr>
<tr>
<td>Total</td>
<td>81/145 (55.9)</td>
<td>107/312 (34.3)</td>
<td>188/457 (41.1)</td>
<td>2.42</td>
<td>1.59–3.70</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
load. A recommendation for treatment with high-dose penicillin has been made for patients infected with intermediately penicillin-resistant strains causing pneumonia in Spain [28].

Nonmeningitic infections due to penicillin-resistant pneumococci (MIC, \(\geq 2 \mu g/mL\)) can be treated with high-dose penicillin G (10 mg/kg every 2 hours; 180,000–200,000 \(\mu g/(kg \cdot d)\)), third-generation cephalosporins, vancomycin, or other antimicrobial agents according to susceptibility. Our own experience has been limited largely to strains for which the MICs were 2 \(\mu g/mL\). For higher levels of penicillin resistance, alternative agents are preferred. It is not clear whether the response to penicillin therapy will be adequate in immunocompromised AIDS patients with penicillin-resistant strains, since outcome may be influenced by the underlying disease.

The increase in the frequency of intermediately penicillin-resistant strains is significant in terms of the treatment of meningitis, where intermediate penicillin resistance is sufficient to cause clinical failure [29]. Since CSF concentrations of penicillin are probably inadequate for treatment of meningitis, a third-generation cephalosporin such as cefotaxime or ceftriaxone should be used. Infections due to organisms with high-level penicillin resistance can be treated with vancomycin plus a third-generation cephalosporin.

For infection due to multiply resistant strains, therapy must be guided by the results of susceptibility tests. This problem has particular relevance in developing countries, where fewer patients receive full laboratory confirmation of diagnosis, and therapy may be restricted to inexpensive antibiotics.

There is little information on the clinical efficacy of orally administered antibiotics such as amoxicillin, second- and third-generation cephalosporins, and oral macrolides for nonmeningitic infection caused by intermediately penicillin-resistant \(S. pneumoniae\) in HIV-infected patients. Since many pneumococcal infections are treated on an outpatient basis, this would seem to be an important area for further research.

Two preventive options exist. One is the use of antibiotics as chemoprophylactic agents. The use of TMP-SMZ for \(Pneumocystis carinii\) pneumonia prophylaxis could be increased because this regimen is known to reduce the rate of bacteriologically confirmed pneumonia by approximately two-thirds [7]. However, many HIV-positive patients are not identified in the local community. A negative consequence of the increased use of TMP-SMZ prophylaxis may be increased resistance to penicillin and TMP-SMZ. Prophylactic use of penicillin has been recommended for preventing recurrences of pneumococcal infection [8]. In view of our findings and the escalating AIDS epidemic, we cannot agree with this recommendation in our setting. Other investigators have expressed reservations about the use of antibiotics as chemoprophylactic agents in view of the increasing incidence of disease caused by drug-resistant \(S. pneumoniae\), suggesting that this use of antibiotics may contribute to the problem of resistance to penicillin and may facilitate the spread of multidrug-resistant organisms [30, 31].

The other option is increased use of pneumococcal polysaccharide vaccine in HIV-infected patients early in the course of infection, even though efficacy data are limited [30]. Most of the pneumococci isolated from the adults in our study are represented in the 23-valent polysaccharide vaccine for adults, and 85 (86.7%) of the 98 isolates from the children in our study are represented in the 9-valent conjugate vaccine (serogroups or serotypes 1, 4, 5, 6, 9, 14, 18, 19, and 23) for children (41 [91%] of 45 HIV-positive children). The use of the more immunogenic conjugate vaccines in children <2 years of age may be of value and should be tested in clinical trials. Even if the antibody levels generated are suboptimal and are not sustained, the occurrence of invasive pneumococcal infections may be reduced.

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References

13. National Committee for Clinical Laboratory Standards. Performance standards for anti microbial susceptibility testing. NCCLS document M100-


