Recurrent Pneumococcal Bacteremia
Risk Factors and Outcomes
Glenn S. Turett, MD; Steve Blum, PhD; Edward E. Telzak, MD

Background: Recurrent pneumococcal bacteremia receives infrequent mention in the literature, usually in association with patients who are immunocompromised.

Objective: To examine recurrent cases of pneumococcal bacteremia to determine risk factors and outcomes (mortality rates and emergence of resistance) associated with recurrences.

Methods: We retrospectively reviewed all cases of pneumococcal bacteremia identified by our microbiology laboratory from January 1, 1992, through December 31, 1996. Demographic, clinical, and laboratory data were abstracted.

Results: There were 462 bacteremic episodes in 432 patients; 23 of these patients had 30 recurrent episodes. The 5.3% recurrence rate (23/432) is greater than that previously described. The median time to recurrence was 200 days. The mean age of patients with recurrences was 34 years, 70% were women, all were black or Hispanic (in near equal numbers), and 87% were infected with the human immunodeficiency virus (HIV). Human immunodeficiency virus infection, coexistent cancer, and female sex were independent predictors of recurrence. Only patients who were HIV-infected had multiple recurrences. Isolates from recurrent bacteremias were more likely to be penicillin-resistant than were initial bacteremic isolates (relative risk, 2.0; \( P = .16 \)). Patients with recurrences had a higher (although not statistically significant) mortality rate than those without recurrences (22% vs 16%; \( P = .33 \)). There was an inverse relationship between severity of illness and likelihood of recurrence.

Conclusions: Rates of recurrent pneumococcal bacteremia may be higher than previously reported. In patients with recurrent pneumococcal bacteremia, the presence of an underlying immunodeficiency should be investigated.

Arch Intern Med. 2001;161:2141-2144

Recurrence pneumococcal bacteremia is an uncommon event. Although most reports in the literature are of isolated cases, recently some larger case series have been described. Episodes of recurrent pneumococcal bacteremia have been reported primarily in patients with underlying immunodeficiencies. The increased incidence of invasive pneumococcal disease in patients infected with human immunodeficiency virus (HIV) is well documented, but there are only limited references relating HIV infection and recurrent pneumococcal disease. Our medical center serves a community with one of the highest rates of HIV infection in the United States. In reviewing our overall experience with pneumococcal bacteremias during 5 years, we observed a higher rate of recurrence than that previously reported and a marked association between HIV infection and recurrences. We looked to determine what other variables besides HIV infection were associated with recurrent pneumococcal bacteremia and what effect recurrences had on mortality rates and on emergence of penicillin resistance.

RESULTS
During the study, there were 462 episodes of pneumococcal bacteremia in 432 patients. Twenty-three patients had 30 episodes of recurrent bacteremia: 17 had single recurrences, 5 had 2 recurrences, and 1 patient had 3 recurrences. Overall, 5.3% of the patients (23/432) had recurrent pneumococcal bacteremia. The median time to recurrence was 200 days (range, 32-1196 days). All 6 patients with multiple recurrences were HIV-infected. Patients with a first recurrence were almost 5 times more likely to have another recurrence compared with the likelihood...
PATIENTS AND METHODS

Bronx-Lebanon Hospital Center is an acute-care facility serving an inner-city patient population of nearly half a million in the south Bronx, NY. All episodes of pneumococcal bacteremia between January 1, 1992, and December 31, 1996, were identified by retrospective review of microbiology records. Hospital inpatient and outpatient records were reviewed, and demographic, clinical, and laboratory data were abstracted on all identified patients. A description of this entire cohort and predictors of mortality have been previously published.21

Recurrent pneumococcal bacteremia was defined as the presence of Streptococcus pneumoniae in the blood at least 4 weeks after initial isolation and following a course of therapy with antibiotics that had in vitro activity against the initial isolate and evidence of a clinical response. Severity of illness was graded as severe or not severe based on clinical status and arterial blood gas measurements; illness was deemed severe if there was need for intensive care unit evaluation, hemodynamic instability, or an arterial PO2 of less than 50 mm Hg.

In vitro susceptibility of the isolates to penicillin was initially determined using the oxacillin sodium disk diffusion test. If resistance was found by this method, a minimal inhibitory concentration was subsequently determined using the E-test. Levels of resistance to penicillin were defined according to criteria of the National Committee for Clinical Laboratory Standards.22

The main outcomes of interest were episodes of recurrent pneumococcal bacteremia, emergence of penicillin resistance, and mortality. Statistical analyses included bivariate and multivariate analyses of the effects of all variables on recurrent pneumococcal bacteremia. The χ2 or Fisher exact test (for expected cell frequencies <5) was used for bivariate examination of categorical data, and forward stepwise logistic regression techniques were used to determine the effects of continuous and categorical variables (with P<.10 on bivariate analysis) on recurrent episodes of pneumococcal bacteremia. Also, the relationships between recurrences and penicillin resistance and recurrences and mortality rates were explored using similar statistical methods.

Table 1

Table 1 compares demographic and clinical characteristics of the patients with and without recurrent pneumococcal bacteremia and shows the statistical associations between the different variables and recurrences using bivariate analysis. Documented HIV infection, coexisting cancer, and female sex were the only characteristics significantly associated with recurrent pneumococcal bacteremia. Age, race, ethnicity, CD4+ cell count, trimethoprim-sulfamethoxazole use among those known to be HIV-infected, chest roentgenogram findings, involvement of other sterile sites, presence of underlying disease (other than HIV infection), and penicillin resistance were similar in the 2 groups and were not associated with recurrences (P=.30 for all variables). In those patients without severe manifestations of disease on presentation, there was a trend toward developing recurrent pneumococcal bacteremia, compared with those presenting with severe manifestations of disease (7% vs 2%, P=.06).

Table 2 demonstrates the results of the forward multiple stepwise logistic regression analysis to determine factors independently associated with recurrent pneumococcal bacteremia. Coexistent cancer, HIV infection, and female sex all remained independent predictors of recurrence.

To try to understand the association between female sex and recurrence, further bivariate analyses were done on all variables according to sex. Women were younger, less severely ill on presentation, and had higher CD4+ cell counts among those who were HIV-infected. None of these findings explain the increased recurrences seen in women.

The mean and median ages of the patients infected with HIV who had recurrences were 30 and 32 years, respectively. This was significantly lower than the mean of 36 years and the median of 39 years for the patients with HIV without recurrences (P=.049). The mean age of the 3 patients without HIV infection who had recurrences was 63 years. Two of these patients had multiple myeloma, and the third had cirrhosis of the liver.

Five (22%) of the 23 patients with recurrences died, compared with 67 (16%) of 409 patients with single bacteremic episodes (P=.33). Isolates from recurrent bacteremias were twice as likely to be penicillin-resistant than were isolates from initial bacteremias (13.3% [4/30] vs 6.7% [29/432]; relative risk, 2.0; P=.16).

COMMENT

In this study, HIV infection, cancer, and female sex were each independent predictors of recurrent pneumococcal bacteremia. Others have previously described the association between cancer,5-7 HIV infection,6,17-19 and recurrent pneumococcal bacteremia. However, the association between female sex and recurrent pneumococcal bacteremia has not been previously noted, and this finding remains unexplained, despite extensive analysis.

Our series of 23 patients with recurrent pneumococcal bacteremia is among the largest reported to date; previous descriptions ranged from isolated case reports to series of up to 15 patients.1-7,17 A recent article from San Francisco, Calif,16 that examined the relationship between HIV and invasive pneumococcal disease described 28 patients who were HIV-infected who had recurrent pneumococcal bacteremia, with a rate of recurrence of almost 15%. However, these authors defined recurrent disease as “isolation of S. pneumoniae from a normally sterile site more than 7 days after the original episode.”16,18,19 Although the actual mean, median, and/or range of times to recurrence were not reported. By using such a short interval between initial and subsequent isolation as the criterion for recurrence, some episodes classified as recurrent may actually have been persistent initial infections. Our definition of recur-
rence is more stringent and is more consistent with that in the literature (eg, infection-free for 30 days between episodes, or 22-947 days [mean, 268 days; median, 180 days] between episodes). The 5.3% overall rate of recurrent pneumococcal bacteremia we observed is greater than the 1.5% to 4.1% rates previously reported. One possible explanation for our increased rate of recurrence is the greater proportion (48%) of patients who were HIV-infected in our cohort compared with the 7% to 33% seen in the other series.\(^7\)\(^\text{-11}\) Frankel et al\(^\text{11}\) noted a greater relative risk of recurrent pneumococcal bacteremia with HIV than we did (15 vs 7.3). Redd and associates\(^\text{11}\) found an increased risk (relative risk, 1.6) that did not reach statistical significance (P = .11).

Our 22% mortality associated with recurrent bacteremias was not significantly higher than the 16% seen during initial episodes (P = .33). Rodriguez-Creixems et al\(^\text{6}\) in reviewing their 10-year experience with recurrent pneumococcal bacteremia, noted a mortality of 47%. Like our patients, all of theirs were immunosuppressed with malignancies, HIV infection, or cirrhosis. Their mean age was 52 years. On multivariate analysis, they found multiple myeloma to be the only clear predictor of recurrent bacteremia. The younger mean age (34 years) in our patients with recurrences may in part explain the lower mortality rate we saw compared with that of Rodriguez-Creixems et al.

Patients in our cohort with recurrences were twice as likely to be infected with resistant pneumococcus as...
those with single episodes. This is not unexpected considering all had recently been hospitalized and received antibiotics (primarily β-lactams), factors previously associated with penicillin-resistant pneumococci. Similarly, Rodriguez-Creixems et al found penicillin resistance to be more common among their recurrent cases, although also not statistically significantly so.

Those patients without severe illness were more likely to have recurrences, and this finding approached statistical significance (P = .06). This inverse relationship between severity of illness and recurrence (relative risk, 0.3) may be explained by the fact that severe illness was an independent predictor of mortality in the entire cohort with pneumococcal bacteremia; 56% of those presenting with severe manifestations of disease died, compared with only a 3% mortality in those not presenting with severe manifestations of disease. So, if one did not survive a first episode of pneumococcal bacteremia, he or she would not have the opportunity to develop recurrent bacteremia.

One drawback of this study was that no serotyping of pneumococcal isolates was done. Hence, we were unable to distinguish if these recurrences represented relapses or reinfections. Also, the rate of recurrent pneumococcal bacteremia described herein is greater than that in most previous reports, but it is likely that this rate is an underestimate because it includes only those patients who returned to and were evaluated at our institution. It is probable that some patients, of whom we were unaware, presented to other institutions with recurrent disease.

This series of patients with recurrent pneumococcal bacteremia confirms the previously reported associations with coexistent cancer and HIV infection, and illustrates the newly found association with female sex and the inverse relationship with severity of illness. More than 1 recurrence appears suggestive of HIV infection. When caring for a patient with recurrent pneumococcal bacteremia, clinicians should explore the possibility of an underlying immunocompromising condition, offer HIV testing, search for an occult malignancy, and look for other immunodeficiencies.

Accepted for publication February 22, 2001.

Presented as a poster at the 38th Annual Meeting of the Infectious Diseases Society of America, New Orleans, La, September 8-9, 2000.

Corresponding author: Glenn S. Turett, MD, Section of Infectious Diseases, Department of Medicine, Saint Vincents Hospital and Medical Center, Cronin Bldg, Room 1003, 153 W 11th St, New York, NY 10011 (e-mail: gsturett@onebox.com).

Table 2. Forward Stepwise Logistic Regression Analysis to Determine Factors Independently Associated With Recurrent Pneumococcal Bacteremia

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Odds Ratio (95% Confidence Interval)</th>
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<tr>
<td>Cancer</td>
<td>10.7 (4.8-24.0)</td>
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<tr>
<td>HIV infection</td>
<td>9.1 (4.8-17.5)</td>
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<tr>
<td>Female sex</td>
<td>3.5 (2.1-5.7)</td>
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*Severity of illness was also included in the model but was not an independent predictor. HIV indicates human immunodeficiency virus.

References


