Combination Antibiotic Therapy Lowers Mortality among Severely Ill Patients with Pneumococcal Bacteremia


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Retrospective studies have suggested that combination antibiotic therapy for severe bacteremic pneumococcal pneumonia may reduce mortality. We assessed this issue in a prospective, multicenter, international observational study of 844 adult patients with bacteremia due to Streptococcus pneumoniae. The effect of combination antibiotic therapy versus monotherapy on mortality was examined by univariate analyses and by logistic regression models. The 14-day mortality was not significantly different for the two groups. However, among critically ill patients, combination antibiotic therapy was associated with lower 14-day mortality (23.4 versus 55.3%, p = 0.0015). This improvement in survival was independent of country of origin, intensive care unit support, class of antibiotics, or in vitro activity of the antibiotics prescribed. Combination antibiotic therapy improved survival among critically ill patients with bacteremic pneumococcal illness.

Keywords: bacteremia; community-acquired pneumonia; Streptococcus pneumoniae

Does combination antibiotic therapy improve survival among patients with severe community-acquired pneumonia? As emphasized in one commentary (1), treatment guidelines (2–5) from several authoritative groups support the use of empiric combination antibiotic regimens for patients with severe pneumonia. Combination regimens ensure coverage of Legionella species and “typical” bacterial pathogens. Streptococcus pneumoniae remains the most common cause of death among patients with severe pneumonia and the prognosis is worse for those who develop complicating bacteremia.

Data from three retrospective analyses of patients with bacteremic pneumococcal pneumonia (6–8) suggest that combination antibiotic therapy is associated with reduced mortality as compared with that seen among those who receive only antibiotic monotherapy. In one of the studies (7), adults with severe bacteremic pneumococcal pneumonia had a significantly greater risk of dying if they received monotherapy rather than combination antibiotic therapy on the first day of hospital admission. The remaining two studies (6, 8) focused on the addition of a macrolide to β-lactam antibiotic treatment and also demonstrated improved survival among those who received combination antibiotic therapy.

The authors of the three studies and of associated editorials (1, 9) acknowledged the potential biases and confounding factors that characterize retrospectively conducted treatment assessments. We therefore provide the findings of a prospectively conducted, observational, international investigation that examines the role, if any, of combination antibiotic therapy in reducing the mortality of bacteremic pneumococcal illness. To our knowledge, this work represents the first prospective evaluation of the impact of combination therapy on mortality.

METHODS

Details of this observational study have been presented elsewhere (10), so the following represents an abbreviated version. Between December 1,
1998 and December 31, 2000, 844 consecutive adults with pneumococcal bacteremia were enrolled in 21 hospitals in 10 countries on 6 continents. Patients were monitored for at least 14 days after the first positive blood culture or longer if the patient remained hospitalized.

All patients 15 years of age and older who had at least one blood culture positive for *S. pneumoniae* during the 25-month study period were included. Patients were classified as “elderly” if they were 65 years of age or older; “immunosuppressed” if they had human immunodeficiency virus infection, hematologic malignancy, or an autoimmune disorder, had received either organ or bone marrow transplant or cancer chemotherapy within 4 weeks of pneumococcal bacteremia, or had undergone prior splenectomy; and/or as having “underlying chronic disease” if they had heart, lung, liver, or renal disease or diabetes mellitus. Patients were defined as critically ill as calculated by a Pitt bacteremia score greater than 4, as described previously (10, 11). The APACHE (Acute Physiology and Chronic Health Evaluation System) II score was calculated for patients admitted directly to the intensive care unit (ICU).

Antibiotic therapy was eligible for analysis if the total daily dose of an agent was at least the minimum dose recommended for treatment of systemic infection. Patients who did not receive antibiotic(s) on the day of admission were excluded. Monotherapy was defined as receipt of the same single antibiotic within the first 2 days of obtaining a positive blood culture; likewise, combination therapy was defined as receipt of the same two antibiotics within the first 2 days of positive blood culture. Patients who received no antibiotic therapy or delayed treatment (more than 24 hours after admission), or had no consistent antibiotic regimen (e.g., 1 day of monotherapy plus 1 day of combination therapy) over the initial 2 days of admission were excluded.

Differences in categorical variables were calculated by χ² test with the Yate correction or Fisher exact test. The Kaplan–Meier product limit method was used to construct survival curves for patients receiving combination and monotherapy regimens. The patients were stratified by severity of illness and the survival curves were compared using the Mantel–Cox test (12). A logistic model was used to adjust for additional risk factors in evaluation of the impact of combination therapy on 14-day mortality. Factors associated with increased mortality by univariate analysis were entered into the model in addition to receipt of combination therapy.

**RESULTS**

Eight hundred forty-four consecutive cases of pneumococcal bacteremia were enrolled. Patients were excluded if they received no antibiotic therapy (43); received no antibiotic therapy on Day 2 (30); received delayed (more than 24 hours after admission) antibiotic therapy (23); underwent an inconsistent regimen (e.g., 1 day of monotherapy plus 1 day of combination therapy) (86); or underwent different monotherapy or combination therapy regimens on Day 1 and Day 2 (70). The remaining 592 patients were available for analyses of monotherapy versus combination therapy.

As we have reported previously, 16.5% of patients (139 of 844) died by Day 14 (10). The risk of death was almost eightfold greater for critically ill patients compared with patients who were less ill at hospital admission (54.6 versus 7.3%, p = 0.0001). The 14-day mortality was not significantly different for all patients receiving combination versus monotherapy (10.4 versus 11.5%, p = NS). Among critically ill patients (n = 94), however, combination antibiotic therapy was associated with lower mortality (14-day mortality, 23.4 versus 55.3%, p = 0.0015) (Figure 1). The most common monotherapy regimens prescribed for the critically ill patients were β-lactam agents (43, with 25 receiving a third-generation cephalosporin), azithromycin (2), ciprofloxacin (1), and clindamycin (1). The most frequent combination therapies prescribed were β-lactam/macrolide (14), vancomycin/β-lactam (12), β-lactam/aminoglycoside (7), vancomycin/other antibiotic (4), β-lactam/quinolone (4), double β-lactam therapy (2), β-lactam/chloramphenicol (2), β-lactam/trimethoprim-sulfamethoxazole (1), and clindamycin/quinolone (1).

This difference in mortality remained significant when analyzed according to *in vitro* activity, as defined by the National Committee for Clinical Laboratory Standards (NCCLS), of the monotherapy or combination drug therapy. Penicillin-susceptible isolates (minimal inhibitory concentration, less than 0.12 μg/ml) and penicillin-nonsusceptible isolates (minimal inhibitory concentration, 0.12 μg/ml or more) were distributed equally between the two groups (Table 1). One hundred percent (94 of 94) and 98.9% (93 of 94) were susceptible to ceftriaxone and cefotaxime, respectively, using recent NCCLS breakpoints (13). When all treatments were active *in vitro*, mortality for combination versus monotherapy was 19.4 versus 60% (p = 0.0006), respectively. When at least one of the drugs of the combination therapy was active *in vitro*, mortality for combination therapy versus monotherapy was 18.2 versus 60% (p = 0.0003), respectively. No patient received combination therapy in which both antibiotics were inactive *in vitro*. The demographics for the monotherapy versus combination therapy groups were comparable except for human immunodeficiency virus type and mechanical ventilation (Table 1). When adjusted for mechanical ventilation and human immunodeficiency virus positivity by multivariate analysis, combination therapy remained a significant factor in decreasing mortality (Table 2). Severity of illness as measured by APACHE II or Pitt bacteremia score was essentially identical for the two groups.

One hundred twelve patients were admitted to the ICU on admission; note that not all were critically ill, and therefore the number is not 94. The severity of illness was nearly identical in patients receiving combination therapy and monotherapy (mean Pitt bacteremia score, 5.0 versus 5.5, respectively; APACHE II score, 19.0 versus 19.2, respectively). Nevertheless, the patients...
Penicillin susceptibility
COPD 20% 11.6% NS
Asplenia 2.1% 2.1% NS
Neutropenic 19.1% 11.1% NS
Immunosuppressed† 47.8% 32.6% NS

residuals were also tested for normality using the Shapiro–Wilk test.

mycin (6.3%, p = 0.008).

When therapy was analyzed by country of origin, insufficient statistical power existed for analysis for some individual countries; when the number of cases exceeded 12 in a country, there was a clear-cut trend for superiority of combination therapy in those countries. When adjusted for country, patients receiving combination therapy remained a significant factor in decreasing mortality in logistic regression models (data not shown).

**DISCUSSION**

Findings from this large, prospective, international investigation suggest that the administration of combination antibiotic therapy results in increased survival among critically ill patients with pneumococcal bacteremia (Figures 1A and 1B). There was a more than twofold increase in survival among recipients of combination antibiotic therapy as compared with that for recipients of monotherapy regimens. Receipt of combination therapy and mechanical ventilation were significant factors in improving outcome by both univariate and multivariate analyses. The findings of significant increases in mortality for both critically ill and elderly patients (10), two well recognized subgroups at increased risk of dying, bolster the validity of the study’s principal observation that outcome is improved with combination antibiotic therapy for severely ill patients with pneumococcal bacteremia.

The *in vitro* antibiotic resistance for monotherapy or one of the two antibiotics in the combination regimen did not significantly affect mortality. The clinical impact of *in vitro* resistance as defined by current NCCLS guidelines has been described in an earlier report derived from this study in which penicillin and third-generation cephalosporin *in vitro* resistance was not a risk factor for mortality (10). Specifically, outcomes in both critically ill and noncritically ill patients were not influenced by whether they received concordant or discordant therapy based on pneumococcal *in vitro* susceptibility results.

There are several strengths of the current investigation that are not shared by the three previous retrospectively conducted studies (6–8) that examined the impact of combination therapy on mortality. Our study enrolled 844 consecutive patients who were prospectively enrolled from 21 hospitals in 10 countries of 6 continents between December 1, 1998 and January 2001. In contrast, the three previously published studies (6–8) were retrospectively conducted and enrolled patients from three geographically

**TABLE 1. DEMOGRAPHICS OF THE TWO STUDY GROUPS OF SEVERELY ILL* PATIENTS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Combination (n = 47)</th>
<th>Monotherapy (n = 47)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, &gt; 65 yr</td>
<td>20.0%</td>
<td>16.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital acquired</td>
<td>8.5%</td>
<td>10.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Community acquired</td>
<td>91.5%</td>
<td>89.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Underlying chronic disease†</td>
<td>48.8%</td>
<td>34.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppressed†</td>
<td>47.8%</td>
<td>32.6%</td>
<td>NS</td>
</tr>
<tr>
<td>HIV</td>
<td>11.4%</td>
<td>37.0%</td>
<td>0.01</td>
</tr>
<tr>
<td>Neutropenic</td>
<td>19.1%</td>
<td>11.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Asplenia</td>
<td>2.1%</td>
<td>2.1%</td>
<td>NS</td>
</tr>
<tr>
<td>COPD</td>
<td>20%</td>
<td>11.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Penicillin susceptibility in vitro‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistant</td>
<td>13.0%</td>
<td>13.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Intermediate</td>
<td>17.4%</td>
<td>16.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Sensitive</td>
<td>69.6%</td>
<td>69.8%</td>
<td>NS</td>
</tr>
<tr>
<td>High-level resistance</td>
<td>12.8%</td>
<td>12.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>78.7%</td>
<td>51.1%</td>
<td>0.01</td>
</tr>
<tr>
<td>APACHE score, mean ± SE</td>
<td>19 ± 1.1</td>
<td>19 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Pitt bacteremia score, mean ± SE</td>
<td>6.6 ± 0.3</td>
<td>6.3 ± 0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** APACHE = Acute Physiology and Chronic Health Evaluation System; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

*Severely ill, defined as Pitt bacteremia score > 4.
† Immunosuppressed and underlying chronic disease are defined in Methods.
‡ Penicillin susceptibility in vitro: high-level resistance, minimal inhibitory concentration (MIC) > 3 µg/ml; resistant, MIC > 2 µg/ml; intermediate, MIC = 0.12–1 µg/ml; susceptible, MIC < 0.12 µg/ml.

Receiving combination therapy had a significantly lower 14-day mortality than those receiving monotherapy (8.2 versus 23.1%, p = 0.03). The superiority of combination therapy was also evident in various logistic regression models of ICU patients (data not shown).

The combination regimens were further examined to determine whether the difference seen in mortality rates between the two groups of critically ill patients was due to a specific antibiotic or combination of antibiotics. This was not the case; when compared with monotherapy, mortality rates were lower for antibiotic combinations that included β-lactams (26.8%, p = 0.007), vancomycin (6.3%, p = 0.0006), or macrolides (14.3%, p = 0.007).

**TABLE 2. LOGISTIC REGRESSION MODELS ASSESSING COMBINATION THERAPY**

<table>
<thead>
<tr>
<th>Survival</th>
<th>Odds Ratio</th>
<th>SE</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for HIV Status*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>3.2</td>
<td>1.7</td>
<td>0.028</td>
<td>1.1–9.2</td>
</tr>
<tr>
<td>HIV</td>
<td>0.09</td>
<td>0.06</td>
<td>0.000</td>
<td>0.02–0.3</td>
</tr>
<tr>
<td>Adjusted for mechanical ventilation†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>2.9</td>
<td>1.5</td>
<td>0.04</td>
<td>1.1–7.7</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>8.1</td>
<td>4.2</td>
<td>0.0001</td>
<td>3.0–2.2</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** CI = confidence interval; HIV = human immunodeficiency virus.

Variables that were evaluated in the logistic models were those that were significant in univariate analysis at the 0.05 level. The end point was survival at Day 14. There were no significant interactions between the main effects in the models. Main effects did not show collinearity. The models were tested for goodness of fit using the Pearson χ² and the deviance χ². The standard deviance residuals were also tested for normality using the Shapiro–Wilks test.

* Combination antibiotic therapy had a significant positive association with survival even when adjusted for HIV status.
† Combination antibiotic therapy had a significant positive association with survival even when adjusted for mechanical ventilation.
confined areas, two (6, 7) of which were in the United States and one in Spain (8). The applicability of findings from these earlier investigations may be limited because case-fatality rates of community-acquired bacteremic pneumococcal illness differ greatly by geographic locale (14). The numbers of patients included in these three trials were fewer than that enrolled in our study. Our patient enrollment was performed more recently in the era of increasing antibiotic resistance, whereas the other studies were performed in 1978, 1991, and 1996, respectively. A retrospective analysis of a hospital claims-made database, which included more than 44,000 patients seen between 1997 and 1999 for community-acquired pneumonia, also found that combination antibiotic therapy reduced mortality (15).

It should be noted that the definition of combination antibiotic therapy was only 1 day in the Waterer and coworkers study (7) and was not specified in the other two retrospective studies (6, 8). Although our analyses given in the Results applied to the 2-day definition of duration of antibiotic therapy, we also assessed the impact of combination therapy 1 and 3 days after admission because our previous study showed that 64.5% of these patients died not more than 72 hours after blood culture had been obtained (10). Mortality for combination therapy remained significantly lower for all durations used (Results). We evaluated quality of support services other than antibiotics by analyzing a subgroup of patients admitted to the ICU. Again, combination therapy led to significantly lower mortality than monotherapy. Finally, mortality was significantly lower for combination therapy versus monotherapy when controlled for ICU admission and country of origin.

There were limitations to our study. First, as with other studies exploring this issue, these results were not from a randomized controlled study. However, the combination and monotherapy groups were generally comparable (Table 1), and severity of illness as measured by APACHE II and Pitt bacteremia scores was identical.

Second, we were unable to define optimal duration of combination therapy because antibiotic therapy was changed in 35% of patients by Day 5. Patients receiving monotherapy who were doing poorly often received additional antibiotics, whereas patients receiving combination therapy often had antibiotics tapered because of knowledge of in vitro susceptibility or improvement in clinical status.

Third, we were unable to clearly delineate the basis for the superiority of the combination regimen, and we were unable to precisely determine which specific components of combination therapy would be most effective. Earlier retrospective analyses (6, 8) of two smaller study populations suggested that the addition of a macrolide to a β-lactam was the best combination regimen. In our study not only were regimens that included macrolides as one of the combination agents associated with better outcomes, but macrolide combination regimens were also successful in reducing mortality among the severely ill patients. Thus, the unique role of macrolides possessing antiinflammatory activity and/or coverage against atypical pathogens postulated by other investigators could not be supported.

In the report of a retrospective study of pneumococcal bacteremia, Austrian and Gold demonstrated that some patients, despite appropriate antibiotic therapy and critical supportive care (as was available more than four decades ago), “cannot be prevented from dying” (16). It is difficult to make direct comparisons between this retrospective study (14) and our prospective observational study. Nevertheless, the dramatic reduction in early mortality among severely ill patients in our current investigation has led us to speculate that combination antibiotic therapy might salvage some critically ill patients who might be otherwise “destined to die” (6). We emphasize that the potential benefits of combination antibiotic therapy in our study and in the Waterer and coworkers study (7) were limited to more severely ill patients. For noncritically ill patients, there was no difference in the 14-day mortality for patients treated with monotherapy versus combination therapy (Figure 1A). Because the overall mortality of patients with mild illness due to bacteremic pneumococcal illness is so low, minimal benefit will be gained by adding a second antibiotic. As mentioned, the optimal duration of combination therapy is undefined, but because mortality is highest within the first 3 days (Figure 1) (10), it seems both intuitive and reasonable that 3–5 days might be sufficient. If our conclusions are confirmed by other prospective studies, we recommend that clinicians target combination antibiotic treatment only for those patients who are critically ill, and limit the duration of the combination to 3–5 days. Such an approach may be beneficial yet minimize antibiotic overuse.

Conflict of Interest Statement: L.M.B. received $10,660 from Bristol-Myers Squibb for 2001 and $5,000 for 2002 for speaking at conferences and received $4,500 in 2001 and $7,000 in 2002 from Schering for speaking at conferences; V.L.Y. declares that Roche is providing funding for a study of bacterial meningitis that is distinct from this study and that the submitted study was unfunded; K.P.K. has served as a consultant, member of an advisory board, and attended symposia sponsored by Abbott Laboratories, Bayer Corporation, Bristol-Myers Squibb Company, GlaxoSmithKline Pharmaceuticals, Aventis, and Wyeth Ayerst Laboratories and his research unit currently receives research funding from Roche, Bayer, Aventis, and Otsice Pharmaceuticals and he has served as an expert witness for GSK and GENESOFT; C.F. has acted on the advisory board of pharmaceutical companies marketing antibiotics (Abbott, Aventis, Bristol-Meyers Squibb, Pfizer/Phar- macia, and MSD), has been reimbursed for lectures sponsored by pharmaceutical companies (Pfizer, Abbreviated, Mead-Johnson, Aventis, and MSD), and has attended conferences sponsored by pharmaceutical companies (Abbott, Bristol-Meyers Squibb, Aventis, Pfizer, and GlaxoSmithKline); A.O. received two $2,000 in 2001 and $2,000 in 2002 for serving on an advisory board for Bayer and $1,000 in 2001 for speaking at conferences sponsored by Bayer; J.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.B.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.M. has participated as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies (Merck, Sharpe & Dohme; Bayer; Pfizer; Bristol-Myers; and Squibb); D.R.S. has received unrestricted and restricted research support from Merck, Astra Zeneca, Pfizer, and Bayer in 2003 and 2004 and from Wyeth Ayerst in 2004 and has lectured on behalf of Bayer, Merck, Roche, and Pfizer in the past year; W.C.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.B.F.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.S.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.A. has a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.C.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.C.X. declares that Roche is providing funding for a study of bacterial meningitis that is distinct from this study and that the submitted study was unfunded; J.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.B.F.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; L.T.D. has been a consultant for the past 5 years for Gilead Sciences, Inc. and has received grants from Gilead Sciences, Inc. for research; J.D. has received grant support from: Genentech, Inc., Genzyme Corporation, the National Institute of General Medical Sciences, and the National Cancer Institute.

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