Monotherapy May Be Suboptimal for Severe Bacteremic Pneumococcal Pneumonia

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Background: Although monotherapy for pneumococcal pneumonia is standard, a survival benefit of combination β-lactam and macrolide therapy has been suggested.

Hypothesis: Initial empirical therapy with a combination of effective antibiotic agents would have a better outcome than a single effective antibiotic agent in patients with bacteremic pneumococcal pneumonia.

Methods: A review of adult bacteremic pneumococcal pneumonia within the Methodist Healthcare System, Memphis, Tenn, between January 1, 1996, and July 31, 2000. Empirical therapy was defined as all antibiotic agents received in the first 24 hours after presentation. On the basis of culture results, empirical therapy was classified as single effective therapy (SET), dual effective therapy (DET), or more than DET (MET). Acute Physiology and Chronic Health Evaluation II (APACHE II)–based predicted mortality, and Pneumonia Severity Index scores were calculated.

Results: Of the 225 patients identified, 99 were classified as receiving SET, 102 as receiving DET, and 24 as receiving MET. Compared with the other groups, patients who received MET had statistically significantly more severe pneumonia as measured by the Pneumonia Severity Index score \( (P = .04) \) and predicted mortality \( (P = .03) \). Mortality within the SET group was significantly higher than within the DET group \( (P = .02, \text{ odds ratio, } 3.0 \ [95\% \text{ confidence intervals, } 1.2-7.6]) \), even when the DET and MET groups \( (P = .04) \) were combined. In a logistic regression model including antibiotic therapy and clinical risk factors for mortality, SET remained an independent predictor of mortality with a predicted mortality–adjusted odds ratio for death of 6.4 (95% confidence intervals, 1.9-21.7). All deaths occurred in patients with a Pneumonia Severity Index score higher than 90, and the predicted mortality–adjusted odds ratio for death with SET in this subgroup was 5.5 (95% confidence intervals, 1.7-17.5).

Conclusions: We found that SET is associated with a significantly greater risk of death than DET. Therefore, monotherapy may be suboptimal for patients with severe bacteremic pneumococcal pneumonia who have Pneumococcal pneumonia Severity Index scores higher than 90.

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SUBJECTS, MATERIALS, AND METHODS

STUDY DESIGN AND SUBJECTS

We performed a retrospective case analysis based on data available in the subjects’ medical records. Subjects were all patients age 18 years or older admitted to hospitals within the Methodist Le Bonheur Healthcare System, Memphis, Tenn, with a diagnosis of CAP and pneumococcal bacteremia between January 1, 1996, and July 31, 2000. Three tertiary, 2 secondary, and 8 rural community hospitals comprise the Methodist Le Bonheur Healthcare system. Patients with blood cultures positive for pneumococci were identified from a microbiological database and the medical records were then reviewed to determine whether they met the enrollment criteria for inclusion in the study.

INCLUSION CRITERIA

All patients with a diagnosis of CAP and at least 1 positive blood culture for *S pneumoniae* taken within 48 hours of presentation to the hospital were included in the analysis. To be diagnosed with CAP, patients had to have had an acute illness (<10 days of symptoms), a new chest radiographic infiltrate confirmed by a radiologist, and clinical signs suggestive of acute pneumonia including either 1 major criterion of fever (temperature, >37.8°C), hypothermia (temperature, <36.0°C), cough, or sputum production or 2 minor criteria of dyspnea, pleuritic pain, clinical evidence of lung consolidation, and a leukocyte count of higher than 10,000 cells/µL or lower than 4,500 cells/µL. These criteria are consistent with published guidelines for diagnosing CAP.11

EXCLUSION CRITERIA

Exclusion criteria included patients with severe immunodeficiency as defined by the Centers for Disease Control and Prevention criteria12 for patients with acquired immunodeficiency syndrome; patients receiving chemotherapy in the past 60 days; patients receiving treatment with corticosteroids equivalent to more than 20 mg/d of prednisolone for longer than 14 days; patients receiving immunosuppression following organ transplantation; patients receiving cyclosporine, ciclosporinamide, or azathioprine; and patients hospitalized within the past 30 days. We also excluded any subject who did not receive at least 1 dose of antibiotic agents within the first 24 hours after presentation, and any subject whose pneumococcal isolate was resistant to the initial antibiotic therapy chosen.

Use of combination antibiotic therapy is not uncommon in the treatment of CAP. The potential for a drug-resistant isolate is the principal indication for combination therapy. In addition, increasing recognition of polymicrobial CAP, particularly combinations of *Streptococcus pneumoniae* and atypical pathogens such as *Legionella* spp and *Mycoplasma pneumoniae*.8,11 suggests that a significant proportion of patients, even with bacteremic *S pneumoniae* pneumonia, may have additional pathogens not covered by β-lactam monotherapy.

Combination therapy has not generally been recommended when pneumonia is known to be caused by antibiotic-sensitive *S pneumoniae*. However, 1999 data suggested that patients with bacteremic pneumococcal CAP treated with a combination of a β-lactam and a macrolide may have a better outcome.9

DATA COLLECTION

Demographic data, medical history, clinical features at presentation, antibiotic treatment, daily vital signs, microbiological culture results, and outcome were all recorded. Clinical data sufficient to calculate both the Acute Physiology and Chronic Health Evaluation II (APACHE II) score13 and the Pneumonia Severity Index (PSI) score as defined by Fine et al14 were collected. The PSI score was calculated from data available at the time of admission. The APACHE II scores were calculated from the worst physiological scores during the first 24 hours after presentation. Predicted mortality (PM) was calculated based on the APACHE II score.13

Empirical antibiotic therapy was defined as any antibiotic therapy administered within the first 24 hours after presentation to the hospital. Based on the subsequent culture and sensitivity results, empirical antibiotic therapy was classified as single effective therapy (SET), dual effective therapy (DET), or more than DET (MET).

DEFINITIONS OF RESISTANCE

The antibiotic sensitivity of isolates from all hospitals was determined at a central laboratory. All isolates are classified as antibiotic resistant according to the 2000 guidelines of the National Committee for Clinical Laboratory Standards.15 Definitions of resistance for the main antibiotic agents used were penicillin, minimum inhibitory concentration (MIC) 2 µg/mL or higher (high-level resistance); cefotaxime sodium and/or ceftriaxone sodium, 2 µg/mL or higher; erythromycin lactobionate, 1 µg/mL or higher; and levofloxacin, 2 µg/mL or higher. Although debate exists regarding the applicability of in vitro definitions of antibiotic resistance, we chose the conservative definitions to favor the null hypothesis, including classifying all macrolides according to the level of resistance to erythromycin.

DATA ANALYSIS

Univariate analysis was performed using GraphPad (In-Stat Version 3.01; GraphPad Software Inc, San Diego, Calif). Differences in continuous variables were assessed using a 2-tailed t test after confirming they were normally distributed. Differences in categorical variables were calculated using the Fisher exact test. *P*<.05 was considered statistically significant. Odds ratios (ORs) are expressed as ORs (95% confidence intervals [CIs]).

To control for potential confounding factors, a multivariate logistic regression analysis was performed evaluating the possible covariates of antibiotic therapy, age, sex, underlying chronic disease (history of cardiac disease, renal disease, chronic obstructive pulmonary disease, liver disease, cerebrovascular disease, or neoplastic disease), excess alcohol consumption, and APACHE II–based PM was performed. The calculated ORs and 95% CIs after adjusting for confounding factors are expressed as an approximation of relative risk.
In our institution, we have observed that physicians usually follow the published antibiotic guidelines in patients with mild to moderate CAP, but the use of multiple antibiotics in excess of guidelines increases with the severity of the pneumonia. This allowed us to test the hypothesis that the use of a combination of effective antibiotic agents as empirical therapy is superior to a single effective antibiotic agent in patients with bacteremic pneumonia. Effective antibiotic agents in patients with bacteremic pneumonia are usually follow the published antibiotic guidelines in patients with mild to moderate CAP, but the use of multiple antibiotics in excess of guidelines increases with the severity of the pneumonia. This allowed us to test the hypothesis that the use of a combination of effective antibiotic agents as empirical therapy is superior to a single effective antibiotic agent in patients with bacteremic pneumonia.

Two hundred twenty-five subjects met the inclusion criteria for analysis. A further 7 cases of CAP with pneumococcal bacteremia were identified but were excluded because the isolate was resistant to the empirical therapy the patient received. A summary of demographic information, severity indices, and outcome by empirical antibiotic therapy classification is listed in Table 1. The subjects who received MET were significantly sicker than the subjects who received SET or DET as measured by the PSI (P = .04) and APACHE II–based PM (P = .03). Data in Table 2 demonstrate that there was no statistically significant difference between the prevalence of chronic disease states between the SET and DET groups.

Table 1. Comparison of Severity Indices in Each Empirical Antibiotic Therapy Group*

<table>
<thead>
<tr>
<th>Variable</th>
<th>SET Group (n = 99)</th>
<th>DET Group (n = 102)</th>
<th>MET Group (n = 24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, No. (%)</td>
<td>18 (18.2)</td>
<td>7 (6.9)</td>
<td>4 (16.7)</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Age, y</td>
<td>61.3 ± 17.8</td>
<td>61.1 ± 19.6</td>
<td>56.5 ± 17.5</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>APACHE II score†</td>
<td>13.9 ± 6.9</td>
<td>14.6 ± 6.9</td>
<td>16.6 ± 8.8</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>PSI score†</td>
<td>96.5 ± 41.5</td>
<td>101.4 ± 39.0</td>
<td>116.8 ± 50.8</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Predicted mortality, %</td>
<td>21.6 ± 17.4</td>
<td>23.2 ± 16.4</td>
<td>28.5 ± 23.0</td>
<td>&gt;.1</td>
</tr>
</tbody>
</table>

*All data are given as mean ± SD unless otherwise stated. SET indicates single effective therapy; DET, dual effective therapy; and MET, more than DET. For further explanation see “Subjects, Materials, and Methods” section.
†APACHE II indicates Acute Physiology and Chronic Health Evaluation II; PSI, Pneumonia Severity Index.

Table 2. Chronic Organ Failure in the SET and DET Groups*

<table>
<thead>
<tr>
<th>Variable</th>
<th>SET Group (n = 99)</th>
<th>DET Group (n = 102)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>12 (12.1)</td>
<td>15 (14.7)</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>7 (7.1)</td>
<td>12 (11.8)</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>2 (2.0)</td>
<td>3 (2.9)</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>11 (11.1)</td>
<td>14 (13.7)</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (17.2)</td>
<td>19 (18.6)</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>14 (14.1)</td>
<td>16 (15.7)</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Chronic obstructive</td>
<td>21 (21.2)</td>
<td>22 (20.6)</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>pulmonary disease</td>
<td>&gt;2 Chronic diseases</td>
<td>14 (14.1)</td>
<td>&gt;.1</td>
</tr>
</tbody>
</table>

*SET indicates single effective therapy; DET, dual effective therapy.
†APACHE II (Acute Physiology and Chronic Health Evaluation II)–based predicted mortality minus mean (SD).

In our institution, we have observed that physicians usually follow the published antibiotic guidelines in patients with mild to moderate CAP, but the use of multiple antibiotics in excess of guidelines increases with the severity of the pneumonia. This allowed us to test the hypothesis that the use of a combination of effective antibiotic agents as empirical therapy is superior to a single effective antibiotic agent in patients with bacteremic pneumococcal CAP.

In the SET group (n = 99), 18 (18.2%) died. The plot of mortality over time for each antibiotic therapy group shows a Kaplan-Meier plot of mortality over time for each antibiotic therapy group. Mortality with the SET group was significantly higher than with the DET group (P = .02; OR, 3.0 [95% CI, 1.2-7.6]). Even when the DET and MET groups are combined, the mortality was still significantly higher in the DET group (P = .04; OR, 2.3 [95% CI, 1.0-5.2]). Because only a few subjects received MET and the subjects who received MET were significantly sicker than the other subjects, subsequent analysis is confined to the SET and DET groups.

Because subjects who received SET had a lower PM than those who received DET, we used a logistic regression model to calculate the OR for death of SET vs DET adjusted for PM, which was 6.4 (95% CI, 1.9-21.7). All deaths occurred in patients with a PSI score higher than 90 (PSI classes IV and V). In subjects with PSI class IV

Table 3. Antibiotic Therapy in the SET and DET Groups*

<table>
<thead>
<tr>
<th>Antibiotic therapy</th>
<th>No. of Subjects</th>
<th>Mortality, No. (%) of Subjects</th>
<th>Predicted Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SET Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third-generation cephalosporin</td>
<td>55</td>
<td>7 (12.7)</td>
<td>19.3 (13.5)</td>
</tr>
<tr>
<td>+ macrolide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third-generation cephalosporin + quinolone</td>
<td>25</td>
<td>6 (24.0)</td>
<td>25.8 (23.1)</td>
</tr>
<tr>
<td>+ vancomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third-generation cephalosporin + other</td>
<td>7</td>
<td>0</td>
<td>21.3 (9.0)</td>
</tr>
<tr>
<td>+ vancomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third-generation cephalosporin + other</td>
<td>1</td>
<td>1 (100)</td>
<td>22.3 (24.1)</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
<td>18 (18.2)</td>
<td>21.6 (17.4)</td>
</tr>
<tr>
<td><strong>DET Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third-generation cephalosporin + macrolide</td>
<td>41</td>
<td>2 (4.9)</td>
<td>18.3 (12.3)</td>
</tr>
<tr>
<td>Third-generation cephalosporin + quinolone</td>
<td>20</td>
<td>3 (15.0)</td>
<td>25.0 (16.8)</td>
</tr>
<tr>
<td>+ vancomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third-generation cephalosporin + other</td>
<td>12</td>
<td>1 (8.3)</td>
<td>30.0 (25.3)</td>
</tr>
<tr>
<td>+ vancomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third-generation cephalosporin + other</td>
<td>7</td>
<td>0</td>
<td>35.1 (20.4)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolone + quinolone + vancomycin</td>
<td>6</td>
<td>0</td>
<td>11.8 (5.9)</td>
</tr>
<tr>
<td>Quinolone + other + β-lactam</td>
<td>4</td>
<td>0</td>
<td>18.3 (3.5)</td>
</tr>
<tr>
<td>Quinolone + macrolide + β-lactam</td>
<td>2</td>
<td>0</td>
<td>11.0 (5.7)</td>
</tr>
<tr>
<td>Quinolone + macrolide</td>
<td>2</td>
<td>0</td>
<td>30.5 (2.1)</td>
</tr>
<tr>
<td>Quinolone + other</td>
<td>2</td>
<td>0</td>
<td>24.0 (8.9)</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>1 (16.7)</td>
<td>38.2 (13.7)</td>
</tr>
<tr>
<td>Total</td>
<td>102</td>
<td>7 (6.9)</td>
<td>23.2 (16.4)</td>
</tr>
</tbody>
</table>

*SET indicates single effective therapy; DET, dual effective therapy; "APACHE II (Acute Physiology and Chronic Health Evaluation II)–based predicted mortality minus mean (SD)."
or V CAP who were given SET, the PM-adjusted OR for death was 5.5 (95% CI, 1.7-17.5).

As antibiotic therapy would be expected to have little influence on early deaths, we reanalyzed SET vs DET groups after excluding all deaths that occurred within 48 hours of presentation (n=4, 3 in the SET group and 1 in the DET group). Univariate analysis of this subgroup showed a trend to better outcome with DET compared with SET (94% survival vs 85%, respectively, P=.06). Multivariate analysis again confirmed that SET was an independent predictor of worse outcome (P=.01), with the PM-adjusted OR for death in subjects given SET being 4.9 (95% CI, 1.6-18.3).

Subgroup analysis did not show any significant trends to suggest any advantage or disadvantage of any specific antibiotic agents or combinations of antibiotic agents. One hundred seventy-two subjects (76.4%) were given antibiotic coverage for atypical organisms (ie, Legionella spp, M pneumoniae, or Chlamydia pneumoniae). Seventeen (9.9%) of these 172 patients died, compared with 12 (22.6%) of the 53 subjects without atypical coverage (P=.02), although culture and serological studies were not performed to confirm or exclude the presence of these pathogens. Subjects who did not receive coverage for atypical organisms had a significantly higher PM (27.3% vs 21.8%, P=.047), which was also reflected in a trend to higher APACHE II (15.9 vs 14.1, P=.09) and PSI scores (110.1 vs 98.1, P=.07). In a multivariate nominal regression model, coverage of atypical organisms was not a significant predictor of outcome when corrected for PM at presentation (P=.17).

We have found that patients with bacteremic pneumococcal CAP who receive at least 2 effective antibiotic agents within the first 24 hours after presentation to a hospital have a significantly lower mortality than patients who receive only 1 effective antibiotic agent. In fact, among high-risk patients (PSI class IV or V), receiving only 1 effective antibiotic agent increases mortality over 5-fold compared with patients receiving 2 effective antibiotic agents. Although our findings need to be confirmed by a prospective study, current approaches to the empirical therapy of severe CAP may need to be reevaluated.

Increasing antibiotic resistance in pneumococci, particularly to penicillin, has become a problem worldwide, leading to the increased use of broad-spectrum antibiotic agents, including the newer fluoroquinolones as empirical therapy for CAP. Controversy exists over the current in vitro MIC susceptibility guidelines for S pneumoniae, with a widely held view that the cutoff of 2 µg/mL for penicillin is too low in patients with pneumonia. However, in our study, we chose to remove antibiotic resistance as a factor by excluding all subjects who did not receive at least 1 antibiotic agent in the first 24 hours to which the pneumococcal isolate was sensitive. Furthermore, we deliberately chose conservative definitions of antibiotic resistance that would have favored the SET group.

Many potential mechanisms may explain a benefit of DET over SET. Although sensitive pneumococci are rapidly killed by antibiotics in normal hosts, a synergistic combination of antibiotic agents may still be valuable in critically ill or immunocompromised hosts. The combination of a β-lactam and an aminoglycoside has been shown to reduce mortality in patients with bactere mic Klebsiella species pneumonia. Synergy has been demonstrated for cefotaxime and vancomycin hydrochloride against some isolates of pneumococci, but this combination represented only 8% of the DET group. Synergy has been shown between many quinolones and vancomycin against pneumococci, although not levofloxacin and vancomycin, the only combination used in our subjects. Most patients in the DET group received either a macrolide-cephalosporin or quinolone-cephalosporin combination. To our knowledge, no studies showing synergistic effects of these combinations have been published. Whether an additive but nonsynergistic combination could be sufficient to have an influence on mortality in a critically ill host is unknown.

Although the MICs indicated the pneumococcal isolates were antibiotic sensitive, there may still be significant differences in the rate of death of pneumococci after antibiotic exposure, which may, in turn, influence the outcome. Using time-kill studies, different strains of S pneumoniae have been shown to have different rates of death following antibiotic exposure in experimental meningitis. Similarly, although the MIC value may indicate that the pneumococcal isolate is susceptible to an antibiotic agent, bacterial death following antibiotic exposure does not necessarily occur. Up to 20% of pneumococcal isolates within our community exhibit antibiotic tolerance, and a completely tolerant bacteria may be missed by disk diffusion testing. In the event that the infecting pneumococcal strain was penicillin tolerant, a second antibiotic agent may be clearly beneficial.

Apart from synergy, interaction between antibiotic agents with respect to the modulation of the immune response to pneumococcal infection may also be important. Compared with other classes of antibiotic agents, β-lactam therapy results in significantly greater endotoxin release and subsequent cytokine production, including tumor necrosis factor α, in patients with gram-negative sepsis. In mice with pneumococcal meningitis, cefotaxime and vancomycin were superior to cefotaxime alone. Thestdio effects of the combination were indicated in the mortality rate of mice treated with both agents compared with mice treated with vancomycin alone (P<.05). The in vitro and in vivo results suggest that β-lactam agents and aminoglycosides may be synergistic against some pneumococcal isolates. Whether the in vivo results observed in mice can be extrapolated to patients is unknown. Whether the efficacy of a synergistic combination of β-lactam agents and aminoglycosides varies with the in vitro susceptibility of the pneumococcal isolate is also unknown. Further studies are needed to determine whether the in vivo results of synergy with in vitro results.

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disease, significantly less tumor necrosis factor α accumulation occurs in macrophages following clindamycin hydrochloride compared with oxacillin sodium. Greater or more rapid release of bacterial products may cause or exacerbate proinflammatory complications of sepsis, such as septic shock. Macrolides were the second antibiotic agents in 46% of the DET regimens, but only 8% of the SET regimens. The potential anti-inflammatory or immunomodulatory properties of macrolides, including the reduction of tumor necrosis factor α production, may also be relevant, particularly in patients with severe sepsis. Another potential benefit of macrolides is the finding that subinhibitory concentrations of erythromycin reduce the adherence to and disruption of respiratory epithelial cells by pneumococci. Other antibiotic classes may also have beneficial immunomodulatory properties in pneumococcal disease, further increasing the possibility that antibiotic-host interactions may be responsible for some or all of the benefit of DET.

The coexistence of multiple pathogens in patients with CAP seems to be common and could also explain an advantage of DET over SET. Because diagnostic studies for atypical pathogens were not performed, we cannot exclude coinfection with an atypical pathogen as a confounding factor. However, multivariate analysis suggested that coverage of these organisms did not contribute to the apparent benefit of DET over SET. Dual effective therapy with a quinolone may also be advantageous if a coinfection of S pneumoniae with other commonly antibiotic-resistant pathogens, such as Hemophilus influenzae or K pneumoniae existed. However, equivalence of quinolone and macrolide combinations would suggest this is not a major determinant.

Another explanation for our findings is that rather than DET being superior, the SET administered may have been inadequate. Although in vitro techniques confirmed the appropriateness of antibiotic therapy in subjects given SET, concern has been expressed over the adequacy of the standard dose (500 mg/d) of levofloxacin prescribed in the United States, particularly in patients with severe sepsis. We did not find an excess mortality for patients with levofloxacin-based SET compared with other SET regimens. It is possible that the newer quinolones such as gatifloxacin and moxifloxacin, which have lower MICs against pneumococci and more favorable pharmacodynamic properties, may be more effective SET in pneumococcal disease, but, to our knowledge, there are no clinical trials to support this.

Because of the retrospective nature of our analysis, care must be taken not to over interpret the results. Although there are many potential sources of bias, both the univariate and multivariate analyses strongly suggest that patients receiving SET had less severe pneumonias than patients receiving DET. Also, no difference in the prevalence of chronic organ disease between the groups existed. Although a systematic bias toward DET is unlikely, one potential confounding factor, which we could not control for, is the time taken to receive the first dose of effective antibiotic agents, since a delay in the institution of an antibiotic agent is associated with higher mortality. An additional limitation of our study is that a wide range of antibiotic agents and antibiotic combinations were used, making it impossible to draw any conclusions about specific antibiotic agents or antibiotic regimens. It was interesting that the lowest mortality was seen in in subjects receiving the combination therapy of cefalosporin-macrolide, in keeping with the findings of Mufson and Stanek. The optimal duration of DET could also not be determined as patients were classified as receiving MET, DET, or SET based on antibiotic treatment received in the first 24 hours after presentation. Subsequent changes in antibiotic therapy may be an additional confounding factor, although historical data suggest that any change in antibiotic therapy would take several days to have any influence on outcome, limiting the potential influence since 50% of the deaths occurred before day 5.

Trials comparing the combination of a cephalosporin and a macrolide with a quinolone have not shown any advantage of combination therapy, but the number of subjects with pneumococcal bacteremia in each of these studies was small. As the newer fluoroquinolones cover atypical pathogens as well as S pneumoniae, until now there has been no justification for any trial investigating the efficacy of these agents combined with cephalosporins.

Only a prospective, randomized, double-blind trial will resolve whether DET is truly more effective than SET for bacteremic pneumococcal pneumonia. However, the strength of the association we have demonstrated provides significant justification for undertaking such a trial. As SET was adequate therapy in patients with a PSI score lower than 90, a prospective trial should focus on patients with PSI class IV or V CAP. Newer diagnostic tools such as pneumococcal urinary antigen testing, and the rapid detection of pneumococcal DNA in serum by polymerase chain reaction-based techniques, will make it easier to identify subjects with CAP who are most likely to have pneumococcal bacteremia.

After accounting for antibiotic resistance, we have found a substantial benefit of DET over SET for patients with bacteremic pneumococcal pneumonia. The finding that subjects receiving a SET, after adjusting for the severity of pneumonia, were 6.4 times more likely to die of their illness is a strong argument for a randomized, double-blind, prospective study of combination therapy vs SET in patients suspected of having bacteremic pneumococcal pneumonia.

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