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CONCISE ARTICLE

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Lack of effect of combination antibiotic therapy on mortality in patients with pneumococcal sepsis

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Abstract In order to determine whether combination antibiotic therapy decreases mortality after severe pneumococcal infection, a retrospective study of a cohort of 1,840 adult patients with severe sepsis or septic shock enrolled in two multicenter clinical trials between 1994 and 1999 was conducted. Among 107 patients with monobacterial pneumococcal sepsis, the case-fatality rate was 20% (five of 25) for patients who received antibiotic monotherapy compared with 19.5% (16 of 82) for patients who received combination therapy (adjusted hazard ratio, 1.1; 95% CI, 0.4–3.1). Similarly, monotherapy did not increase the risk of death (adjusted hazard ratio, 1.0; 95% CI, 0.2–4.8) among bacteremic patients (n=75). However, the latter analysis may have been underpowered (power, 58%) to detect a difference in mortality. Overall, in contrast to recently published reports, these results suggest that combination antibiotic therapy does not decrease mortality after severe pneumococcal sepsis.

Introduction

Severe pneumococcal sepsis remains a therapeutic challenge despite advances in supportive treatment. Several recently published studies have suggested that combination antibiotic therapy may improve survival among critically ill patients with pneumococcal bacteremia [1–3]. Among these, one international study including 844 patients from ten countries observed that among 94 critically ill patients, the 14-day mortality was 55% for patients receiving monotherapy compared with 23% for those receiving different regimens of combination therapy (adjusted odds ratio, 2.9; 95% confidence interval [CI] 1.1–7.7) [3]. Based on these findings, several experts have recommended that clinicians should consider combination antibiotic therapy for suspected or confirmed pneumococcal sepsis [3, 4].

To test this hypothesis and to assess the impact of antibiotic monotherapy on survival after life-threatening pneumococcal sepsis, we conducted a retrospective study of a cohort of critically ill patients with severe sepsis or septic shock caused by *Streptococcus pneumoniae*, who were enrolled in two large clinical trials between 1994 and 1999 [5, 6].

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Patients and methods

We reviewed a database containing data collected prospectively from 1,840 adult patients with severe sepsis or septic shock, who were enrolled in two placebo-controlled multicenter trials to determine the safety and efficacy of p55 IgG tumor necrosis factor receptor fusion protein (lenercept) [5, 6]. In the final analysis, there was no significant difference in 28-day mortality between patients treated with placebo or lenercept [6]. Inclusion criteria, details of the study design, and results of the trials have been published elsewhere [5–7].

For the current retrospective analysis, we included all patients >18 years of age who had severe sepsis or septic shock caused by monobacterial, pneumococcal illness (with or without positive blood cultures). The infection was considered to be caused by *S. pneumoniae* when this organism was isolated from pure culture of a clinically relevant sample [8]. Patients with neutropenia secondary to chemotherapy, HIV infection and corticosteroid use (>1 mg/kg/day) were excluded. Severity of illness at baseline was calculated using a mortality risk prediction model based on the Simplified Acute Physiology Score II [6].

We defined monotherapy as receipt of a single antimicrobial agent within the first 48 h of treatment after study inclusion, whereas combination therapy was defined as

receipt of the same two agents during the first 48 h of treatment [3]. As suggested by Baddour et al. [3], patients who had inconsistent treatment regimens and changes in antimicrobial treatment after 24 h of therapy were excluded.

All patients received full standard supportive care and antibiotic therapy. Antibiotic susceptibility testing was performed at each participating institution. Organisms reported as intermediately susceptible to a particular antibiotic were classified as sensitive for this report. The primary study endpoint was the 28-day all-cause mortality.

We used the Student *t* test to compare continuous variables and the chi-square test to compare proportions. Mortality was explored graphically by plotting Kaplan-Meier survival curves and was analyzed using Cox proportional hazards regression. Results of standard tests showed no disagreement with the proportional-hazards assumption. The actual sample size of 107 patients gave the study a power of 79% to detect a substantial increase in mortality (from 23 to 55%, as observed in the study by Baddour et al. [3]) after pneumococcal sepsis treated by antibiotic monotherapy. Considering only bacteremic patients (n=75), our study had a power of 58% to detect a similar increase in mortality during the course of severe pneumococcal bacteremia. Assumptions included the use of a two-tailed test and a 5% level of statistical significance.

Results and discussion

Among 167 patients with at least one specimen yielding *S. pneumoniae*, 30 were excluded because of polymicrobial infection or simple colonization (e.g., tracheobronchitis) that was not considered causative of sepsis, and 30 others could not be evaluated because of inconsistent treatment regimens. Among the 107 remaining patients with monobacterial pneumococcal illness causing severe sepsis or septic shock, 25 (23%) received antibiotic monotherapy, either with a penicillin agent (n=13), a third-generation cephalosporin (n=10) or another agent (n=2). Combination therapies prescribed were β-lactam agents/macrolides (n=34), β-lactam/clindamycin (n=11), β-lactam/vancomycin (n=10), aminoglycoside-containing regimens (n=9), double β-lactam therapy (n=9), fluoroquinolone-containing regimens (n=6) or combination regimens including other antibiotic classes (n=3). Two isolates expressed resistance to penicillin and three isolates were resistant to macrolides; none of these patients received antibiotic monotherapy. Characteristics of the two patient groups are presented in Table 1. Patients receiving antibiotic monotherapy were more likely to be enrolled in Europe, but the two groups were well balanced for other baseline characteristics.

Death occurred in 21 (19.6%) cases. The case-fatality rate was 20% (5 of 25) among patients with antibiotic monotherapy compared with 19.5% (16 of 82) among patients receiving combination therapy. One of five (20%) deaths in the monotherapy group occurred within 4 days after hospital admission compared with 7 of 16 (44%) deaths in the combination therapy group (p=0.61). None of these prematurely deceased patients received inappropriate initial antibiotic therapy.

Figure 1 illustrates survival curves for both cohorts. The unadjusted hazard ratio (HR) for death following monotherapy was 1.0 (95% CI, 0.4–2.7; p=1.0). The risk of death remained almost unchanged after adjusting for the number of organ dysfunctions and the severity of illness at baseline (adjusted HR, 1.1; 95% CI, 0.4–3.1; p=0.88). A separate regression analysis, which stratified patients according to their study drug allocation (lenercept vs. placebo) or

Table 1 Baseline characteristics of 107 patients with severe pneumococcal sepsis, according to receipt of antibiotic monotherapy or combination therapy

Characteristic	Monotherapy (n=25)	Combination therapy (n=82)	p value
Age in years (mean±SD)	56±18	54±15	0.70
Male gender (%)	14 (56)	47 (57)	0.91
Study region, Europe (%)	15 (60)	31 (38)	0.05
Lenercept treatment (%)	12 (48)	43 (52)	0.70
Septic shock (%)	19 (76)	62 (76)	0.97
SAPS II risk quartiles (%)			0.44
1st (predicted mortality, 0–18%)	3 (12)	21 (26)	
2nd (predicted mortality, 19–31%)	5 (20)	16 (20)	
3rd (predicted mortality, 32–45%)	10 (40)	22 (27)	
4th (predicted mortality, >45%)	7 (28)	23 (28)	
Organ dysfunctions (mean±SD)	1.2±1.0	1.5±1.1	0.46
Positive blood cultures (%)	16 (64)	59 (72)	0.45

SAPS Simplified Acute Physiology Scoring System

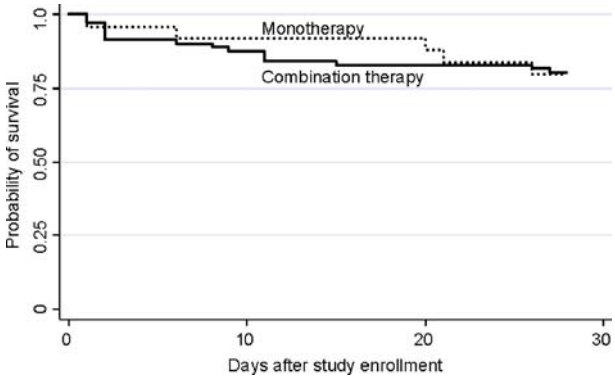

Fig. 1 Kaplan-Meier probability estimates of survival for patients suffering from severe pneumococcal sepsis, stratified by receipt of antibiotic monotherapy (n=25) vs. combination therapy (n=82). The median interval to death was 20 days (interquartile range, 6–21 days) for the monotherapy group and 7 days (interquartile range, 2–11 days) for the combination therapy group. The log-rank test was not significant (p=0.99), thus demonstrating equality of the survivor functions

country (to avoid confounding by possible cluster effects), confirmed this lack of association.

We observed 75 cases of pneumococcal bacteremia. After stratifying for receipt of antibiotic monotherapy (n=16; mortality, 12.5%) or combination therapy (n=59; mortality, 20.3%), exposure to monotherapy was not associated with a significantly increased risk of death (adjusted HR, 1.0; 95% CI, 0.2–4.8). Among bacteremic patients, the mortality rate was 15.9% (7 of 44) for those who received a cephalosporin-containing combination regimen as compared with 16.7% (1 of 6) for those who received a third-generation cephalosporin as monotherapy (HR, 1.1; 95% CI, 0.1–9.3).

These results do not confirm the recently reported association between combination antibiotic therapy and decreased risk of death after severe pneumococcal sepsis. Several reasons may explain the discrepancy between our findings and the results reported in the literature by others. (i) Previous studies included mainly cases with bacteremic pneumococcal pneumonia [1–3]. We included not only patients with bacteremia, but also those with severe, blood culture-negative pneumococcal sepsis. However, in our subgroup analysis of 75 patients with positive blood cultures, no different effect was observed. (ii) The sample size of our study may have been too small to show a deleterious effect of monotherapy in bacteremic patients. For instance, once-daily dosing of ceftriaxone in critically ill patients with hypoalbuminemia may shorten the half-life of this agent and may cause inadequate bacterial killing curves and adverse outcomes [9]. Considering the 95% confidence interval of our estimates and the sample-size calculations showing a power of 58%, we cannot exclude the possibility that the analysis of patients with pneumococcal bacteremia may have been underpowered. (iii) Our analysis was based on two clinical trials conducted in the 1990s, when high-level resistance to penicillin was rare in the participating centers. However, Baddour et al. [3] reported that outcome in critically ill patients was not influenced by whether or not patients received inappropriate antibiotic therapy based on pneumococcal susceptibility results. (iv) Confounding by indication may bias the findings of non-randomized studies [4]. This systematic bias occurs when correct adjustments are not made for imbalances in treatment assignment. To further control for differences between patient groups, future studies should use propensity scores [7]. (v) Only 41% (34/82) of patients in the combination treatment group received a β-lactam/macrolide combination, which has been suggested to be the most beneficial for survival. However, in the study by Baddour et al. [3], only 30% (14/47) of patients received a macrolide-containing combination regimen and non-macrolide combination regimens were also successful in reducing mortality among critically ill patients. (vi) Since HIV-positive and neutropenic patients were excluded, we were not able to evaluate any harmful effect of monotherapy in these patient groups.

Important strengths of this analysis include the large size and multinational nature of the cohort, the heterogeneity of the patient population, and the detailed data on illness severity, evolving organ dysfunctions and antibiotic treatment. All variables were collected prospectively, validated rigorously due to the requirements of the original trial protocol, and analyzed using survival regression methods, which adjust for the time interval between onset of pneumococcal sepsis and discharge or death.

Overall, our results suggest that although antibiotic monotherapy is not frequently used as empiric treatment for severe pneumococcal sepsis, it may not be independently associated with 28-day mortality. Therefore, we believe that caution should be applied when generalizing previously reported findings to other settings and patient populations.

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