Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Identify the organism most often isolated in patients with community-acquired pneumonia.
2. Describe the advantages and disadvantages of mono- and combination antibiotic therapy.
3. Use this information in a clinical setting.

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Objective: **To assess whether combination antibiotic therapy improves outcome of severe community-acquired pneumonia in the subset of patients with shock.**

Design: **Secondary analysis of a prospective observational, cohort study.**

Setting: **Thirty-three intensive care units (ICUs) in Spain.**

Patients: **Patients were 529 adults with community-acquired pneumonia requiring ICU admission.**

Interventions: **None.**

Measurement and Main Results: **Two hundred and seventy (51%) patients required vasoactive drugs and were categorized as having shock. The effects of combination antibiotic therapy and monotherapy on survival were compared using univariate analysis and a Cox regression model. The adjusted 28-day in-ICU mortality was similar ($p = .99$) for combination antibiotic therapy and monotherapy in the absence of shock. However, in patients with shock, combination antibiotic therapy was associated with significantly higher adjusted 28-day in-ICU survival (hazard ratio, 1.69; 95% confidence interval, 1.09–2.60; $p = .01$) in a Cox hazard regression model. Even when monotherapy was appropriate, it achieved a lower 28-day in-ICU survival than an adequate antibiotic combination (hazard ratio, 1.64; 95% confidence interval, 1.01–2.64).**

Conclusions: **Combination antibiotic therapy does not seem to increase ICU survival in all patients with severe community-acquired pneumonia. However, in the subset of patients with shock, combination antibiotic therapy improves survival rates. (Crit Care Med 2007; 35:1493–1498)**

KEY WORDS: community-acquired pneumonia; *Streptococcus pneumoniae*; combination therapy; bacteremia; macrolide

The introduction of antibiotic agents dramatically reduced the mortality rate for community-acquired pneumonia (CAP). However, the mortality rate due to severe CAP has shown little improvement in the past 3 decades, remaining between 25% and 40% in patients admitted to the intensive care unit (ICU) (1–5). The aging population, the increased prevalence of comorbid illness, HIV infection, and increasing microbial resistance have all probably contributed to the persistence of the high mortality rate, despite advances in medical care. However, most interventions have focused

*See also p. 1617.

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on patients with low severity of illness; less attention has been paid to patients with severe CAP requiring ICU admission. Several authors have studied severe CAP in ICU patients but concentrated mainly on microbiological etiology (4, 6) or short-term mortality (7), and the implications of empirical therapy for severe CAP remain unknown. A few retrospective studies in both CAP in general and in the subset of patients with bacteremic pneumococcal disease in particular (8, 9) have suggested that the combination of a macrolide and a third-generation cephalosporin provides a survival advantage over other antibiotic regimens (10). The suggestion that the potential benefits are limited to more severely ill patients corroborates previous reports by Waterer et al. (8) and Baddour et al (9). It seems obvious that the overall mortality of patients with mild illness due to pneumonia is lower and that benefits of therapeutic interventions in terms of survival would be minimal. Other observational studies by Mufson and Stanek (11), Waterer (12), Martinez et al. (13), Baddour et al. (9), and Weiss and Tillotson (14) have all reported significant mortality reductions in patients who received combination antibiotic therapy in comparison with patients who received monotherapy. However, these conclusions are based on patients with bacteremic pneumococcal pneumonia and cannot be extrapolated to the treatment of all patients hospitalized with CAP. Our hypothesis was that combination therapy improves survival in ICU patients with shock caused by CAP. Here we provide the findings of a secondary analysis of a prospective, observational multicenter investigation (1) that examines the role of combination antibiotic therapy in patients with severe CAP admitted to the ICU.

METHODS

Details of this observational study have been presented elsewhere (1, 15). Briefly, 529 consecutive patients with severe CAP admitted to ICUs in 33 hospitals in Spain were enrolled between December 1, 2000, and February 28, 2002. Institutional review board approval was obtained in accordance with local requirements. Patients were observed until death or ICU discharge, but following Food and Drug Administration recommendations for clinical trials, 28-day survival was chosen as primary end point. Patients discharged from ICU before 28 days were considered as survivors.

Community-acquired pneumonia (CAP) was defined as an acute lower respiratory tract infection characterized by a) an acute pulmonary infiltrate evident on chest radiographs and consistent with pneumonia; b) confirmatory findings of a clinical examination; and c) acquisition of the infection outside a hospital, long-term care facility, or nursing home.

The patients enrolled were consecutive patients aged ≥18 yrs, with conclusive evidence of pneumonia as primary diagnosis, confirmed by chest radiograph and clinical findings. The study focused on patients in the ICU and excluded patients with respiratory infection other than pneumonia (e.g., exacerbation of chronic obstructive pulmonary disease). Patients with and without shock were compared in this secondary analysis. Shock was defined as the need for vasopressors for >4 hrs after fluid replacement at the time of ICU admission. Details of other definitions, including chronic obstructive pulmonary disease, smokers, and so on, have been reported elsewhere (1, 15).

Antibiotic therapy was analyzed if the total daily dose of an agent was at least the minimum dose recommended for treatment of systemic infection. Monotherapy was defined as administration of the same single antibiotic during the first 2 days of ICU admission. Combination therapy was defined as administration of the same two antibiotics within the first 2 days of ICU admission (9).

A wide range of demographic, clinical, and laboratory measures were recorded in each patient, as described elsewhere (1). In the current study, particular emphasis was placed on presence of shock, severity of illness measured using the Acute Physiology and Chronic Health Evaluation (APACHE) II score, and class of antibiotic treatment received. Treatment decisions for all study participants, including type of shock treatment, determination of the need for intubation, and type of antibiotic therapy administered (class of antibiotic and monotherapy or combination therapy), were not standardized and were made by the attending physician.

Differences in categorical variables were calculated by chi-square test with the Yates correction or Fisher's 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 Cox proportional hazards regression adjusted by APACHE II score as a continuous variable. A p value ≤.05 was considered as significant. In addition to p values, odds ratio and hazard ratio (HR) and 95% confidence interval (CI) were calculated using Confidence Interval Analysis software 1.2 (MJ Gardner & DG Altman, London) and SPSS 11.0 (SPSS, Chicago, IL), respectively.

We calculated *post hoc* that we would need a sample size of 103 patients for each group to identify an absolute reduction of 20% in 28-day in-ICU mortality rate in patients with combination therapy with a power of 0.8 (two-tailed) at a level of significance of .05.

Table 1. Demographic characteristics

Variable	Patients With Shock (n = 270)	Patients Without Shock (n = 259)
Age, mean yrs (SD)	61.3 (14.6)	58.4 (17.3)
Age >75 yrs, n (%)	42 (15.5)	48 (18.5)
Age <50 yrs, n (%)	53 (19.6)	77 (29.7)[a]
Male gender, n (%)	196 (72.9)	184 (71.0)
Mean APACHE II score (SD)	21.6 (7.1)[a]	16.7 (6.0)
Mean APS score (SD)	14.1 (9.7)[a]	10.3 (8.4)
Length of stay ICU, days (SD)[b]	20.1 (19.3)[a]	12.2 (11.2)
Comorbidity or risk factors, n (%)		
Alcohol use	78 (28.9)	57 (22.0)
Smoking	131 (48.5)	112 (43.2)
Malignancy	21 (7.8)	16 (6.2)
Immunocompromise	40 (14.8)	24 (9.3)
COPD	101 (37.4)	95 (36.7)
Cardiomyopathy	90 (33.3)	66 (25.5)
Diabetes	66 (24.4)	55 (21.2)
Documented etiology, n (%)	158 (58.5)	118 (55.7)
Mechanical ventilation, n (%)	234 (86.7)[a]	115 (44.4)
Empyema, n (%)	15 (5.6)	17 (6.6)
Bacteremia, n (%)	61 (22.6)[a]	28 (10.8)
Rapid radiographic spread, n (%)	171 (63.3)[a]	79 (30.5)
Mortality rate, n (%)	130 (48.1)[a]	18 (6.9)
>75 yrs	29 (69.0)[a]	5 (10.4)
<50 yrs	19 (35.8)[a]	2 (2.6)

APACHE, Acute Physiology and Chronic Health Evaluation; APS, Acute Physiology Score; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease.

[a]$p < .05$; [b]only for survivors.

Table 2. Prevalence of microorganisms isolated in patients with and without shock

Microorganisms	Overall (n = 274)		Patients With Shock (n = 158)		Patients Without Shock (n = 118)	
	No. (%)	Mortality Rate, No. (%)	No. (%)	Mortality Rate, No. (%)	No. (%)	Mortality Rate, No. (%)
Streptococcus pneumoniae	143 (52.2)	32 (22.4)	73 (46.2)	31 (42.4)	70 (59.3)	1 (1.4)
Staphylococcus aureus[a]	22 (8.0)	10 (45.4)	16 (10.1)	10 (62.5)[b]	6 (5.0)[b]	0
Legionella pneumophila	23 (8.4)	6 (26.0)	14 (8.8)	6 (42.8)	9 (7.6)	0
Pseudomonas aeruginosa	20 (7.3)	11 (55.0)	13 (8.2)	10 (76.9)	7 (5.9)	1 (16.9)
Haemophilus influenzae	22 (8.0)	3 (13.6)	12 (7.6)	2 (16.6)	10 (8.4)	1 (10)
Escherichia coli	8 (2.9)	5 (62.5)	6 (3.8)	5 (83.3)	2 (1.6)	0
P. jirovecii	10 (3.6)	7 (70.0)	6 (3.8)	5 (83.3)	4 (3.4)	2 (50)
Other Gram-positive coccus	9 (3.3)	2 (22.2)	9 (5.7)	2 (22.2)	0	0
Mycobacterium tuberculosis	8 (2.9)	3 (37.5)	5 (3.1)	3 (60.0)	3 (2.5)	0
Klebsiella pneumoniae	5 (1.8)	3 (60.0)	4 (2.5)	3 (75.0)	1 (0.8)	0
Streptococcus pyogenes	4 (1.4)	1 (25.0)	3 (1.9)	1 (33.3)	1 (0.8)	0
Varicella-zoster	8 (2.9)	0	3 (1.9)	0	5 (4.2)	0
Enterococcus faecalis	2 (0.7)	1 (50.0)	2 (1.2)	1 (50.0)	0	0
Enterobacter aerogenes	3 (1.1)	0	1 (0.6)	0	2 (1.6)	0
Aspergillus species	1 (0.3)	1 (100)	1 (0.6)	1 (100)	0	0
Cytomegalovirus	2 (0.7)	2 (100)	1 (0.6)	1 (100)	1 (0.8)	1 (100)
Moraxella catarrhalis	1 (0.3)	0	1 (0.6)	0	0	0
Proteus mirabilis	2 (0.7)	1 (50.0)	1 (0.6)	1 (100)	1 (0.8)	0
Eikenella corrodens	1 (0.3)	1 (100)	1 (0.6)	1 (100)	0	0
Stenotrophomonas maltophilia	1 (0.3)	0	0	0	1 (0.8)	0
Nocardia species	1 (0.3)	0	0	0	1 (0.8)	0
Mycoplasma	1 (0.3)	0	0	0	1 (0.8)	0

[a]Including two episodes of oxacillin-resistant *S. aureus;* [b]including one episode of oxacillin-resistant *S. aureus.*

Table 3. Characteristics of 529 patients with severe community-acquired pneumonia receiving combination therapy or monotherapy and and initial antibiotic therapy with and without macrolide

Variables	Combination Therapy (n = 414)	Monotherapy (n = 115)	Therapy With Macrolide (n = 290)	Therapy Without Macrolide (n = 239)
Age, mean yrs (SD)	59.3 (16.4)	62.2 (14.3)	60.1 (16.7)	59.7 (15.2)
Male gender, n (%)	291 (70.3)	89 (77.4)[a]	206 (71.0)	174 (72.8)
Mean APACHE II score (SD)	19.4 (7.15)	18.4 (6.7)	19.4 (7.4)	19.0 (6.7)
Comorbidity or risk factors, n (%)				
Alcohol use	101 (24.4)	34 (29.6)	74 (25.5)	61 (25.5)
Smoking	184 (44.4)	59 (51.3)	127 (43.0)	116 (48.5)
Malignancy	28 (6.8)	9 (7.8)	12 (4.1)	25 (10.5)[b]
Immunocompromise	53 (12.8)	11 (9.6)	28 (9.7)	36 (15.1)[b]
COPD	148 (35.7)	48 (41.7)	105 (36.2)	91 (38.1)
Cardiomyopathy	118 (28.5)	38 (33.0)	89 (30.7)	67 (28.0)
Diabetes	102 (24.6)	19 (16.5)	80 (27.6)[b]	41 (17.2)
Documented etiology, n (%)	212 (51.2)	64 (55.7)	153 (52.8)	123 (51.5)
Orotracheal intubation, n (%)	269 (65.0)	76 (66.1)	182 (62.8)	163 (68.2)
Empyema, n (%)	27 (6.5)	5 (4.3)	19 (6.6)	13 (5.4)
Shock, n (%)	218 (52.7)	52 (45.2)	139 (47.9)	131 (54.8)
Bacteremia, n (%)	76 (18.4)	13 (11.3)	54 (18.6)	35 (14.6)
Rapid radiographic spread, n (%)	201 (48.6)	49 (42.6)	128 (44.1)	122 (51.0)
ICU mortality rate, n (%)	114 (27.5)	34 (29.6)	74 (25.5)	74 (31.0)

APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.
[a]$p = .01$ when comparing combination therapy vs. monotherapy; [b]$p < .01$ when comparing therapy with macrolide vs. without macrolide.

RESULTS

In total, 529 patients were recruited for the original study (1), of whom 270 (51.0%) developed shock. Differences in baseline characteristics between patients with and without shock are summarized in Table 1. As we reported previously, 148 patients (27.9%) died in the ICU. Twenty-six of these deaths (seven in the monotherapy group) occurred within 48 hrs of ICU admission. The risk of death was higher in patients with shock than in those without (48.1% vs. 6.9%, $p < .01$; odds ratio, 12.4; 95% CI, 7.28–21.2). Bacteremia was present in 22.6% (n = 61) of patients with shock vs. 10.8% (n = 28) of patients without ($p < .01$; odds ratio, 2.41; 95% CI, 1.48–3.91). As expected, *Streptococcus pneumoniae* (n = 73, 46.2%) was identified as the leading pathogen in patients with shock, followed by *Staphylococcus aureus* (n = 16, 10.1%), *Legionella pneumophila* (n = 14, 8.8%), and *Pseudomonas aeruginosa* (n = 13, 8.2%). Table 2 details the prevalence of microorganisms isolated in patients with shock. No significant differences in etiological agents were documented.

Two hundred and eighteen (80.7%) patients with shock and 196 (75.7%) patients

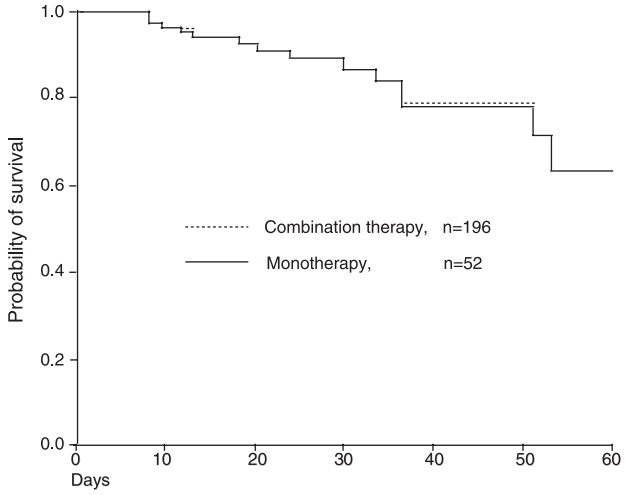

Figure 1. Survival graph for patients without shock stratified by severity of illness (censored at 60 days).

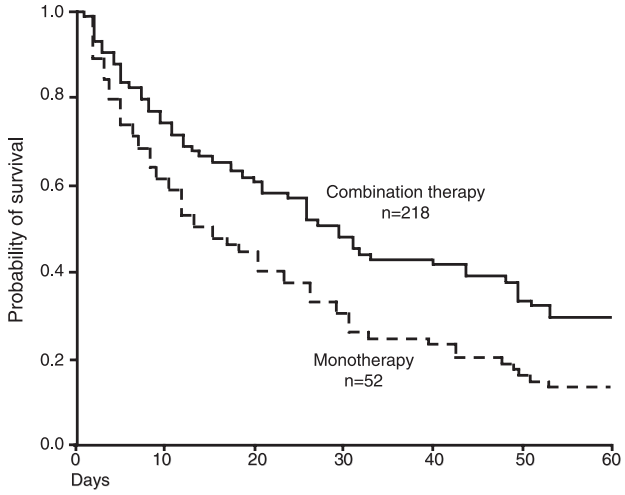

Figure 2. Survival graph for patients with shock stratified by severity of illness (censored at 60 days).

without shock received combination therapy (p = .19). The characteristics of patients who received monotherapy or combination therapy (and macrolide or other antibiotic therapies) are shown in Table 3. The 28-day adjusted in-ICU survival did not differ significantly for the overall population receiving combination vs. monotherapy (HR, 1.45; 95% CI, 0.96–2.18; p = .07), being similar (HR, 1.00) in patients without shock (Fig. 1). However, among patients with shock (Fig. 2), combination antibiotic therapy was associated with a significantly higher 28-day adjusted in-ICU survival (HR, 1.69; 95% CI, 1.09–2.60; p = .01). This difference remained statistically significant when patients who died within first 48 hrs were excluded (HR, 1.69; 95% CI, 1.05–2.73; p = .03). When crude ICU mortality was the end point assessed, the excess of mortality was estimated to be 11.8% (95% CI, −3% to 20%) (Table 4). In survivors, number of ventilation-days was significantly higher for monotherapy (20.9 ± 28.3) than combination therapy (12.7 ± 14.9, p = .04).

The most common monotherapy regimens (n = 52) prescribed for patients with shock were β-lactam (48.2%) and fluoroquinolone (42.2%). Macrolides (55% clarithromycin and 45% erythromycin) were not administered in monotherapy. The two most frequent combination therapies prescribed were β-lactam/macrolides (n = 131; 48.5%) and β-lactam/fluoroquinolones (n = 54; 20.0%). Information on antibiotic choices is shown in Table 5. In patients with shock, the demographics for monotherapy vs. combination or macrolide vs. no macrolide therapies were comparable (Table 4), except for malignancy and immunocompromise (p = .01) in patients without macrolide therapy and for inappropriate initial antibiotic (p = .04) in monotherapy. When only immunocompetent shocked patients were considered, 28-day adjusted in-ICU survival for combination remained statistically higher than for monotherapy (HR, 1.73; 95% CI, 1.08–2.78; p = .02). In addition, even if monotherapy is appropriate *in vitro*, it provides a lower 28-day adjusted in-ICU survival than an adequate antibiotic combination (HR, 1.64; 95% CI, 1.01–2.64; p = .04).

The combination regimens were further examined to determine whether the difference seen in survival rate with combination or monotherapy was due to a specific antibiotic or combination of antibiotics. When compared with monotherapy, survival rates were higher for antibiotic combinations, including β-lactam plus macrolide (HR, 1.73; 95% CI, 1.08–2.76; p = .02) and β-lactam plus fluoroquinolones (HR, 1.77; 95% CI, 1.01–3.15; p = .05). The numbers were too small to allow for analysis of other combination therapies.

DISCUSSION

Findings from this secondary analysis of a large, prospective, multicenter investigation suggest that the administration of combination therapy results in increased survival among patients with shock and CAP controlled for severity of illness at ICU admission. Until now many physicians have believed that antibiotic therapy may not really affect patients' outcome in the most severe cases (i.e., with shock). The present data, although observational in nature, strongly challenge this idea. There was an increase of >60% in survival rate among recipients of combination antibiotic therapy compared with recipients of monotherapy regimens. These observations are not only of academic interest but may provide an opportunity to improve outcomes in patients with CAP.

The 2003 Infectious Diseases Society of America guidelines did not mention whether patients in shock require specific management. Many microbiologists and intensivists consider that one antibiotic is appropriate and that the effects of antibiotics in patients with shock are secondary. Our findings, consistent with our hypothesis, show a clear difference in the subset with shock. In view of these results, there seems to be no reason for prescribing combination therapy to ICU patients who do not have vasoactive drug requirements. Our results are consistent with other observational studies suggesting that combination therapy improves

Table 4. Characteristics of 270 patients with severe community-acquired pneumonia and shock receiving combination therapy or monotherapy and initial antibiotic therapy with or without macrolide

Variable	Combination Therapy (n = 218)	Monotherapy (n = 52)	Therapy With Macrolide (n = 139)	Therapy Without Macrolide (n = 131)
Age, mean yrs (SD)	61.2 (14.9)	62.0 (13.5)	62.0 (15.3)	60.6 (14.1)
Mean APACHE II score (SD)	21.9 (7.2)	20.6 (6.6)	22.1 (7.6)	21.1 (6.4)
Male gender, n (%)	156 (71.6)	40 (76.9)	101 (72.7)	95 (72.5)
Comorbidity or risk factor, n (%)				
Alcohol use	61 (28.0)	17 (32.7)	41 (29.5)	37 (28.2)
Smoking	104 (47.7)	27 (51.9)	64 (46.0)	67 (51.1)
Malignancy	17 (7.8)	4 (7.7)	5 (3.6)	16 (12.2)[a]
Immunocompromise	34 (15.6)	6 (11.5)	13 (9.4)	27 (20.6)[a]
COPD	78 (35.8)	23 (44.2)	51 (36.7)	50 (38.2)
Cardiomyopathy	71 (32.6)	19 (36.5)	50 (36.0)	40 (30.5)
Diabetes	57 (26.1)	9 (17.3)	42 (30.2)	24 (18.3)
Endotracheal intubation, n (%)	185 (84.9)	47 (90.4)	118 (84.9)	114 (87.0)
Inappropriate initial antibiotic, n (%)	17 (13.4)	9 (31.0)[b]	15 (17.2)	11 (15.9)
Bacteremia, n (%)	54 (24.8)	7 (13.5)	38 (27.3)	23 (17.6)
Empyema, n (%)	14 (6.4)	1 (1.9)	9 (6.5)	6 (4.6)
Rapid radiographic spread, n (%)	137 (62.8)	34 (65.4)	84 (60.4)	87 (66.4)
ICU mortality rate, n (%)	100 (45.9)	30 (57.7)[c]	61 (43.9)	69 (52.7)

APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

[a]$p = .01$ when comparing therapy with macrolide vs. without macrolide; [b]$p = .04$ when comparing combination vs. monotherapy; [c]$p = .16$ when comparing combination vs. monotherapy.

Table 5. Antibiotic choice therapies in 270 patients with community-acquired pneumonia and shock

	Monotherapy (n = 52)			Combination therapy (n = 218)	
	No.	%		No.	%
β-lactam			β-lactam/macrolide		
Amoxicillin-clavulanate	17	32.7	Third-generation cephalosporins	126	57.8
Third-generation cephalosporins	6	11.5	Amoxicillin-clavulanate	5	2.3
Piperacillin-tazobactam	2	3.9			
Fluoroquinolones			β-lactam/fluoroquinolones		
Levofloxacin	22	42.3	Third-generation cephalosporins	45	20.6
			Piperacillin-tazobactam	5	2.3
			Amoxicillin-clavulanate	4	1.8
Other	5	9.6	Fluoroquinolone/macrolide	3	1.3
			Other	30	13.9

survival in the subset of the most severe patients with bacteremic pneumococcal infection (16). What is not clear is the mechanism by which addition of a second antibiotic to a third-generation cephalosporin achieves this beneficial effect. The low incidence of atypical pathogens in severe episodes (8) and the balanced distribution of atypical pathogens in our cohort with shock make it unlikely that coverage of infection by *Legionella pneumophila* or other atypical pathogens is the mechanism involved. Other explanations, such as nonribosomal anti-pneumococcal activity (impairment of epithelial resistance and the anti-inflammatory and immunomodulatory properties inherent to macrolides) (17) have been proposed. Moreover, the use of combination therapy may be associated with other therapeutic measures (such as improved hemodynamic or ventilatory management) that are beneficial for patients.

This study has several strengths. First, in contrast to previous studies, a large proportion of patients with severe respiratory failure were intubated and received vasoactive drugs. Second, >500 consecutive patients from 33 hospitals were enrolled over two consecutive winters, and they were not exposed to biases associated with temporal outbreaks or conditions specific to a single institution. Third, in contrast to most other studies, our patients were enrolled prospectively. Fourth, the probability of correctly identifying a difference between the two groups (combination therapy vs. monotherapy in patients with shock) was adequate, according to a calculated power of 0.69 with continuity correction for 28-day mortality. Fifth, whereas most prior studies evaluating combination therapy in CAP have been limited to bacteremic episodes, this condition represented only one fifth of our study population, facilitating clinical implications at the bedside.

The major limitation is that this is not a randomized controlled study. Prescription of antibiotics and measures of resuscitation were left to the discretion of the attending physician and were not standardized. However, combination therapy and monotherapy groups were generally comparable (Table 3), and severity of illness as measured by APACHE II score was practically identical. In addition, this sec-

ondary analysis from a large observational study provides preliminary evidence that can be used as the basis for a hypothesis in randomized controlled trials. However, it is unlikely that trials of this kind will be conducted in the coming years. A second limitation is that it is not clear how the addition of a second antibiotic achieved its beneficial effect: Possible explanations have been detailed elsewhere (8, 9, 10, 15, 18, 19). Third, follow-up was not prolonged after ICU discharge, and we can only speculate about the long-term impact of our findings. It has been reported that patients surviving CAP are exposed to an increase in mortality months after discharge (20), and the effects of different antibiotic choices remain unknown. Fourth, distribution of pathogens and ICU admission criteria may present variability and cannot be generalized to other wards or other geographic areas. However, one would not expect to find many patients with vasoactive drugs outside an ICU. Fifth, it is unclear if these findings can be extrapolated to patients in earlier phases of septic shock, such as severe sepsis before ICU admission.

CONCLUSIONS

Our findings support the hypothesis that combination therapy achieves significantly lower adjusted 28-day ICU mortality rates than monotherapy. As in the reports by Baddour et al. (9) and Waterer et al. (8), the potential benefits of combination therapy were limited to more severely ill patients. Our findings suggest that combination therapy does not increase survival in all ICU patients with severe CAP. In contrast to previous studies (8, 9, 11, 12), our study population was not limited to patients with *S. pneumoniae* bacteremia. Our findings are consistent with prior retrospective studies suggesting that the best outcome is obtained by the addition of a second antibiotic to a third-generation cephalosporin. For the subset of patients with CAP who develop shock, we recommend that clinicians target initial combination antibiotic therapy.

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APPENDIX 1

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