MAJOR ARTICLE

Addition of a Macrolide to a β-Lactam–Based Empirical Antibiotic Regimen Is Associated with Lower In-Hospital Mortality for Patients with Bacteremic Pneumococcal Pneumonia

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(See the editorial commentary by File and Mandell on pages 396–8)

To assess the association between inclusion of a macrolide in a β-lactam–based empirical antibiotic regimen and mortality among patients with bacteremic pneumococcal pneumonia, 10 years of data from a database were analyzed. The total available set of putative prognostic factors was subjected to stepwise logistic regression, with in-hospital death as the dependent variable. Of the 409 patients analyzed, 238 (58%) received a β-lactam plus a macrolide and 171 (42%) received a β-lactam without a macrolide. Multivariate analysis revealed 4 variables to be independently associated with death: shock ($P < .0001$), age of ⩾65 years ($P = .02$), infections with pathogens that have resistance to both penicillin and erythromycin ($P = .04$), and no inclusion of a macrolide in the initial antibiotic regimen ($P = .03$). For patients with bacteremic pneumococcal pneumonia, not adding a macrolide to a β-lactam–based initial antibiotic regimen is an independent predictor of in-hospital mortality. However, only a randomized study can definitively determine whether this association is due to a real effect of macrolides.

Several observational studies conducted during the past few years have suggested that mortality and length of hospital stay for patients admitted to the hospital with community-acquired pneumonia (CAP) or bacteremic pneumococcal pneumonia may be decreased by initial antimicrobial regimens that include either a macrolide plus a β-lactam, a fluoroquinolone, or any combination of 2 effective drugs [1–5]. Two of these investigations [3, 4], which collected data on a large series of patients with CAP of undefined etiology in ⩾60% of the cases, were able to show that the lower mortality rate at 30 days after presentation associated with combination therapy remained significant after adjusting for several prognostic factors, such as age, severity of disease, comorbidity, delay in the initiation of antimicrobial therapy, transfer from a long-term care facility, and need for intensive care unit (ICU) admission. Of 2 additional studies that focused on bacteremic pneumococcal pneumonia, one [1] made no attempt to adjust for potential confounding variables, and the other [5] was more concerned with exploring the association between any dual effective therapy and mortality than with addressing the specific issue of including a macrolide as part of a β-lactam–based empirical regimen.

This recent evidence has had practical consequences: the Infectious Diseases Society of America has endorsed the recommendation of use of a macrolide plus a β-lactam for empirical treatment of any patient with CAP

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requiring hospital admission [6]. However, many aspects of the apparently beneficial effect of the β-lactam/macrolide combination remain speculative or controversial. The first unsettled matter is whether all of the antipneumococcal β-lactams are effective in terms of reducing mortality, because the largest study to date favored second- and third-generation cephalosporins over β-lactams and β-lactamase inhibitors, which, in fact, have been associated with higher mortality rates [3]. The second problem may be one of consistency, because some authors have been unable to observe the same effect in different years [7]. This finding may direct attention to the importance of confounding by epidemiological variables, such as the changing incidence over time of atypical organisms. The third important question has to do with the fact that, no matter how prevalent atypical organisms may be, *Streptococcus pneumoniae* is still the most common cause of CAP, even in patients for whom the etiologic organism has not been definitively identified [8], and there is evidence that the combination of a β-lactam (penicillin) and a macrolide (erythromycin) is antagonistic against this microorganism in vitro and in animal models of invasive disease [9]. The last relevant issue derives from the fact that physicians base their therapeutic choices on clinical presentation or patient characteristics, and this is a potential confounding variable in any observational study in which antimicrobial therapy has not been selected at random.

We analyzed a relatively large series of patients with bacteremic pneumococcal pneumonia at our institution during a 10-year period with the aim of assessing whether the inclusion of a macrolide as part of a β-lactam–based empirical regimen is associated with a lower in-hospital mortality rate. Patients with pneumonia and pneumococcal bacteremia represent a population with ⩾1 unquestionable etiologic diagnosis, among whom, although the contribution of coinfection with atypical organisms cannot be ruled out, probably most of the in-hospital mortality is directly attributable to the deleterious effect of the organism isolated from the bloodstream.

PATIENTS AND METHODS

Setting. The study was conducted in the Hospital Clinic of Barcelona (Spain), a 700-bed, tertiary care university hospital.

Microbiological methods. During the study period, blood samples were processed with use of an automatic nonradiometric system. Isolates were identified with use of standard techniques. Susceptibility was assessed by determining the MIC (by microdilution) in accordance with the methodology of the National Committee for Clinical Laboratory Standards (NCCLS) [10]. The breakpoints used for the interpretation of susceptibility to penicillin were those currently proposed by the NCCLS. For erythromycin, an MIC of ⩾4 mg/L was considered indicative of resistance and an MIC of ⩽0.5 mg/L was considered indicative of susceptibility; during the study period, no bacteremic strains with MICs of 1–2 mg/L were found.

Patient description. The present study focused on patients who were admitted to the hospital during the period of January 1991 through December 2000 with bacteremic pneumonia due to *S. pneumoniae* and who received a β-lactam, with or without other antibiotics, as part of empirical therapy. Patients were consecutively enrolled and prospectively observed until in-hospital death or discharge. The following data were obtained from all patients: age, sex, preexisting comorbidities, prognosis of the underlying disease, prior antibiotic therapy, prior surgery, current administration of >20 mg of corticosteroids per day, current administration of antineoplastic chemotherapy, leukocyte count, ICU admission, origin of the infection (community or hospital acquired), duration of hospitalization before the diagnosis of bacteremia, need for mechanical ventilation, empirical and definitive antibiotic treatment received, susceptibility of isolates to penicillin and other antibiotics, presence of shock, and in-hospital mortality rate.

Study design. Since 1983, all patients with episodes of bacteremia diagnosed at our institution have been prospectively observed from hospital admission to discharge. This is a retrospective analysis of the existing database about the subset of patients with pneumococcal bacteremia from a pulmonary source admitted to the hospital during a 10-year period.

Definition of terms. "Bacteremic pneumococcal pneumonia" was defined as ⩾1 blood culture positive for *S. pneumoniae* for a patient with a new pulmonary infiltrate documented by chest radiography. "Comorbidity" was defined as any disease or risk factor that could predispose patients to infection, alter defense mechanisms, or cause functional impairment, such as the following: diabetes mellitus, liver cirrhosis, renal failure, alcoholism (consumption of >100 g of alcohol per day), active neoplastic disease, solid-organ or hematopoietic stem cell transplantation, neutropenia, severe chronic obstructive pulmonary disease, severe cardiac disease with symptomatic heart failure, severe dementia, injection drug addiction, and HIV infection. Prognosis of the underlying disease was classified, in accordance with a modification of the criteria of McCabe and Jackson [11], as "rapidly fatal" (when death was expected in <3 months), "ultimately fatal" (when death was expected within a period of ⩾3 months but <5 years), and "nonfatal" (when life expectancy was ⩾5 years).

Antibiotic therapy was considered to be empirical if it had been administered before the results of blood culture were known. "Shock" was defined as a systolic blood pressure of <90 mm Hg that was unresponsive to fluid treatment or required vasoactive drug therapy.

Follow-up. Patients were observed from the time of diagnosis of bacteremia until in-hospital death or discharge from the hospital.

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Table 1. Empirical antibiotic regimens used to treat patients with bacteremic pneumococcal pneumonia in 10-year retrospective study.

Antibiotic	Therapy received, no. (%) of patients: β-Lactam plus a macrolide (*n* = 238)	β-Lactam without a macrolide (*n* = 171)	*P*
Second-generation cephalosporin	32 (13)	19 (11)	.5
Cefotaxime, ceftriaxone, or cefepime	194 (82)	106 (62)	<.0001
Ceftazidime	16 (9)	6 (4)	.2
Penicillins or aminopenicillins	6 (3)	22 (13)	.0001
Cloxacillin	1 (0.4)	1 (0.6)	1
Carbapenems	0 (0)	7 (4)	.002
Erythromycin	161 (68)	—	—
Azithromycin	69 (29)	—	—
Clarithromycin	8 (3)	—	—
Other	26 (11)	62 (36)	<.0001
Aminoglycosides	24 (10)	38 (22)	.001
Clindamycin	4 (2)	10 (6)	.04
Rifampin	5 (2)	0	.07
Ciprofloxacin	1 (0.4)	4 (2)	.16
Vancomycin	1 (0.4)	6 (4)	.02
TMP-SMZ	1 (0.4)	11 (6)	.001

NOTE. Some patients received >1 antibiotic. TMP-SMZ, trimethoprim-sulfamethoxazole.

Statistical analysis. Categorical variables were compared by χ^2 test with Yates's correction or Fisher's exact test, when necessary. To assess the independent predictors of death, the whole set of putative prognostic factors was subjected to a nonconditional stepwise logistic regression procedure with in-hospital death as the dependent variable. For the purpose of analysis, age (the only continuous variable analyzed) was dichotomized in 2 categories (≥65 years and <65 years), the strains with intermediate resistance to penicillin were grouped together with the penicillin-susceptible strains, and the entire period of the study was divided into intervals of 1, 2, and 5 years.

RESULTS

A total of 409 patients met the inclusion criteria, of whom 238 (58%) received a β-lactam plus a macrolide, with or without other antibiotics, and 171 (42%) received a β-lactam with or without other antibiotics, but not a macrolide. Specific regimens used for both groups of patients are shown in table 1. Cefotaxime, ceftriaxone, or cefepime were administered to 73% of patients, and they were administered more frequently in combination with a macrolide (82%) than alone or with other antibiotics (62%; $P < .0001$). Penicillin and carbapenems were rarely prescribed and never concurrently with a macrolide. The rate of use of second-generation cephalosporins decreased progressively over time, from 47% (16 of 34 patients) during 1991 to 3.2% (1 of 31 patients) in 1996, and use virtually ceased after 1997. Conversely, the rate of administration of third-generation cephalosporins with good antipneumococcal activity increased during the study period, from 35.2% (12 of 34 patients) in 1991 to 70% (28 of 40 patients) in 1995, and it remained at 86%–95% thereafter. Prevalence of macrolide use ranged from a minimum of 38.7% (12 of 31 patients) during 1996 to a maximum of 70.5% (24 of 34 patients) during 1991. During 1997–2000, 60%–65% of patients treated with a β-lactam also received a macrolide as part of the empirical regimen. Until 1997, the only macrolide in use was erythromycin. Other antibiotics were more frequently given when a macrolide was not administered (36%) than when it was (11%; $P < .0001$). Of these antibiotics, aminoglycosides were the most common.

During the study period, none of the *S. pneumoniae* strains had MICs of penicillin, ampicillin, or cefotaxime of >4 mg/L. As a whole, 337 isolates (82%) had MICs of penicillin of ≤1 mg/L, and 340 (83%) were considered to be susceptible to erythromycin (MIC, <4 mg/L). Thirty (42%) of 72 fully penicillin-resistant strains were erythromycin resistant, in contrast to 39 (12%) of 337 strains that were susceptible or intermediately resistant to penicillin ($P < .0001$). The prevalence of complete penicillin resistance increased during the first 5 years of the study, starting at 6% in 1991 and peaking at 33% in 1995, but there was a steady decrease afterward, to a minimum of 6% in the last year of the study. The prevalence of erythromycin resistance, although it fluctuated more, also showed a similar up-and-down pattern, with a peak of 35% in 1997 that halved to 18% during 1999 and 2000.

Patients who did not receive a macrolide were more likely to have a comorbidity ($P = .0002$), particularly HIV infection and hematologic malignancies, an ultimately or rapidly fatal underlying disease ($P < .0001$), neutropenia ($P = .002$), an infection of nosocomial origin ($P < .0001$), and infection with a penicillin-resistant microorganism ($P = .02$). In addition, these patients had increased rates of exposure to corticosteroids, antineoplastic chemotherapy, and prior antibiotic use. On the other hand, patients who received macrolides more frequently had experienced shock at the time of presentation ($P < .0001$) and were more likely to be admitted to an ICU ($P < .0001$; table 2). The latter 2 characteristics were strongly associated (63% of patients with shock were admitted to an ICU vs. 6% of patients without shock; $P < .0001$).

A total of 35 patients (9%) died during hospitalization, 10

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Table 2. Characteristics of patients with bacteremic pneumococcal pneumonia who received or did not receive a macrolide.

Characteristic	Initial treatment with macrolide, no. (%) of patients		
	No (n = 171)	Yes (n = 238)	P
Age ⩾65 years	76 (44)	125 (53)	.1
Male sex	105 (61)	147 (62)	.9
Comorbidity	152 (89)	176 (74)	.0002
Ultimately or rapidly fatal underlying disease	95 (56)	75 (32)	<.0001
Neutropenia	12 (7)	3 (1)	.002
Received corticosteroid treatment	29 (17)	12 (5)	.0001
Underwent cancer chemotherapy	11 (6)	1 (0.4)	.0004
Received prior antibiotic treatment	25 (15)	16 (7)	.008
Nosocomial infection	21 (12)	2 (0.8)	<.0001
Intensive care unit admission	9 (5)	38 (16)	.0008
Shock	9 (5)	31 (13)	.009
Infecting agent had susceptibility to erythromycin	140 (82)	200 (84)	.5
Infecting agent had susceptibility to penicillin[a]	132 (77)	205 (86)	.019
Infecting agent had penicillin and erythromycin resistance	14 (8)	16 (7)	.5
Empirical treatment received			
Cefotaxime, ceftriaxone, or cefepime	106 (62)	194 (82)	<.0001
Ceftazidime	16 (9)	6 (3)	.002
Second-generation cephalosporin	19 (11)	32 (13)	.4
Penicillins or aminopenicillins	22 (13)	6 (3)	<.0001
Carbapenem	7 (4)	0 (0)	.002
Cloxacillin	1 (0.6)	1 (0.4)	1
Nonmacrolide, non–β-lactam antibiotics	62 (36)	26 (11)	.0004
Received treatment during 1996–2000	91 (53)	138 (58)	.3
Died while in the hospital	17 (10)	18 (8)	.3

[a] Includes strains with an MIC of penicillin of <2 mg/L.

of whom died ⩽48 h after admission. The mortality rate showed year-to-year fluctuations, ranging from 2% in 1998 to 16% in 1997, but an obvious trend was not observed. On univariate analysis, in-hospital mortality was associated with shock (P < .0001), administration of antibiotics other than β-lactams and macrolides (P = .001), infections with pathogens that had resistance to both penicillin and erythromycin (P = .02), and ICU admission (P < .0001; table 3). A trend toward increased mortality among patients aged ⩾65 years was evident (P = .08). When all of the evaluated variables were subjected to a stepwise logistic regression procedure, in which the strains with intermediate resistance to penicillin were considered to be susceptible, the following characteristics were found to be independently associated with death: shock (P < .0001), age of ⩾65 years (P = .02), infection with pathogens that had resistance to both penicillin and erythromycin (P = .04), and no inclusion of a macrolide in the initial antibiotic regimen (P = .03; table 4). The association between initial macrolide therapy and a lower in-hospital mortality rate remained significant after the exclusion of patients who died ⩽48 h after admission (adjusted OR, 4; 95% CI, 1.23–13.4). A subgroup analysis of patients who exclusively received cefotaxime, ceftriaxone, or cefepime, with or without a macrolide, showed again that the inclusion of a macrolide as part of the initial regimen was associated with a lower mortality rate in both the whole population (adjusted OR, 0.28; 95% CI, 0.09–0.9) and among patients who survived for >48 h after hospitalization (adjusted OR, 0.12; 95% CI, 0.03–0.6).

After the results of blood culture were known, 245 patients (60%) who had survived for >48 h after hospital admission received a β-lactam without a macrolide as part of the definitive treatment, 147 (36%) received a β-lactam plus a macrolide, 7 (2%) received a macrolide without a β-lactam, and 6 (1%) received other classes of antibiotics. Definitive therapy with a

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Table 3. Association between characteristics of patients with bacteremic pneumococcal pneumonia and in-hospital mortality.

Characteristic	Died while in the hospital, no. (%) of patients		
	Yes (n = 35)	No (n = 374)	P
Age ⩾65 years	22 (63)	179 (48)	.08
Male sex	22 (63)	230 (61)	.8
Comorbidity	31 (89)	297 (79)	.2
Ultimately or rapidly fatal underlying disease	17 (49)	153 (41)	.3
Neutropenia	3 (9)	12 (3)	.1
Received corticosteroid treatment	4 (11)	37 (10)	.7
Underwent cancer chemotherapy	2 (6)	1 (0.3)	.0004
Received prior antibiotic treatment	4 (11)	37 (10)	.7
Nosocomial infection	3 (9)	20 (5)	.4
Intensive care unit admission	12 (34)	35 (9)	<.0001
Shock	16 (46)	24 (6)	<.0001
Infecting agent had erythromycin resistance	9 (26)	60 (16)	.1
Infecting agent had penicillin resistance	8 (23)	64 (17)	.3
Infecting agent had penicillin and erythromycin resistance	6 (17)	24 (6)	.02
Empirical treatment received			
Cefotaxime, ceftriaxone, or cefepime	29 (83)	271 (72)	.2
Ceftazidime	4 (11)	20 (5)	.1
Second-generation cephalosporin	1 (3)	50 (13)	.1
Penicillins or aminopenicillins	1 (3)	26 (7)	.3
Carbapenem	1 (3)	6 (2)	.5
Nonmacrolide, non–β-lactam antibiotics	15 (43)	73 (20)	.001
Initially received macrolide treatment	18 (51)	220 (59)	.3
Received treatment during 1996–2000	18 (51)	211 (56)	.5

β-lactam plus a macrolide was not associated with in-hospital mortality (data not shown).

DISCUSSION

In this study, we evaluated a relative large series of patients with bacteremic pneumococcal pneumonia initially treated with β-lactams to assess whether the inclusion of a macrolide as part of an empirical β-lactam–based regimen was associated with a lower in-hospital mortality rate. This analysis showed that, indeed, failure to include a macrolide in the initial treatment of patients with bacteremic pneumococcal pneumonia was an independent predictor of death. However, the link between these 2 variables was not straightforward. In fact, univariate analysis did not reveal a link, and it was not until we adjusted for shock that the association was fully uncovered. In this patient population, shock—and, to a lesser degree, age—acted as negative confounders of the association between inclusion of a macrolide as part of the empirical antibiotic regimen and a better prognosis. Obviously, the negative confounding was due to the fact that a macrolide was more frequently given to patients with shock, which, in turn, was the main predictor of death.

We have been using macrolides on a regular basis as part of the empirical treatment of CAP (particularly for patients with severe disease) since the late 1980s, after some investigations conducted by our own group [12] and other authors from our country [13] emphasized the etiologic role of *Legionella pneumophila* in CAP requiring ICU admission. The continuous influx of epidemiological data regarding the relatively high prevalence of atypical organisms among hospitalized patients with CAP [14], the recognition of the eventual life-threatening nature of the associated disease, and the frequency of coinfection and its possible effects on morbidity [15] have all contributed to reinforce the liberal use of macrolides in our setting, despite the doubts raised by some authors about the prognostic implications of atypical microorganisms and the routine use of this antibiotic family [16]. These considerations may help to explain the higher prevalence of shock and ICU admission

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Table 4. Prognostic factors independently associated with in-hospital mortality by logistic regression analysis.

Prognostic factor	OR (95% CI)	*P*
Age ⩾65 years	2.52 (1.12–5.67)	.025
Shock	18.3 (7.48–45)	<.0001
Receipt of empirical macrolide therapy	0.4 (0.17–0.92)	.03
Macrolide and penicillin resistance	3.1 (1.05–9.17)	.04

among patients receiving a macrolide in the present series, because both characteristics are unquestionable markers of CAP severity.

Our data agree with those of recent studies showing that initial treatment with either a second- or third-generation cephalosporin plus a macrolide was independently associated with increased survival rates among elderly individuals [3] or that initial treatment with a macrolide plus a second- or third-generation cephalosporin or a β-lactam or β-lactamase inhibitor was independently associated with increased survival rates in a mixed population of patients with CAP [4]. The present data expand this finding to patients with bacteremic pneumococcal pneumonia and agree with the findings of a prior 20-year longitudinal study on the same subject that showed that patients receiving any macrolide antibiotic in combination with a β-lactam had the lowest case-fatality rate [1]. Some authors have found that the association of a particular antibiotic regimen with prognosis may vary, depending on the period considered [7], raising the possibility of confounding by the well-known temporal variability of the incidence of atypical pneumonia. In this respect, we were unable to note any influence related to a particular period of time throughout the whole span of the study.

We do not have a satisfactory explanation for the independent association between resistance to both macrolides and β-lactams and mortality. The possibility that these strains were more virulent than those that are susceptible to penicillin, to macrolides, or to both seems unlikely [17]. Another possible explanation is that resistance to erythromycin negates the putative beneficial effect of macrolides on bacteremic pneumococcal pneumonia, particularly when it is due to penicillin-resistant strains. This is an interesting hypothesis deserving further study, but it does not agree with current opinion, which tends to attribute the effect of macrolides to their modulatory activity on proinflammatory responses of leukocytes and other host cells [18]. The last possible explanation—and perhaps the most plausible one—is that patients who were infected with strains that are resistant to both classes of antibiotics, in fact, had a more serious disease. We cannot rule out this possibility, because, besides age and comorbidity, the only real markers of severity considered in this study—shock and ICU admission—were too stringent.

The present work has the shortcomings common to any observational study in which empirical antimicrobial therapy has not been selected at random. As long as physicians base their therapeutic choice on clinical presentation or patient characteristics, there is always room for residual nonadjustable confounding on the observed association between outcome and a particular antimicrobial regimen. The reason for this association cannot be determined from the present study, and the question of whether it reflects any real effect of macrolides or is rather the result of physicians' choice of therapy on the basis of patient presentation (and, therefore, ultimate outcome) can be definitively answered only by a randomized clinical trial. However, to make such a study feasible may be difficult.

In conclusion, the data from this study suggest that addition of a macrolide to an initial β-lactam–based antibiotic regimen is associated with a lower in-hospital mortality rate for patients with bacteremic pneumococcal pneumonia. Therefore, this study supports the recommendation of combination therapy with a β-lactam plus a macrolide for treatment of patients with CAP requiring hospital admission when a positive diagnosis (based on results of a reliable test) is not immediately available, even if the most probable causal agent is *S. pneumoniae.*

References

1. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American city: a 20-year longitudinal study, 1978–1997. Am J Med **1999**; 107(Suppl 1A):34S–43S.
2. Stahl JE, Barza M, DesJardin J, Martin R, Eckman MH. Effect of macrolides as part of initial empiric therapy on length of stay in patients hospitalized with community-acquired pneumonia. Arch Intern Med **1999**; 159:2576–80.
3. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ. Association between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med **1999**; 159: 2562–72.
4. Dudas V, Hopefl A, Jacobs R, Guglielmo BJ. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. Ann Pharmacother **2000**; 34:446–52.
5. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med **2001**; 161:1837–42.
6. Bartlett JG, Dowell SF, Mandell LA, File TM, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Clin Infect Dis **2000**; 31:347–82.
7. Houck PM, MacLehose RF, Niederman MS, Lowery JK. Empiric antibiotic therapy and mortality among Medicare pneumonia inpatients in 10 western states. Chest **2001**; 119:1420–6.
8. Ruiz-González A, Falguera M, Nogués A, Rubio-Caballero M. Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. Am J Med **1999**; 106:385–90.
9. Johansen HK, Jensen TG, Dessau RB, Lundgren B, Frimodt-Moller N. Antagonism between penicillin and erythromycin against *Streptococcus pneumoniae* in vitro and in vivo. J Antimicrob Chemother **2000**; 46: 973–80.
10. National Committee for Clinical Laboratory Standards (NCCLS). Performance standards for antimicrobial susceptibility testing, 12th in-

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ternational supplement. NCCLS document M100-S12 Wayne, PA: NCCLS, **2002**.
11. McCabe WR, Jackson GG. Gram-negative bacteremia. I. Etiology and ecology. Arch Intern Med **1962**; 110:847–55.
12. Torres A, Serra-Batlles J, Ferrer A, et al. Severe community-acquired pneumonia: epidemiology and prognostic factors. Am Rev Respir Dis **1991**; 144:312–9.
13. Pachon J, Prados MD, Capote F, Cuello JA, Garnacho J, Verano A. Severe community-acquired pneumonia: etiology, prognosis, and treatment. Am Rev Respir Dis **1990**; 142:369–73.
14. Marston BJ, Plouffe JF, File TM, et al. Incidence of community-acquired pneumonia requiring hospitalization: results of a population-based active surveillance study in Ohio. Arch Intern Med **1997**; 157: 1709–18.
15. Kauppinen MT, Saikku P, Kujala P, Herva E, Syrjälä H. Clinical picture of community-acquired *Chlamydia pneumoniae* pneumonia requiring hospital treatment: a comparison between chlamydial and pneumococcal pneumonia. Thorax **1996**; 51:185–9.
16. Mundy LM, Oldach D, Auwaerter PG, et al. Implications for macrolide treatment in community-acquired pneumonia. Chest **1998**; 113: 1201–6.
17. Azoulay-Dupuis E, Rieux V, Muffat-Joly M, et al. Relationship between capsular type, penicillin susceptibility and virulence of human *Streptococcus pneumoniae* isolates in mice. Antimicrob Agents Chemother **2000**; 44:1575–7.
18. Hoyt JC, Robbins RA. Macrolide antibiotics and pulmonary inflammation. FEMS Microbiol Lett **2001**; 205:1–7.

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