Drug-Resistant Pneumococcal Pneumonia: Clinical Relevance and Related Factors

Javier Aspa,[1] Olga Rajas,[1] Felipe Rodríguez de Castro,[4] José Blanquer,[5] Rafael Zalacain,[6] Asunción Fenoll,[3] Rosa de Celis,[7] Antonio Vargas,[8] Francisco Rodríguez Salvanés,[2] Pedro Pablo España,[9] Jordi Rello,[10] and Antoni Torres,[7] on behalf of the Pneumococcal Pneumonia in Spain Study Group[a]

[1] Servicio de Neumología and [2]Unidad de Epidemiología Clínica, Hospital de la Princesa, and [3]Laboratorio de Referencia de Neumococos, Servicio de Bacteriología, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, [4]Servicio de Neumología, Hospital de Gran Canaria Dr. Negrín, Las Palmas, [5]Unidad de Cuidados Intensivos, Hospital Clínico, Valencia, [6]Servicio de Neumología, Hospital de Cruces, Bilbao, [7]Servei de Pneumología i Alergia Respiratoria, Institut Clínic de Pneumología i Cirugía Torácica, Hospital Clínic, Barcelona, [8]Servicio de Neumología, Hospital Universitario de Puerto Real, Puerto Real, Cádiz, [9]Hospital de Galdakao, Galdakao, Vizcaya, and [10] Hospital Universitario Joan XXIII, Tarragona, Spain

A multicenter study of 638 cases of community-acquired pneumonia due to *Streptococcus pneumoniae* (SP-CAP) was performed to assess current levels of resistance. Of the pneumococcal strains, 35.7% had an minimum inhibitory concentration (MIC) of penicillin of $\geqslant 0.12$ μg/mL (3 isolates had an MIC of 4 μg/mL), 23.8% had an MIC of erythromycin of 128 μg/mL, and 22.2% were multidrug resistant. Logistic regression determined that chronic pulmonary disease (odds ratio [OR], 1.44], human immunodeficiency virus infection (OR, 1.98), clinically suspected aspiration (OR, 2.12), and previous hospital admission (OR, 1.69) were related to decreased susceptibility to penicillin, and previous admission (OR, 1.89) and an MIC of penicillin of MIC $\geqslant 0.12$ μg/mL (OR, 15.85) were related to erythromycin resistance (MIC, $\geqslant 1$ μg/mL). The overall mortality rate was 14.4%. Disseminated intravascular coagulation, empyema, and bacteremia were significantly more frequent among patients with penicillin-susceptible SP-CAP. Among isolates with MICs of penicillin of $\geqslant 0.12$ μg/mL, serotype 19 was predominant and was associated with a higher mortality rate. In summary, the rate of resistance to β-lactams and macrolides among *S. pneumoniae* that cause CAP remains high, but such resistance does not result in increased morbidity.

The increasing incidence of multiple-antimicrobial resistance among *Streptococcus pneumoniae* isolates is becoming a problem throughout the world [1, 2]. Recent data from the Alexander Project show that there are high rates of penicillin resistance among *S. pneumoniae* in France and Spain, with intermediate and resistant strains currently accounting for ∼50% of isolates [3–6]. *S. pneumoniae* strains that are resistant to penicillins also have decreased susceptibility to other antibiotics [7, 8], which may limit the choice of available antimicrobials for empirical treatment of community-acquired pneumonia (CAP). Macrolide resistance among pneumococci is also increasing in Europe and in the United States and other countries [5, 9–11].

Recognition of patients with an increased risk of acquiring drug-resistant pneumococcal pneumonia is essential for control of the epidemic spread of these strains and selection of appropriate initial antimicrobial treatment. Several risk factors for aquisition of penicillin- and multidrug-resistant pneumococci have been reported [12–16], but the risk factors for acquisition of

pneumonia caused by erythromycin-resistant *S. pneumoniae* have been studied less frequently [11, 17]. Moreover, the clinical impact of drug-resistant *S. pneumoniae* is controversial. All currently available studies suggest that the MIC of penicillin ($\leqslant 2$ μg/mL) is not independently associated with an increased mortality rate, but an effect of resistance on morbidity is not so evident [18–26]. Therapeutic failures involving macrolides have been reported among patients who are infected with erythromycin-resistant pneumococci [27]. To better understand the epidemiological and clinical aspects of drug-resistant *S. pneumoniae* pneumonia, a prospective, multicenter study was conducted in Spain, a country with a high rate of multiple antimicrobial–resistant pneumococci.

PATIENTS, MATERIALS, AND METHODS

Design and study population. From January 1999 through April 2000, a multicenter, observational, prospective study was performed in 35 Spanish hospitals. All consecutive adult (age, >16 years) patients who received a diagnosis of pneumococcal CAP were included. A diagnosis of CAP was assumed in the presence of acute onset of signs and symptoms suggesting lower respiratory tract infection at hospital admission and radiographic evidence of a pulmonary infiltrate that neither was preexisting nor had another known cause.

Diagnostic criteria. Microbial investigation techniques were ordered at the discretion of the attending physician. A diagnosis of probable pneumococcal pneumonia was made in cases in which there was a predominance of gram-positive cocci in pairs and chains and heavy growth of *S. pneumoniae* on validated sputum and/or tracheobronchial aspirate (BAS) cultures. A definite diagnosis of pneumococcal pneumonia was considered when (1) there was a diagnosis of probable pneumococcal pneumonia and a urinary antigen test result was positive for *S. pneumoniae,* or (2) one of the following criteria were met: (a) $\geqslant 1$ blood culture was positive for *S. pneumoniae*; (b) pleural fluid, transthoracic needle aspiration, or lung biopsy specimens yielded *S. pneumoniae;* or (c) there was bacterial growth of $\geqslant 10^3$ cfu/mL of *S. pneumoniae* with a protected specimen brush and/or $\geqslant 10^4$ cfu/mL with a bronchoalveolar lavage specimen. Mixed infections were diagnosed when another likely microorganism was identified and $\geqslant 1$ of the following criteria were met: (1) there was a $\geqslant 4$-fold increase in IgG titers for *Chlamydia pneumoniae, Chlamydia psittaci, Legionella pneumophila, Coxiella burnetii,* or respiratory viruses; (2) there was a single elevated IgM titer for *Mycoplasma pneumoniae;* (3) a urinary antigen test was positive for *Legionella pneumophila;* (4) another bacterial pathogen was identified (in accordance with standard methods) in samples other than sputum or BAS samples.

Data collection. Baseline data on patient demographic characteristics and clinical and laboratory findings were collected by clinical research using a standardized data collection form. The presence or absence of the following conditions and characteristics was assessed: residence, smoking, alcohol or illicit drug abuse, chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, cardiovascular diseases, diabetes mellitus, solid or hematologic malignancy, chronic renal or hepatic disease, neurologic disease, suspicion of aspiration, swallowing dysfunction, previous use of β-lactams (for $\geqslant 5$ days in the past 3 months), use of glucocorticosteroids or immunosuppressive drugs, HIV infection, immunologic disease, splenectomy, prior pneumonia, and hospitalization within the previous 3 months.

All laboratory tests were performed using conventional equipment. The included samples were obtained from the patient in the emergency department. Complications that occurred $\leqslant 30$ days after presentation with CAP were recorded; these consisted of worsening of any major underlying disease and/or presence of shock (blood pressure of $\leqslant 90$ mm Hg that was not corrected by administration of intravenous fluids or for which pressor medication was required), disseminated intravascular coagulation (DIC), renal insufficiency (serum creatinine level of >1.5 mg/dL and/or blood urea nitrogen level of >20 mg/dL in patients with previously normal function), respiratory failure (partial pressure of oxygen/fraction of inspired oxygen of <300 mm Hg or of <200 mm Hg in patients with COPD), and extrapulmonary involvement of pneumococcal pneumonia. The need for hospital admission, Pneumonia Severity Index (PSI) score [28], transfer to the intensive care unit or receipt of mechanical ventilation, and mortality at 30 days after presentation were assessed for all patients. Duration of antibiotic therapy (oral and intravenous) was also evaluated. Thirty days after the diagnosis of CAP, patients were asked about the presence of respiratory symptoms, and a new chest radiograph was obtained.

Antimicrobial susceptibility testing. Antibiotic susceptibility tests were done during routine patient care at each institution. All pneumococcal isolates were subcultured, stored frozen at -70°C, and subsequently submitted to the National Center of Microbiology (Majadahonda, Madrid) for serotyping [6, 29] and antimicrobial susceptibility testing. Susceptibility or resistance of pneumococci to antimicrobials was assessed by dilution in agar, in accordance with the recommendations of the 2002 NCCLS guidelines [30]. The following antibiotics were tested: penicillin, amoxicillin, cefuroxime, cefotaxime, imipenem, vancomycin, teicoplanin, erythromycin, tetracycline, chloramphenicol, levofloxacin, and trovafloxacin. Clarithromycin and azithromycin were considered to be the same as erythromycin with regard to susceptibility and resistance. Ceftriaxone and cefotaxime were also considered to be equivalent. Multidrug resistance was defined as intermediate resistance or

resistance to penicillin plus intermediate resistance or resistance to ≥2 non–β-lactam agents.

Other variables' definitions. Smokers were considered to be current smokers even if they had quit smoking ≤6 months before the beginning of the study. Alcohol abuse was established as an estimated daily consumption of ≥80 g of alcohol for at least the preceding year. Chronic pulmonary disease included COPD, chronic bronchitis, bronchiectasis, and chronic pulmonary conditions other than asthma. Immunosuppressive treatment was defined as the administration of any cytotoxic agent or corticosteroids (at dosages of ≥15 mg q.d. for prednisone) during the previous 6 months. A "typical clinical syndrome" was defined as presence of ≥3 of the following symptoms: cough, expectoration, pleuritic pain, fever, and onset or increase of dyspnea.

Statistical analysis. Results are expressed as mean ± SD. Continuous variables were compared using Student's t test; categorical variables were compared using Fisher's exact test and the χ^2 test (with Yates' correction, when necessary). The association between serotypes and mortality was performed in accordance with the method described by Freeman [31] and Martín Andrés and Luna del Castillo [32]. To define which variables were significantly and independently associated with resistance, regression logistic analyses that tested several models were performed. Significance was defined as $P < .05$; 95% CIs were based on the estimated variance of the regression coefficients. The choice of models was performed on the basis of the criteria defined by Hommer and Lemeshow [33].

RESULTS

Patient characteristics. There were a total of 638 patients (413 of whom were men), with a mean age of 61.5 years (range, 16–97 years). The main demographic characteristics, comorbidities, clinical symptoms, radiographic patterns, and PSI scores [28] are summarized in table 1. A definite diagnosis of pneumococcal CAP was noted for 466 patients (73%). A total of 459 (71.9%) of the *S. pneumoniae* isolates were recovered from blood and pleural fluid specimens. Serological samples were obtained from 340 patients (53.3%; single samples for 147 patients and paired samples for 193 patients). IgM titers for *M. pneumoniae* were determined for 109 patients. One hundred sixty urine samples were analyzed for *Legionella* antigen. Mixed infections were present in 34 patients (5.3%). There were 28 double infections and 6 triple infections.

Antimicrobial susceptibilities. The in vitro activities of 12 antimicrobial agents against 638 *S. pneumoniae* isolates (1 strain per patient) are shown in table 2. Sixty-five of the 638 patients were infected with penicillin-resistant pneumococcus (the MIC was 2 μg/mL in 62 [9.7%] of 638 cases [95% CI, 7.53%–12.3% and 4 μg/mL in 3 [0.5%] cases [95% CI, 0.09%–1.37%). Pen-

icillin-nonsusceptible strains (MIC, ≥0.12 μg/mL) were more frequently recovered from patients classified as having probable pneumococcal pneumonia (χ^2, 25.71; $P < .00001$) than among those who were not. Sixty-six specimens recovered from the upper respiratory tract (i.e., sputum samples; 50%), 34 samples recovered from the lower respiratory tract (i.e., BAS, protected specimen brush, transthoracic needle aspiration, and bronchoalveolar lavage samples; 54.8%), and 129 invasive isolates (i.e., blood and pleural fluid samples; 29.1%) had intermediate or high-level resistance to penicillin (χ^2, 30.11; $P = .0000$). Overall, cefotaxime and amoxicillin were the most active β-lactam agents. One hundred seventy-four strains (27.4%) were characterized as being erythromycin nonsusceptible (MIC, ≥1 μg/mL). Four strains had an MIC of 2 μg/mL, 2 had an MIC of 8 μg/mL, 3 had an MIC of 16 μg/mL, 7 had an MIC of 32 μg/mL, and 6 had an MIC of 64 μg/mL. The MIC of erythromycin was 128 μg/mL for 152 pneumococcal isolates (23.8%; 95% CI, 20.5%–27.1%). Again, isolates recovered from blood specimens exhibited a lower rate of erythromycin resistance than did isolates recovered from the respiratory tract. The MIC for the 4 levofloxacin-resistant isolates (0.62%; 95% CI, 0.17%– 1.6%) was 16 μg/mL, and all of these isolates were multidrug resistant. Only 27 (4.2%; 95% CI, 2.81%–6.1%) of the levofloxacin-susceptible strains had an MIC of 2 μg/mL. Of this collection of pneumococcal isolates, 142 (22.2%) of 638 were found to be resistant to multiple drugs. Cross-resistance data are shown in tables 3 and 4).

Penicillin-nonsusceptible SP-CAP was more likely to be diagnosed in patients with chronic pulmonary diseases (OR, 1.44; 95% CI, 1.02–2.04; $P = .03$), HIV infection (OR, 1.98; 95% CI, 1.12–3.47; $P = .01$), suspicion of aspiration (OR, 2.12; 95% CI, 1.17–3.85; $P = .01$), or prior admissions to the hospital (OR, 1.69; 95% CI, 1.05–2.27; $P = .02$). Previous hospital admissions (OR, 1.89; 95% CI, 1.06–3.88; $P = .031$) and an MIC of penicillin of ≥0.12 μg/mL (OR, 15.85; 95% CI, 10.16–24.72) were also related with erythromycin-resistant pneumococcus (tables 5 and 6).

Serotypes. Frequency, nonsusceptibility to penicillin, and associated mortality for different serotypes are shown in figure 1. Among the 36 different serotypes identified in our series, the most common, accounting for 35% of the total, were serotypes 3 (16.9%), 19 (10.7%), and 14 (7.5%). Among the penicillin-nonsusceptible pneumococcal isolates, serotype 19 was the predominant serotype (22.7%), followed by serotypes 14 (19.2%) and 9V (16.2%). Serotypes were stratified into 3 groups according to mortality rate. There were no deaths associated with group A (serotypes 1, 5, 8, 10, 13, 17, 18A, 18F, 20, 23F, 25, 34, 37, 38, and 42). The mortality rate associated with group B (serotypes 3, 4, 6A, 6B, 7, 9N, 9V, 11, 12, 14, 15A, 15F, 16, 18C, 22, 23A, 23B, 31, 33, and 35 and nontypeable

Table 1. General features, main clinical findings, and radiological data at initial assessment for 638 patients.

Characteristic	Value	95% CI[a]
Age, mean years	61.58	60.02–63.14
Sex		
Male	413 (64.7)	61.0–68.4
Female	225 (35.3)	31.6–39.0
Nursing home	34 (5.3)	3.72–7.37
Consumption of tobacco		
Yes	377 (59.1)	55.3–62.9
No	261 (40.9)	37.1–44.7
Mean no. of packs of cigarettes smoked per year	46.50	42.43–50.56
Alcohol use		
Alcohol abuse	144 (22.6)	19.3–25.8
Amount consumed, mean g per day	85.13	67.91–102.34
Use of illicit drugs	63 (9.9)	8.4–13.4
Comorbidities or risk factors		
Cardiological conditions	102 (16.0)	13.1–18.8
Chronic pulmonary disease	254 (39.8)	36.0–43.6
Asthma	43 (6.7)	4.92–8.97
Diabetes	112 (17.6)	14.6–20.5
Neurological conditions	59 (9.2)	7.11–11.8
Neoplastic conditions	44 (6.9)	5.05–9.15
Liver	74 (11.6)	9.11–14.1
Receipt of immunosuppressive treatment	61 (9.6)	7.39–12.1
HIV infection	61 (9.6)	7.39–12.1
Receipt of transplant	5 (0.8)	0.25–1.82
Suspected aspiration	51 (8.0)	6.01–10.4
Previous β-lactam therapy	62 (9.7)	7.53–12.3
Previous hospital admission	86 (13.5)	10.8–16.1
Polymicrobial pneumonia	34 (5.3)	3.72–7.37
Renal events	79 (12.4)	9.83–14.9
Typical clinical symptoms	532 (83.4)	80.5–86.3
Bilateral involvement	99 (15.5)	12.7–18.3
Pleural effusion	129 (20.2)	17.1–23.3
PSI score		
Class I	69 (10.8)	8.41–13.2
Class II	80 (12.5)	9.97–15.1
Class III	108 (16.9)	14–19.8
Class IV	234 (36.7)	32.9–40.4
Class V	147 (23.0)	19.8–26.3

NOTE. Data are no. (%) of patients, unless otherwise indicated. PSI, Pneumonia Severity Index.

[a] Data are expressed in percentages, except when they refer to mean values.

isolates) was 17%, and it was 28% among patients infected with a serotype 19 pneumococcal isolate ($P \leqslant .05$).

Prognoses and outcomes for patients. Ninety-three percent of the patients were initially admitted to the hospital (95% CI, 90.8%–94.9%). Outcomes and complications (according to the susceptibility of the isolated pneumococcal strains) are shown in tables 7 and 8. We could not demonstrate any effect of antimicrobial resistance on morbidity and mortality. Only patients with DIC, empyema, or bacteremia were significantly more likely to be infected with penicillin-susceptible *S. pneumoniae*. Bacteremia was also significantly more common among patients infected with erythromycin-susceptible pneumococci.

Table 2. Antimicrobial susceptibility of 638 pneumococcal strains isolated in Spain, January 1999 through April 2000.

| Antibiotic | Susceptibility breakpoint, μg/mL | | | Susceptible | | Intermediate | | Resistant | |
	Susceptible	Intermediate	Resistant	No. (%) of isolates	95% CI, %	No. (%) of isolates	95% CI, %	No. (%) of isolates	95% CI, %
Amoxicillin	≤2	4	≥8	604 (94.7)	92.6–96.3	19 (3)	1.8–4.6	15 (2.4)	1.32–3.8
Penicillin	≤0.06	0.12–1	≥2	410 (64.3)	60.5–68	163 (25.5)	22.2–28.9	65 (10.2)	7.8–12.5
Erythromycin	≤0.25	0.5	≥1	463 (72.6)	69.1–76	…	…	175 (27.4)	24–30.9
Cefotaxime	≤1	2	≥4	620 (97.2)	95.6–98.3	16 (2.5)	1.44–4.04	2 (0.3)	0.038–1.13
Cefuroxime	≤0.5	1	≥2	434 (68)	66.4–71.6	20 (3.1)	1.9–4.8	184 (28.8)	25.3–32.4
Imipenem	≤0.12	0.25–0.5	≥1	470 (73.7)	70.3–77.1	141 (22.1)	18.9–25.3	27 (4.2)	2.8–6.1
Vancomycin	≤1	…	…	638 (100)	…	…	…	…	…
Teicoplanin	≤1	…	…	638 (100)	…	…	…	…	…
Levofloxacin	≤2	4	≥8	634 (99.4)	98.4–99.8	…	…	4 (0.6)	0.2–1.6
Trovafloxacin	≤1	2	≥4	634 (99.4)	98.4–99.8	…	…	4 (0.6)	0.2–1.6
Tetracycline	≤2	4	≥8	437 (68.5)	64.9–72.1	5 (0.8)	0.255–1.82	196 (30.7)	27.1–34.3
Chloramphenicol	≤4	…	≥8	523 (82)	79–85	…	…	115 (18)	15–21

NOTE. MICs for *Streptococcus pneumoniae* are from [30].

The overall mortality rate for our cohort was 14.4% (95% CI, 11.7%–17.1%). Fifty (12.2%) of 409 patients with CAP caused by penicillin-susceptible pneumococci died, compared with 30 (18.3%) of 164 patients and 12 (18.5%) of 65 patients infected with strains that were intermediately resistant and resistant to penicillin, respectively (*P* = .054).

DISCUSSION

The most important findings of this study are the following: (1) patients with chronic pulmonary disease, HIV infection, or suspected aspiration or who were admitted to the hospital within the previous 3 months were more likely than other patients to have penicillin-resistant pneumococcal pneumonia; (2) previous hospital admissions and decreased susceptibility to penicillin were independent risk factors for erythromycin resistance; (3) DIC, empyema, and bacteremia were significantly more common in patients with drug-susceptible pneumococcal CAP; (4) among pneumococcal-resistant isolates, se-

rotype 19 was predominant, and this serotype was associated with a significantly higher mortality rate than were other serotypes.

In our study, the overall national rate of penicillin resistance among clinical isolates of *S. pneumoniae* was 35.7%. These findings confirm the most recent published results from Spain [4–6, 12] and from the United States [34]. With regard to high-level resistance to penicillin, our series found that the prevalence had apparently decreased to 10.2%, compared with the findings of recent surveys [5]. Of 638 isolates, only 3 had an MIC of 4 μg/mL, and there were no isolates with an MIC of ≥8 μg/mL. Antimicrobial resistance rates are highest among isolates recovered from respiratory specimens and from children; in our study, only adult patients with CAP were included, and 60.2% of isolates were recovered from blood and pleural fluid samples, which may explain these lower rates of high-level pneumococcal penicillin-resistance. Rates of resistance to all β-lactam agents increased in parallel with rates of penicillin resistance, and amoxicillin and cefotaxime nonsusceptibility clustered only in

Table 3. Cross-resistance: intermediate resistance and resistance among strains of *Streptococcus pneumoniae*.

| Antibiotic | No. of patients | Percentage of isolates with decreased susceptibility, by antibiotic | | | | | | |
		Penicillin	Erythromycin	Cefuroxime	Imipenem	Amoxicillin	Cefotaxime	Levofloxacin
Penicillin	229	…	60.3	88.6	73.4	14.8	7.9	1.7
Erythromycin	174	78.9	…	67.4	55.4	13.1	8	2.3
Cefuroxime	204	99	57.6	…	81	16.6	8.8	2
Imipenem	168	99.4	57.4	98.2	…	19.5	10.7	2.4
Amoxicillin	34	100	67.6	100	97.1	…	20.6	0
Cefotaxime	18	100	77.8	100	100	38.9	…	0
Levofloxacin	4	100	100	100	100	0	0	…

NOTE. Decreased susceptibility was defined as intermediate resistance and resistance on the basis of the breakpoints shown in table 2.

Table 4. Cross-resistance with penicillin (intermediate resistance and resistance) among 229 strains of *Streptococcus pneumoniae*.

Antibiotic in combination with penicillin	No. of patients	Percentage of isolates with decreased susceptibility, by antibiotic					
		Erythromycin	Cefuroxime	Imipenem	Amoxicillin	Cefotaxime	Levofloxacin
Erythromycin	138	…	84.1	69.6	16.7	10.1	2.9
Cefuroxime	203	57.1	…	81.3	16.7	8.9	2
Imipenem	168	57.1	98.2	…	19.6	10.7	2.4
Amoxicillin	34	67.6	100	97.1	…	20.6	0
Cefotaxime	18	77.8	100	100	38.9	…	0
Levofloxacin	4	100	100	100	0	0	…

NOTE. Decreased susceptibility was defined as intermediate resistance and resistance on the basis of the breakpoints shown in table 2.

penicillin-resistant *S. pneumoniae.* It is important to note that amoxicillin now has higher breakpoints (susceptible, ≤2 μg/mL; intermediate, 4 μg/mL; resistant, ≥8 μg/mL [30]) than before, which may give the impression that it is more active in vitro than are other antibiotics for which the breakpoints have not been changed. Twenty-four percent of isolates in our series had an MIC of erythromycin of 128 μg/mL. This implies that *ermB*-mediated ribosomal methylation is the predominant macrolide resistance mechanism in this study, whereas most of the erythromycin-resistant pneumococcal isolates in the United States display the efflux phenotype [34].

Relatively high rates of ciprofloxacin resistance in *S. pneumoniae* have been reported recently in Spain, mainly clustered in erythromycin- and penicillin-nonsusceptible strains [5, 35, 36]. Although ciprofloxacin resistance is not a good marker for resistance to newer quinolones, it could be a warning signal for a future increase. Levofloxacin was introduced in Spain in September 1998, which can explain the current low rates of resistance [37, 38]. In our study, 4 strains of *S. pneumoniae* had an MIC of levofloxacin of 16 μg/mL and also showed resistance to 4–5 additional antimicrobials. Multidrug resistance continues to grow as a problem among strains of *S. pneumoniae*. Overall, 22.2% of the pneumococcal isolates tested in this study were resistant to ≥3 different classes of antimicrobials, and 58.4% of these isolates were resistant to ≥4 different antimicrobial classes. Increases in the frequency of resistance to other antimicrobials occurred exclusively among penicillin-resistant isolates. Among the multidrug-resistant isolates in our study, the predominant serotype was 19 (28.9%), suggesting a strong clonal relationship.

In this study, chronic pulmonary disease, HIV infection, suspected aspiration, and previous hospital admissions were each independent predictors of penicillin-resistant pneumococcal pneumonia. In contrast with the most recent recommendations of the American Thoracic Society [2], age, alcoholism, and previous or concomitant therapy with β-lactams or corticosteroids were not found to be significantly associated with pen-

icillin resistance. The limited number of patients who had previously received therapy with β-lactams (9.7%) or immunosuppressive therapy (9.6%) in our series might preclude their identification as potential risk factors for drug-resistant pneumococci. In addition, a longer interval for assessing prior exposure to β-lactams should have been considered [39]. There was a trend for older age (>65 years) and PSI score to be associated with penicillin-resistant SP-CAP (*P* = .057); however, we are uncertain whether the presence of comorbidities, rather than age, is the determining condition that predisposed to this etiology in CAP. In fact, only patients in class V were significantly associated with penicillin-resistant pneumococcal pneumonia. Furthermore, the effect of age as a risk factor has recently been reported to be less clear [8]. Pulmonary comorbidity and HIV infection predisposed patients to pneumonia caused by penicillin-resistant *S pneumoniae.* This is not unexpected, considering that such patients are more likely to be hospitalized and to receive antibiotics—factors that have repeatedly been associated with penicillin-resistant pneumococci [14]. COPD was identified as a major risk factor for acquisition of multidrug-resistant *S. pneumoniae* during an outbreak of nosocomial infection in The Netherlands [40], probably because the spread of pneumococci is biased toward the most vulnerable patients. Ho et al. [41] also reported that patients with COPD could be an important reservoir for levofloxacin-resistant pneumococci. Resistance to erythromycin has increased almost in parallel with resistance to penicillin.

Hospitalization during the previous 3 months was also independently associated with erythromycin-resistant SP-CAP. These findings could be related to the increase in use of antimicrobials and, particularly, of the newer long-acting macrolides [11]. It should be noted that, although there is a clear association between antimicrobial exposure and selection of resistance, antibiotics vary in their ability to select resistant mutants, and macrolides more efficiently induce the emergence of resistant subpopulations than do aminopenicillins [41]. Considering the in vitro rate of macrolide resistance among pneu-

Table 5. Risk factors for community-acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* (MIC, ≥0.12 μg/mL).

Variable	Penicillin-resistant isolates, %	Univariate analysis OR (95% CI)	P	Multivariate analysis OR (95% CI)	P
PSI score			.015		.0566
Class I	21.7	1.00 (referent)		1.00 (referent)	
Class II	32.5	1.7333 (0.8278–3.6293)	…	1.3899 (0.6523–2.9615)	…
Class III	38.9	2.2909 (1.1484–4.5700)	…	1.9932 (0.9834–4.0399)	…
Class IV	34.2	1.8701 (0.9934–3.5205)	…	1.5578 (0.8081–3.0032)	…
Class V	44.9	2.9333 (1.5192–5.6636)	…	2.4455 (1.2368–4.8357)	…
Tobacco use					
Yes	35.0	0.911 (0.656–1.2165)	.615	…	…
No	37.2	…	…	…	…
Alcohol abuse					
Yes	33.3	0.865 (0.584–1.279)	.491	…	…
No	36.6	…	…	…	…
Drug use					
Yes	37.9	1.10 (0.63–1.92)	.775	…	…
No	35.7	…	…	…	…
Chronic pulmonary disease					
Yes	41.3	1.478 (1.064–2.053)	.023	1.4455 (1.0208–2.0467)	.0379
No	32.3	…	…	…	…
Asthma					
Yes	46.5	1.606 (0.862–2.993)	.141	…	…
No	35.1	…	…	…	…
HIV infection					
Yes	45.9	1.587 (0.932–2.702)	.093	1.9808 (1.1297–3.4731)	.0170
No	34.8	…	…	…	…
Diabetes					
Yes	33.9	0.901 (0.586–1.3984)	.666	…	…
No	36.3	…	…	…	…
Receipt of immunosuppressive treatment					
Yes	44.3	1.474 (0.865–2.513)	.162	…	…
No	35	…	…	…	…
Bilateral involvement					
Yes	30.3	0.743 (0.468–1.180)	.254	…	…
No	36.9	…	…	…	…
Suspected aspiration					
Yes	52.9	2.144 (1.206–3.813)	.010	2.1245 (1.1716–3.8524)	.0131
No	34.4	…	…	…	…
Clinical presentation					
Atypical	34	0.903 (0.582–1.4)	.740	…	…
Typical	36.3	…	…	…	…
Previous hospital admission					
Yes	50.0	1.9685 (1.2453–3.1153)	.005	1.6923 (1.0540–2.27167)	.0294
No	33.7	…	…	…	…
Previous β-lactam treatment					
Yes	43.5	1.4286 (0.8403–2.4272)	.210	…	…
No	35.1	…	…	…	…

NOTE. PSI, Pneumonia Severity Index.

Table 6. Risk factors for community-acquired pneumonia erythromycin-resistant *Streptococcus pneumoniae* (MIC, ⩾1 μg/mL).

Variable	Penicillin-resistant isolates,[a] %	Univariate analysis		Multivariate analysis	
		OR (95% CI)	P	OR (95% CI)	P
PSI score					
Class I	14.5	1.00 (referent)	.036	1.00 (referent)	.098
Class II	22.5	1.71 (0.731–4.01)	…	1.276 (0.473–3.44)	…
Class III	35.2	3.20 (1.147–6.97)	…	2.514 (1–6.28)	…
Class IV	28.6	2.37 (1.14–4.9)	…	1.833 (0.78–4.29)	…
Class V	27.9	2.28 (1.07–4.88)	…	1.158 (0.47–2.82)	…
Tobacco use					
Yes	26	1.17 (0.822–1.66)	.384	…	…
No	29.1	…	…	…	…
Alcohol abuse					
Yes	25.7	1.11 (0.727–1.69)	.629	…	…
No	27.7	…	…	…	…
Drug use					
Yes	25.9	1.08 (0.58–2)	.8	…	…
No	27.4	…	…	…	…
Chronic pulmonary disease					
Yes	29.5	0.829 (0.58–1.18)	.298	…	…
No	25.8	…	…	…	…
Asthma					
Yes	32.6	0.762 (0.393–1.479)	.420	…	…
No	26.9	…	…	…	…
HIV infection					
Yes	34.4	0.687 (0.393–1.20)	.187	…	…
No	26.5	…	…	…	…
Diabetes					
Yes	30.4	0.832 (0.532–1.301)	.420	…	…
No	26.6	…	…	…	…
Receipt of immunosuppressive treatment					
Yes	27.9	0.968 (0.537–1.74)	.912	…	…
No	27.2	…	…	…	…
Bilateral involvement					
Yes	29.2	1.205 (0.733–1.98)	.461	…	…
No	27.8	…	…	…	…
Suspected aspiration					
Yes	33.3	0.73 (0.387–1.34)	.311	…	…
No	26.7	…	…	…	…
Clinical presentation					
Atypical	29.2	0.889 (0.561–1.409)	.618	…	…
Typical	26.9	…	…	…	…
Previous hospital admission					
Yes	43	0.43 (0.273–0.698)	.000	1.89 (1.06–3.38)	.031
No	24.8	…	…	…	…
Previous β-lactam treatment					
Yes	33.9	0.706 (0.411–1.190)	.220	…	…
No	26.6	…	…	…	…
Penicillin susceptibility					
Susceptible	8.8	15.625 (10.204–24.39)	.000	15.85 (10.16–24.72)	.000
Not susceptible	60.3	…	…	…	…

NOTE. PSI, Pneumonia Severity Index.
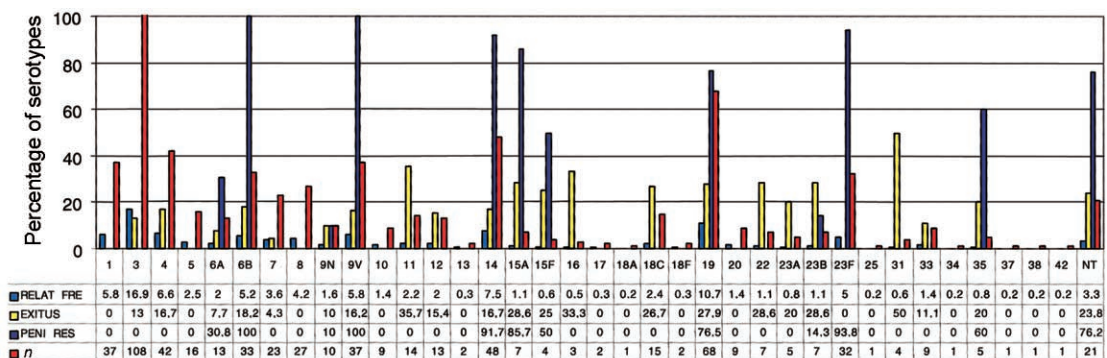
[a] MIC, ⩾0.12 μg/mL.

Figure 1. Distribution of *Streptococcus pneumoniae* serotypes, according to relative frequency, resistance to penicillin, and associated mortality rate. Data are percentage of serotypes, unless otherwise indicated. Exitus, overall associated mortality rate; *n,* number of patients for each serotype; NT, nontypeable serotype; peni res, resistance to penicillin (MIC, $\geqslant$0.12 μg/mL); relat fre, relative frequency of each serotype.

mococci and the median MIC of erythromycin in our study, empirical treatment of CAP with an orally administered macrolide should be reserved for younger and healthier patients with no high-risk factors for drug-resistant *S. pneumoniae* [42].

The impact of drug-resistant *S. pneumoniae* on morbidity and mortality is still controversial. In our study, DIC, empyema, and bacteremia were more frequent among patients infected with a penicillin-susceptible pneumococcus, which may reflect the biological cost that resistance-determining mutations engender on the fitness of bacteria. However, differences are small

and seem unlikely to be clinically significant—that is, they will not affect the choice of antibiotics, because many drug-resistant strains cause bacteremia. This is also true for erythromycin susceptibility. In our series, the mortality rate was higher among patients with strains that were intermediately or highly resistant to penicillin (18.3% and 18.5%, respectively) than among patients with penicillin-susceptible isolates (12.2%), but the differences were not significant ($P = .054$). This trend may have been statistically significant if more patients had been studied. When deaths during the first 4 hospital days were excluded,

Table 7. Outcomes and complications for patients with pneumococcal pneumonia, according to the penicillin susceptibility of the isolate.

Variable	All patients (n = 638)	Patient group, by penicillin susceptibility of the isolate[a]			P
		Susceptible (n = 409)	Intermediate (n = 164)	Resistant (n = 65)	
Total mortality	14.4	12.2	18.3	18.5	.054
Related/total mortality[b]	79.3	84	76.7	66.7	.206
Admission to the ICU	19.6	20.3	18.9	16.9	.507
Receipt of mechanical ventilatory support	13	12	16.5	10.8	.673
Shock	16	15.4	17.1	16.9	.666
Disseminated intravascular coagulation	2	2.9	0.6	0	.038[c]
Renal failure	19.9	21.3	15.2	23.1	.624
Respiratory insufficiency	57.1	56	58.5	60	.488
Empyema	8.3	10	4.9	6.2	.041[c]
Lung abscess	0.9	0.7	1.8	0	.882
Bacteremia[d]	73.6	77.4	61.1	72.9	.022[c]
Extrapulmonary septic focus	1.9	2.7	0	1.5	.128
Admission of patients who were previously outpatients	3.3	3.4	3.1	3.1	.832

NOTE. Data are percentage of patients, unless otherwise indicated. ICU, intensive care unit; related mortality, death attributable to community-acquired pneumoniae, according to the attending physician; total mortality, exitus during the episode of pneumoniae.

[a] Breakpoints for penicillin: susceptible, $\leqslant$0.06 μg/mL; intermediate, 0.12–1 μg/mL; resistant, $\geqslant$2 μg/mL. Patients are grouped by the MIC of penicillin for the isolated pneumococcal strains.
[b] Proportion of patients with related mortality referred to crude (total) mortality.
[c] Statistically significant differences for the 3 categories.
[d] Only analyzed for patients from whom blood samples were obtained for culture.

Table 8. Outcomes and complications for patients with pneumococcal pneumonia, according to the erythromycin susceptibility of the isolate.

| | All patients (n = 638) | Patient group, by erythromycin susceptibility of the isolate[a] | | |
		Susceptible (n = 464)	Resistant (n = 174)	P
Variable				
Total mortality	14.4	12.9	18.4	.08
Related/total mortality[b]	79.3	…	…	…
Admission to the ICU	19.6	19.4	20.1	.839
Mechanical ventilation	13	11.4	17.2	.052
Shock	16	15.1	17.2	.597
Disseminated intravascular coagulation	2	2.4	1.1	.331
Renal failure	19.9	20.9	17.2	.302
Respiratory insufficiency	57.1	56.7	58	.756
Empyema	8.3	9.5	5.2	.079
Lung abscess	0.9	0.6	1.7	.209
Bacteremia[c]	73.6	78.9	57.1	.000[d]
Extrapulmonary septic focus	1.9	2.2	1.1	.405
Admission of patients who were previously outpatients	3.3	3.4	2.9	.717

NOTE. Data are percentage of patients, unless otherwise indicated. ICU, intensive care unit; related mortality, death attributable to community-acquired pneumoniae, according to the attending physician; total mortality, exitus during the episode of pneumoniae.

[a] Resistant, ≥1 μg/mL.
[b] Proportion of patients with related mortality referred to crude (total) mortality.
[c] Only analyzed for patients from whom blood samples were obtained for culture.
[d] Statistically significant difference.

Feikin et al. [21] found that mortality was significantly associated with an MIC of penicillin of ≥4 μg/mL and an MIC of cefotaxime of ≥2 μg/mL. These data suggest that high-level resistance may be associated with adverse outcome. In our study, only 3 patients (0.5%) had CAP caused by *S. pneumoniae* with an MIC of penicillin of 4 μg/mL, and 2 of these patients died. Current levels of resistance to penicillin mostly do not surpass an MIC of 2 μg/mL, and serum and pulmonary levels achieved with β-lactams are several times higher than these MICs. As a consequence, and considering the oversensitive current definition of resistance, only a few patients with penicillin-resistant SP-CAP receive truly discordant antimicrobial treatment, and most studies, including ours, are underpowered to establish the real impact on outcome of these resistant strains.

The serotypes included in the 23-valent vaccine accounted for 88% of resistant strains in our study. According to our data, among pneumococcal-resistant isolates, serotype 19 was predominant, and is also associated with a significantly higher mortality rate in comparison with other serotypes. This may only reflect that serotype 19 was found in a high enough number of patients with sufficient lethality to produce significance when compared with the rest of the serotypes. However, certain serotypes seem to be prone to produce severe disease, and high case-fatality rates have been observed for infections caused by serotypes 3, 6B, and 19F in other studies. Some authors have suggested that serotype may play a more important role than antibiotic susceptibility in mortality due to infection with a pneumococcus [43, 44].

PNEUMOCOCCAL PNEUMONIA IN SPAIN STUDY GROUP

Hospital Universitario Puerto Real, Puerto Real, Cadiz (9 patients): Antonio Vargas (pulmonology [PML]) and Iria J. de la Calle (internal medicine [MCR]); Hospital Virgen Macarena, Sevilla (11 patients): José M. Benítez (PML) and M. José Espinosa de los Monteros (MCR); Hospital Gral. Serranía de Ronda, Ronda, Malaga (25 patients): Francisco J. Cabello (PML), Ana López Cozar (PML), and M. Jesús Pérez Santos (MCR); Hospital Carlos Haya, Malaga (13 patients): Juan J. Martín Villasclaras (PML), Marta Arzola (PML), and Pedro Manchado (MCR); Hospital Juan Ramón Jimenez, Huelva (30 patients): M. Carmen Huertas (PML), José M. Saavedra (MCR), and José D. García Jiménez (PML); Hospital Clínico Universitario, Valencia (39 patients): José Blanquer (respiratory intensive care unit [ICU–PML]), Diego Pérez García (PML), and Rafael Borras (MCR); Hospital Universitario Doctor Peset, Valencia (6 patients): Rafael Blanquer (PML), Ángela Cervera

(PML), and José M. Cervera (MCR); Hospital Francesc de Borja, Gandía, Valencia (7 patients): M. Jesús Cremades (PML), Carlos Navarro (PML), and Rafael Igual (MCR); Hospital Marina Baixa, Villajoyosa, Alicante (20 patients): Adela Martínez Sanchis (PML), José L. Calpe (PML), and M. del Mar López Perezagua (MCR); Hospital La Fe, Valencia (18 patients): Rosario Menéndez Villanueva (PML), José M. Vallés Tarazona (PML), and Miguel Gobernado (MCR); Hospital de Sagunto, Puerto de Sagunto, Valencia (16 patients): Eva Martínez Moragón (PML), Estrella Fernández Fabrellas (PML), and Rosa Escoms (MCR); Hospital Los Arcos, Santiago de la Ribera, Murcia (7 patients): M. Jesús Avilés Anglés (PML) and Margarita Cámara (MCR); Hospital De la Princesa, Madrid (65 patients): Javier Aspa (PML), Olga Rajas (PML), and Buenaventura Buendía (MCR); C. Hospital Ntra Sra De Alarcos, Ciudad Real (4 patients): Amir Mohamed (PML), Fernando Mora (MCR), and M. Dolores Romero (MCR); Hospital Doce de Octubre, Madrid (5 patients): Carlos Álvarez Martínez (PML), M. Dolores Folgueira (MCR), and Manuel Lizasoaín (PML); Hospital Militar del Aire, Madrid (9 patients): Javier Jareño (PML), M. Jesús Chillón (PML), and Francisco Villegas (PML); Fundación Jimenez Díaz, Madrid (10 patients): Rosario Melchor (PML), Javier García López (PML), and Ricardo Fernández Roblas (MCR); Hospital Universitario de Guadalajara, Guadalajara (2 patients): José Gallardo (PML), Jorge Castelao (PML), and M. Teresa Pérez Pomata (MCR); Hospital De Cruces, Cruces-Baracaldo, Vizcaya (49 patients): Rafael Zalacain (PML), Ainhoa Gómez Bonilla (PML), and José L. Hernández Almaraz (MCR); Hospital San Millan-San Pedro, Logroño (7 patients): Manuel Barrón (PML), M. José Gastañares (MCR), and M. Jesús Hermosa (PML); Hospital Cristal Piñor, Orense (25 patients): Julia Tábara (PML), Joaquín Lamela (PML), and Luis Barbeito (MCR); Hospital San Jorge, Huesca (27 patients): Luis Borderías (PML) and Miguel Ferrero (MCR); Hospital Universitario de Canarias, La Laguna, Tenerife (2 patients): Ramón Fernández Álvarez (PML), José. A. Gullón (PML), and Álvaro Torres (MCR); Hospital Central de Asturias, Oviedo, Asturias (9 patients): Luis Molinos (PML) and Isabel Folgueras (MCR); Hospital Universitario Doctor Negrin, Las Palmas, Gran Canaria (12 patients): Felipe Rodríguez de Castro (PML) and Isabel Álamo (MCR); Hospital de Galdakao, Galdakao, Vizcaya (37 patients): Pedro P. España Yandiola (PML), Inmaculada Gorordo (PML), and Pilar Berdonoes (MCR); Hospital Clinico, Barcelona (26 patients): M. Rosa de Celis (PML), Francesc Marco (MCR), and Antoni Torres (PML); Hospital Comarcal de Igualada, Igualada, Barcelona (6 patients): M. José Cardona (PML), Carmen Sarrasela (MCR), and Jordi Zapater (PML); C. Hospital Parc Tauli, Sabadell, Barcelona (37 patients): Jordi Rello (ICU-PML), Miguel Gallego (PML), Manel Lujan (PML), and Dionisia Fontanals (MCR); Hospital Sant Joan, Reus, Tarragona (23 patients): Salvador Hernández Flix

(PML), Rosa M. Tomás Mas (PML), and Frederic Ballester (MCR); Hospital Municipal, Badalona, Barcelona (3 patients): Jaume Oriol (PML), Ignacio Carrasco (PML), and Ana Calderón (MCR); Hospital Santa Creu I Sant Pau, Barcelona (19 patients): Carmen Puzo (PML), Julia Tárrega (PML), and Ferran Sánchez Reus (MCR); Hospital Nostra Sra de Meritxell, Andorra la Vella, Andorra (14 patients): Jordi Roig (PML), Juan Martínez Benazet (PML), and Xavier Casal (MCR); Hospital Germans Trias I Pujol, Badalona, Barcelona (19 patients): Juan Ruiz Manzano (PML), Felipe Andreo (PML), and José Manterola (MCR); Hospital Universitario Dr. Josep Trueta, Girona (27 patients): Montserrat Vendrell (PML), Antonio Castro (IRM), and Jordi Batlle (MCR).

References

1. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. Clin Infect Dis **2000**; 31:347–82.
2. Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med **2001**; 163:1730–54.
3. Felmingham D, Gruneberg RN. The Alexander Project 1996–1997: latest susceptibility data from this international study of bacterial pathogens from community-acquired lower respiratory tract infections. J Antimicrob Chemother **2000**; 45:191–203.
4. Baquero F, Garcia-Rodriguez JA, Garcia de Lomas J, Aguilar L. Antimicrobial resistance of 1,113 *Streptococcus pneumoniae* isolates from patients with respiratory tract infections in Spain: results of a 1-year (1996–1997) multicenter surveillance study. The Spanish Surveillance Group for Respiratory Pathogens. Antimicrob Agents Chemother **1999**; 43:357–9.
5. Perez-Trallero E, Fernandez-Mazarrasa C, Garcia-Rey C, et al. Antimicrobial susceptibilities of 1,684 *Streptococcus pneumoniae* and 2,039 *Streptococcus pyogenes* isolates and their ecological relationships: results of a 1-year (1998–1999) multicenter surveillance study in Spain. Antimicrob Agents Chemother **2001**; 45:3334–40.
6. Fenoll A, Jado I, Vicioso D, Perez A, Casal J. Evolution of *Streptococcus pneumoniae* serotypes and antibiotic resistance in Spain: update (1990 to 1996). J Clin Microbiol **1998**; 36:3447–54.
7. Doern GV, Pfaller MA, Kugler K, Freeman J, Jones RN. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY antimicrobial surveillance program. Clin Infect Dis **1998**; 27:764–70.
8. Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. N Engl J Med **2000**; 343:1917–24.
9. Hsueh PR, Teng LJ, Lee LN, Yang PC, Ho SW, Luh KT. Extremely high incidence of macrolide and trimethoprim-sulfamethoxazole resistance among clinical isolates of *Streptococcus pneumoniae* in Taiwan. J Clin Microbiol **1999**; 37:897–901.
10. Reinert RR, Al-Lahham A, Lemperle M, et al. Emergence of macrolide and penicillin resistance among invasive pneumococcal isolates in Germany. J Antimicrob Chemother **2002**; 49:61–8.
11. Hyde TB, Gay K, Stephens DS, et al. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. JAMA **2001**; 286:1857–62.
12. Ewig S, Ruiz M, Torres A, et al. Pneumonia acquired in the community through drug-resistant *Streptococcus pneumoniae*. Am J Respir Crit Care Med **1999**; 159:1835–42.
13. Clavo-Sanchez AJ, Giron-Gonzalez JA, Lopez-Prieto D, et al. Multi-

variate analysis of risk factors for infection due to penicillin-resistant and multidrug-resistant *Streptococcus pneumoniae:* a multicenter study. Clin Infect Dis **1997**; 24:1052–9.

14. Nava JM, Bella F, Garau J, et al. Predictive factors for invasive disease due to penicillin-resistant *Streptococcus pneumoniae:* a population-based study. Clin Infect Dis **1994**; 19:884–90.

15. Campbell GD Jr, Silberman R. Drug-resistant *Streptococcus pneumoniae.* Clin Infect Dis **1998**; 26:1188–95.

16. Bedos JP, Chevret S, Chastang C, Geslin P, Regnier B. Epidemiological features of and risk factors for infection by *Streptococcus pneumoniae* strains with diminished susceptibility to penicillin: findings of a French survey. Clin Infect Dis **1996**; 22:63–72.

17. Moreno S, Garcia-Leoni ME, Cercenado E, Diaz MD, Bernaldo de Quiros JC, Bouza E. Infections caused by erythromycin-resistant *Streptococcus pneumoniae:* incidence, risk factors, and response to therapy in a prospective study. Clin Infect Dis **1995**; 20:1195–200.

18. Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. Arch Intern Med **2000**; 160:1399–408.

19. Pallares R, Linares J, Vadillo M, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. N Engl J Med **1995**; 333:474–80.

20. Friedland IR. Comparison of the response to antimicrobial therapy of penicillin-resistant and penicillin-susceptible pneumococcal disease. Pediatr Infect Dis J **1995**; 14:885–90.

21. Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995–1997. Am J Public Health **2000**; 90:223–9.

22. Choi EH, Lee HJ. Clinical outcome of invasive infections by penicillin-resistant *Streptococcus pneumoniae* in Korean children. Clin Infect Dis **1998**; 26:1346–54.

23. Deeks SL, Palacio R, Ruvinsky R, et al. Risk factors and course of illness among children with invasive penicillin-resistant *Streptococcus pneumoniae.* The *Streptococcus pneumoniae* Working Group. Pediatrics **1999**; 103:409–13.

24. Turett GS, Blum S, Fazal BA, Justman JE, Telzak EE. Penicillin resistance and other predictors of mortality in pneumococcal bacteremia in a population with high human immunodeficiency virus seroprevalence. Clin Infect Dis **1999**; 29:321–7.

25. Buckingham SC, Brown SP, Joaquin VH. Breakthrough bacteremia and meningitis during treatment with cephalosporins parenterally for pneumococcal pneumonia. J Pediatr **1998**; 132:174–6.

26. Dowell SF, Smith T, Leversedge K, Snitzer J. Failure of treatment of pneumonia associated with highly resistant pneumococci in a child. Clin Infect Dis **1999**; 29:462–3.

27. Lonks JR, Garau J, Gomez L, et al. Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae.* Clin Infect Dis **2002**; 35:556–64.

28. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med **1997**; 336:243–50.

29. Fenoll A, Martin Bourgon C, Munoz R, Vicioso D, Casal J. Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates causing systemic infections in Spain, 1979–1989. Rev Infect Dis **1991**; 13:56–60.

30. NCCLS. Methods for dilution antimicrobial susceptibility test for bacteria that grow aerobically; approved standard M7-A5. Document M-100-S12. Wayne, PA: NCCLS, **2002**:20–1.

31. Freeman DH. Applied categorical data analysis: contingency tables. In: Dekker M, ed. New York: INC, **1987**:55–108.

32. Martín Andrés A, Luna del Castillo J. Bioestadística para las ciencias de la salud. Madrid: Norma Ed, **1999**.

33. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiler and Sons, **1989**.

34. Doern GV, Heilmann KP, Huynh HK, Rhomberg PR, Coffman SL, Brueggemann AB. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999–2000, including a comparison of resistance rates since 1994–1995. Antimicrob Agents Chemother **2001**; 45:1721–9.

35. Garcia-Rey C, Aquilar L, Baquero F. Influences of different factors on prevalence of ciprofloxacin resistance in *Streptococcus pneumoniae* in Spain. Antimicrob Agents Chemother **2000**; 44:3481–2.

36. Linares J, de la Campa AG, Pallares R. Fluoroquinolone resistance in *Streptococcus pneumoniae.* N Engl J Med **1999**; 341:1546–7 [author reply on 1547–8].

37. Chen DK, McGeer A, de Azavedo JC, Low DE. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. N Engl J Med **1999**; 341:233–9.

38. Davidson R, Cavalcanti R, Brunton JL, et al. Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. N Engl J Med **2002**; 346:747–50.

39. Ho PL, Tse WS, Tsang KW, et al. Risk factors for acquisition of levofloxacin-resistant *Streptococcus pneumoniae:* a case-control study. Clin Infect Dis **2001**; 32:701–7.

40. de Galan BE, van Tilburg PM, Sluijter M, et al. Hospital-related outbreak of infection with multidrug-resistant *Streptococcus pneumoniae* in the Netherlands. J Hosp Infect **1999**; 42:185–92.

41. Baquero F, Baquero-Artigao G, Canton R, Garcia-Rey C. Antibiotic consumption and resistance selection in *Streptococcus pneumoniae.* J Antimicrob Chemother **2002**; 50(Suppl C):27–38.

42. Jacobs MR. In vivo veritas: in vitro macrolide resistance in systemic *Streptococcus pneumoniae* infections does result in clinical failure. Clin Infect Dis **2002**; 35:565–9.

43. Henriques B, Kalin M, Örtqvist A, et al. Molecular epidemiology of *Streptococcus pneumoniae* causing invasive disease in 5 countries. J Infect Dis **2000**; 182:833–9.

44. Plouffe JF, Breiman RF, Facklam RR. Bacteremia with *Streptococcus pneumoniae:* implications for therapy and prevention. JAMA **1996**; 275:194–8.