ORIGINAL INVESTIGATION

Community-Acquired Pneumonia Due to Gram-Negative Bacteria and *Pseudomonas aeruginosa*

Incidence, Risk, and Prognosis

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Background: Initial empirical antimicrobial treatment of patients with community-acquired pneumonia (CAP) is based on expected microbial patterns. We determined the incidence of, prognosis of, and risk factors for CAP due to gram-negative bacteria (GNB), including *Pseudomonas aeruginosa*.

Methods: Consecutive patients with CAP hospitalized in our 1000-bed tertiary care university teaching hospital were studied prospectively. Independent risk factors for CAP due to GNB and for death were identified by means of stepwise logistic regression analysis.

Results: From January 1, 1997, until December 31, 1998, 559 hospitalized patients with CAP were included. Sixty patients (11%) had CAP due to GNB, including *P aeruginosa* in 39 (65%). Probable aspiration (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.02-5.2; $P=.04$), previous hospital admission (OR, 3.5; 95% CI, 1.7-7.1; $P<.001$), previous antimicrobial treatment (OR, 1.9; 95% CI, 1.01-3.7; $P=.049$), and the presence of pulmonary comorbidity (OR, 2.8; 95% CI, 1.5-5.5; $P=.02$) were independent predictors of GNB. In a subgroup analysis of *P aeruginosa* pneumonia, pulmonary comorbidity (OR, 5.8; 95% CI, 2.2-15.3; $P<.001$) and previous hospital admission (OR, 3.8; 95% CI, 1.8-8.3; $P=.02$) were predictive. Infection with GNB was independently associated with death (relative risk, 3.4; 95% CI, 1.6-7.4; $P=.002$).

Conclusions: In our setting, in every tenth patient with CAP, an etiology due to GNB has to be considered. Patients with probable aspiration, previous hospitalization or antimicrobial treatment, and pulmonary comorbidity are especially prone to GNB. These pathogens are also an independent risk factor for death in patients with CAP.

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CURRENT GUIDELINES for the management of adult community-acquired pneumonia (CAP) recommend initial empirical antimicrobial treatment.[1-3] This approach is based on microbial patterns derived from several large prospective epidemiological series originating from different regions. One of the major areas of debate includes the incidence of gram-negative bacteria (GNB) and *Pseudomonas aeruginosa*, and, as a result, the need for general coverage of these organisms when designing appropriate empirical antimicrobial treatment strategies. The reported incidences of CAP in the general population have been quite variable, ranging from 0% to 9% for GNB[4,5] and 0% to 5% for *P aeruginosa*.[6,7] On the other hand, these pathogens have repeatedly been found to bear an adverse prognostic potential.[8] Given these variations and the potentially serious prognosis, it seems useful to determine which patients are at risk for these infections, thereby providing an additional target to ensure the adequacy of antimicrobial treatment and obviating the need for a general antimicrobial coverage of these pathogens in all patients. Previous studies in this field originating from the 1960s and 1970s are largely observational and suffer from flaws such as inhomogeneous patient populations and a lack of advanced statistical analysis; therefore, they hardly form a valid basis for current management recommendations.

We performed a large prospective study to determine the incidence of and risk factors for GNB and *P aeruginosa* in a general population with CAP. We also investigated whether the presence of these pathogens represented an independent adverse prognostic factor.

PATIENTS AND METHODS

PATIENTS

From January 1, 1997, through December 31, 1998, we prospectively studied all consecutive and nonselected patients presenting to the

emergency department of a 1000-bed teaching hospital in Barcelona, Spain, with a new infiltrate on chest radiography and symptoms suggestive of a lower respiratory tract infection. Patients were identified by the emergency department physician and then underwent further investigation by the pneumologist or the infectious disease specialist in charge of the study. Admitted patients were eligible for this study. Exclusion criteria included (1) hospitalization within the last 7 days before ambulatory evaluation; (2) severe immunosuppression (eg, solid organ or bone marrow transplantation, neutropenia [<1000/μL], human immunodeficiency virus infection) or treatment with oral corticosteroids in daily doses of at least 20 mg/d of a prednisone equivalent for more than 2 weeks or with azathioprine sodium, cyclosporine, or cyclophosphamide; and (3) other alternative diagnoses emerging during the hospital stay.

DATA COLLECTION

The following variables were recorded at admission: age, sex, smoking and alcohol habits, comorbidity, residence in a nursing home, probable aspiration, current medication, duration of symptoms, clinical symptoms (preceding symptoms of upper airway infection, cough, dyspnea, chest pain, body temperature, chills, respiratory rate, heart rate, and arterial systolic and diastolic blood pressures), results of blood gas analysis (Pa_{O_2}, Pa_{CO_2}, and fraction of inspired oxygen), chest radiograph pattern (alveolar, interstitial, or mixed infiltrate, the number of lobes affected, and the presence of pleural effusion), and serum creatinine level. At the clinical end points of hospital discharge or death, the following variables were retrieved: definite microbial etiology, type of sample on which the definite microbial diagnosis was based (sputum, serology, antigen detection, culture of blood or pleural effusion, or other lower respiratory tract specimen), admission to the intensive care unit (ICU), 30-day in-hospital outcome, antimicrobial treatment administered during the hospital stay, and adequacy of initial antimicrobial treatment.

DEFINITIONS

Cardiac comorbid illness was defined as treatment for coronary artery disease or congestive heart failure or the presence of valvular heart disease. Pulmonary comorbid illness was defined as treatment for asthma, simple chronic bronchitis, or chronic obstructive pulmonary disease (COPD; defined as a documented irreversible airflow obstruction [a forced expiratory volume in 1 second of <80% of that predicted and a ratio of forced expiratory volume in 1 second to vital capacity of <70%], bronchiectasis, or the presence of interstitial lung disorders). Renal comorbidity included preexisting renal disease with documented abnormal serum creatinine levels outside the pneumonia episode. Hepatic comorbidity included preexisting viral or toxic hepatopathy. Disorders of the central nervous system included the presence of symptomatic acute or chronic vascular or nonvascular encephalopathy, with or without dementia. Other comorbid disorders included diabetes mellitus (diagnosis of intolerance to glucose and treatment with oral antidiabetic agents or insulin) and neoplastic disease (any solid tumor active at the time of presentation or requiring antineoplastic treatment within the past year).

Alcohol abuse was defined as the ingestion of more than 80 g/d of alcohol at least during the last year. Current smokers had smoked at least 10 cigarettes per day during the past year.

Previous hospital admission included any hospitalization for more than 48 hours within 30 days but not within the last 7 days of the present hospital admission. Probable aspiration included any witnessed aspiration or the presence of risk factors for aspiration (severely altered consciousness, abnormal gag reflex, or abnormal swallowing mechanism).[9] Previous antimicrobial treatment included any antimicrobial treatment administered within the last 30 days before the present hospital admission; medication with histamine$_2$ (H_2) blockers including any H_2 blocker for at least 30 days before hospital admission; severe sepsis or septic shock; systemic inflammatory response to infection (presence of ≥2 of the following: temperature of >38°C or <36°C, heart rate of >90 beats/min, respiratory rate of >20 breaths/min or Pa_{CO_2} of <32 mm Hg, and leukocyte count of >12 000/mm^3 or >10% band forms) in addition to hypotension (systolic blood pressure of <90 mm Hg or diastolic blood pressure of <60 mm Hg) and/or organ dysfunction, with or without end-organ damage, despite fluid resuscitation on admission or during follow-up; and acute respiratory failure, the presence of a respiratory rate of greater than 30 breaths/min, ratio of Pa_{O_2} to fraction of inspired oxygen of less than 250, or the requirement of mechanical ventilation on admission or during follow-up.

Patients were grouped as having CAP due to GNB in the presence of *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Serratia* species, *Proteus* species, *P aeruginosa,* or *Acinetobacter* species (*Haemophilus influenzae* was not included in this definition). The following infectious agents were grouped as atypical bacterial causes: *Chlamydia pneumoniae, Mycoplasma pneumoniae, Coxiella burnetii,* and *Chlamydia psittaci*. The presence of 2 or more identified pathogens was considered polymicrobial.

Antimicrobial treatment was rated inadequate if at least 1 organism was not covered owing to natural resistance or to the results of susceptibility testing of the isolated organism. In case of the isolation of *P aeruginosa*, adequacy was only accepted if the patient had received a combination treatment with at least 2 drugs to which the organism was fully susceptible.

MICROBIOLOGICAL EVALUATION

Regular sampling included sputum specimens, 2 blood cultures, and paired serologic specimens (at admission and within the forth and eighth week thereafter). Additional diagnostic techniques included pleural puncture, transthoracic needle puncture, tracheobronchial aspirates, flexible bronchoscopy with a protected specimen brush or bronchoalveolar lavage, and urine samples for *Legionella* species antigen. These were applied according to the clinical judgment of the physician in charge.

Sputum samples were gram stained. Representative sputum originating from the lower respiratory tract was defined as containing at least 25 granulocytes and less than 10 epithelial cells per low-power field (total magnification, ×100). Validated sputum samples, blood culture samples, pleural fluid, transthoracic needle aspiration samples, and undiluted and serially diluted tracheobronchial aspirates, protected specimen brush samples, and bronchoalveolar lavage fluid samples were plated on sheep-blood agar, CDC (Centers for Disease Control and Prevention) agar, chocolate agar, and Sabouraud agar media. Identification of microorganisms was performed according to standard methods.[10] Results of quantitative cultures were expressed as colony-forming units (cfu) per milliliter. Susceptibility of antimicrobial drugs was determined by means of an automated microdilution system (Sensititre; AccuMed International Ltd, West Sussex, England) according to the recommendations of the manufacturer. The results were evaluated following the guidelines established by the National Committee for Clinical Laboratory Standards.[11] In detail, susceptibility to the following drugs was tested for all recovered microorganisms: amoxicillin, piperacillin sodium, cefotaxime sodium, ceftazidime, cefepime hydrochloride, ciprofloxacin hydrochloride, imipenem, aztreonam, gentamicin sulfate, amikacin sulfate, and a combination of sulfamethoxazole and trimethoprim.

DIAGNOSTIC CRITERIA

The cause of pneumonia was classified as presumptive if a valid sputum sample yielded 1 or more predominant bacterial strains. It was considered definite if 1 of the following criteria were met: (1) blood cultures yielded a bacterial or fungal pathogen (in the absence of an apparent extrapulmonary focus); (2) pleural fluid and transthoracic needle aspiration cultures yielded a bacterial pathogen; (3) seroconversion (a 4-fold rise in IgG titers for *C pneumoniae* [≥1:512], *C psittaci* [≥1:64], *Legionella pneumophila* [≥1:128], *C burnetii* [≥1:80], and respiratory viruses [influenzaviruses A and B, parainfluenza viruses 1-3, respiratory syncytial virus, and adenovirus] or a rise in IgM titers for *C pneumoniae* [≥1:32], *C burnetii* [≥1:80], and *M pneumoniae* [any titer]) occurred; (4) positive findings for a urinary antigen for *Legionella* species; and (5) bacterial yield in cultures of tracheobronchial aspirates of at least 10^5 cfu/mL, in protected specimen brush cultures of at least 10^3 cfu/mL, and in bronchoalveolar lavage fluid cultures of at least 10^4 cfu/mL.

Growth of fungi in respiratory samples was only considered diagnostic in case of blood cultures that were positive for *Candida* species or isolation of *Histoplasma capsulatum* or *Aspergillus fumigatus* from the lower respiratory tract.

STATISTICAL ANALYSIS

Results are expressed as mean±SD. We used the independent *t* test to compare quantitative variables between patient groups and the χ^2 test to compare proportions.

To identify factors associated with the presence of CAP due to GNB, we used a logistic regression model with categorized variables. Variables were included in the multivariate model when univariate comparisons yielded a level of significance of $P<.10$. The following variables were tested: age (<65 vs ≥65 years), residence in a nursing home, comorbid illnesses, pulmonary comorbid illness, alcohol abuse, smoking, aspiration to the lower airways, previous hospital admission, previous antimicrobial treatment, oral corticosteroid medication, and medication with H_2 blockers.

The association with outcome was also tested in univariate and multivariate analysis, and similar inclusion criteria were applied for the logistic regression analysis ($P<.10$). The following additional variables were tested: severe sepsis or septic shock on admission, acute respiratory failure on admission, and definite etiologic findings due to *Streptococcus pneumoniae*, *Legionella* species, atypical bacterial pathogens, viruses, or GNB. For a subanalysis of *P aeruginosa* pneumonia, all computations were repeated with the same criteria. Results of all multivariate analyses are reported as adjusted odds ratios (ORs) or risk ratios (RRs), 95% confidence intervals (CIs), and exact *P* values. The individual risk in cases with more than 1 risk factor was assessed by means of χ^2 analysis for linear trends.[12] The significance level of all analyses was set to 5%. All data except χ^2 analysis for linear trends (EpiInfo, version 6.03; CDC, Atlanta, Ga) were analyzed and processed on SPSS, version 10.0 (SPSS Inc, Chicago, Ill), on a Windows 98 operating system (Microsoft Corp, Redmond, Wash).

RESULTS

Of 76089 patients presenting to the medical emergency department of the hospital clinic during the study period, 719 had pulmonary infiltrates. We selected 559 (78%) of the 719 episodes for this analysis. The reasons for exclusion from the analyses included the following: no hospitalization (n=50 [7%]); severe immunosuppression (n=123 [17%], including solid organ or bone marrow transplantation in 10 [8%], human immunodeficiency virus infection in 64 [52%], other reasons in 18 [15%], oral corticosteroids in 18 [15%], and treatment with azathioprine, cyclosporine, or cyclophosphamide in 13 [11%]); and other alternative diagnosis during follow-up (n=14 [2%]). Some patients met multiple exclusion criteria.

Community-acquired pneumonia was due to GNB in 60 (11%) of 559 episodes. The episodes included in this analyses occurred in 544 patients, and multiple episodes in the same patient are counted separately. The group with GNB pneumonia included 1 patient with 2 episodes (1/60 [2%]), whereas 13 patients with multiple episodes were included in the non-GNB group (13/499 [3%]; $P=.56$). The clinical characteristics of the population analyzed are summarized in **Table 1**. No differences in mean age or proportions of male patients were found between the 2 groups of patients. A pulmonary comorbidity was found more frequently among patients with CAP due to GNB (45/59 [76%] vs 250/492 [51%]; $P<.001$). Among the patients with a pulmonary comorbidity, bronchiectasis was significantly more frequent in patients with GNB (7/45 [16%] vs 9/250 [4%]; $P=.005$).

Patients with CAP due to GNB had a lower mean body temperature (37.2°C±1.1°C vs 37.6°C±1.1°C; $P=.004$), were less likely to report chills (11/58 [19%] vs 201/490 [41%]; $P=.001$) or preceding symptoms of upper airway infections (6/57 [11%] vs 164/486 [34%]; $P<.001$), and were more likely to present with dyspnea (51/60 [85%] vs 357/499 [72%]; $P=.03$). Serum creatinine levels were slightly higher in patients with CAP due to GNB (1.6±1.9 vs 1.3±1.0 mg/dL [141±168 vs 115±88 µmol/L]; $P=.03$).

Acute respiratory failure (46/60 [77%] vs 284/499 [57%]; $P=.003$) and severe sepsis or septic shock (25/60 [42%] vs 110/499 [22%]; $P=.001$) were present significantly more often on admission in patients with GNB. These patients required ICU admission (17/60 [28%] vs 55/499 [11%]; $P<.001$) and mechanical ventilation (16/60 [27%] vs 38/499 [8%]; $P<.001$) significantly more often.

BACTERIOLOGIC FINDINGS

A definite cause of CAP could be established in 309 (55%) of 559 patients. The definite causes and the diagnostic samples are listed in **Table 2** for both groups.

Among patients with CAP due to GNB, *P aeruginosa* (39/60 [65%]) and *E coli* (12/60 [20%]) were the most frequently isolated microorganisms and represented the third most common pathogens overall. In the group of patients with pneumonia caused by other organisms, *S pneumoniae* (77/249 [31%]) and *C pneumoniae* (43/249 [17%]) were the most common etiologic organisms.

The cause among patients with GNB was most commonly established by cultures of sputum (25/60 [42%]) and other lower respiratory tract specimens (20/60 [33%]). In the non-GNB group, the cause was most often estab-

Table 1. Clinical Characteristics of Patients With CAP and CAP Caused By GNB*

Variable	Other Microorganisms (n = 499)	Gram-Negative Microorganisms (n = 60)	*P* Value	OR or Difference (95% CI)
Demographic data				
Age, mean ± SD, y	69 ± 18	72 ± 13	.12	−3.7 (−8.3 to 1.0)†
Male	330/499 (66)	46/60 (77)	.12	1.7 (0.9 to 3.3)
Comorbidity present	375/499 (75)	56/60 (93)	.002	4.6 (1.6 to 15.3)
Cardiac	95/499 (19)	8/60 (13)	.28	0.7 (0.3 to 1.5)
Pulmonary	250/492 (51)	45/59 (76)	<.001	3.1 (1.6 to 6.1)
Chronic bronchitis	38/250 (15)	2/45 (4)	.08	0.3 (0.04 to 1.2)
COPD	163/250 (65)	29/45 (64)	.97	1.0 (0.5 to 2.0)
Bronchiectasis	9/250 (4)	7/45 (16)	.005	4.9 (1.5 to 15.6)
Asthma	15/250 (6)	1/45 (2)	.45	0.4 (0.02 to 2.7)
Others	27/250 (11)	6/45 (13)	.90	1.3 (0.4 to 3.5)
Renal	34/499 (7)	7/60 (12)	.17	1.8 (0.7 to 4.5)
Hepatic	26/497 (5)	5/60 (8)	.32	1.7 (0.5 to 4.8)
CNS	86/499 (17)	9/60 (15)	.74	0.9 (0.4 to 1.9)
Diabetes mellitus	83/498 (17)	9/60 (15)	.74	0.9 (0.4 to 2.0)
Neoplastic	50/499 (10)	5/60 (8)	.58	0.8 (0.3 to 2.3)
ICU admission	55/499 (11)	17/60 (28)	<.001	3.2 (1.6 to 6.2)
Mechanical ventilation	38/499 (8)	16/60 (27)	<.001	4.4 (2.2 to 9.0)
Acute respiratory failure	284/499 (57)	46/60 (77)	.003	2.5 (1.3 to 4.9)
Septic shock	110/499 (22)	25/60 (42)	.001	2.5 (1.4 to 4.6)
Clinical data on admission, mean ± SD				
Body temperature, °C	37.6 ± 1.1	37.2 ± 1.1	.004	0.4 (0.1 to 0.7)†
Respiratory rate, beats/min	30.7 ± 9.1	31.1 ± 9.1	.71	−0.5 (−2.9 to 2.0)†
Pao_2/Fio_2, mm Hg	268 ± 73	256 ± 70	.21	13 (−7.1 to 32.3)†
Duration of symptoms, d	5.3 ± 6.8	5.2 ± 4.4	.91	0.1 (−1.7 to 1.9)†
Serum creatinine, mg/dL‡	1.3 ± 1.0	1.6 ± 1.9	.03	−0.4 (−0.7 to −0.04)†
Radiograph				
Type of infiltrate				
Alveolar	352/492 (72)	39/60 (65)	.29	0.7 (0.4 to 1.4)
Interstitial	32/492 (7)	6/60 (10)	.31	1.6 (0.6 to 4.2)
Mixed	108/492 (22)	15/60 (25)	.59	1.2 (0.6 to 2.3)
Pleural effusion	75/472 (16)	10/59 (17)	.83	1.1 (0.5 to 2.3)
Symptoms on admission				
Cough	387/497 (78)	45/60 (75)	.62	0.9 (0.4 to 1.7)
Dyspnea	357/499 (72)	51/60 (85)	.03	2.3 (1.0 to 5.1)
Pleuritic chest pain	155/496 (31)	14/60 (23)	.21	0.7 (0.3 to 1.3)
Chills	201/490 (41)	11/58 (19)	.001	0.3 (0.2 to 0.7)
Preceding symptoms of upper airway infections	164/486 (34)	6/57 (11)	<.001	0.2 (0.1 to 0.6)

*Exact numbers are given for each variable; information was not available for all patients. Unless otherwise indicated, data are number (percentage) of patients. CAP indicates community-acquired pneumonia; GNB, gram-negative bacteria; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CNS, central nervous system; ICU, intensive care unit; and Fio_2, fraction of inspired oxygen.

†Given as difference (95% CI).

‡To convert to micromoles per liter, multiply by 88.4.

lished by means of serologic tests (109/249 [44%]) and cultures of sputum (72/249 [29%]). Polymicrobial yield was assessed for patients in whom results of bacterial culture, not serologic tests, established the diagnosis (n=203). This included by definition all patients with GNB. Bacterial growth was polymicrobial in 38 (19%) of 203 with diagnostic samples, with a higher percentage in patients with GNB (20/60 [33%] vs 18/143 [13%]; OR, 3.5; 95% CI, 1.6-7.7; $P<.001$).

ANTIMICROBIAL TREATMENT

Information on antimicrobial treatment in the preceding 30 days of hospital admission were available in 541 (97%) of 559 patients. A total of 117 (22%) of the 541 patients had received the following previous antimicrobial treatment: macrolides (n=25 [21%]), penicillin G sodium (n=22 [19%]), amoxicillin plus clavulanic acid (n=21 [18%]), quinolones (n=15 [13%]), first- or second-generation cephalosporins (n=14 [12%]), third- or fourth-generation cephalosporins (n=11 [9%]), amoxicillin (n=4 [3%]), and others (n=5 [4%]). We found a trend close to significance toward a higher percentage of patients who had received antimicrobial treatment before hospital admission in the GNB group (18/57 [32%] vs 99/484 [20%]; $P=.054$).

The following empirical antimicrobial agents were given to 12 of the 60 patients with GNB as monotherapy after hospitalization: amoxicillin plus clavulanic acid (n=5 [8%]), quinolones (n=2 [3%]), aminoglycosides (n=1 [2%]), and third-generation cephalosporins (n=4 [7%]). Combination regimens included a cephalosporin with antipseudomonal activity in combination with a macrolide and an aminoglycoside (n=5 [8%]); a cephalo-

Table 2. Definite Etiologic Factor and Methods Used for Diagnosis of GNB and Other Pneumonia*

Microorganisms, No.	Diagnostic Method, No. (%)				Total No. (%)
	Blood, Pleural Fluid, TTP	BAL, PSB, or TBAS	Sputum Presumptive Cause	Serologic Test or Urinary Antigen	
GNB					
Escherichia coli	4/12 (33)	6/12 (50)	2/12 (17)	. . .	12/60 (20)
Klebsiella species	2/4 (50)	1/4 (25)	1/4 (25)	. . .	4/60 (7)
Other GNB†	. . .	1/3 (33)	2/3 (67)	. . .	3/60 (5)
Pseudomonas aeruginosa	9/39 (23)	10/39 (26)	20/39 (51)	. . .	39/60 (65)
Acinetobacter species	. . .	2/2 (100)	. . .	. . .	2/60 (3)
All	**15/60** (25)	**20/60** (33)	**25/60** (42)	. . .	**60/60** (100)
Other pneumonia					
Streptococcus pneumoniae	36/77 (47)	4/77 (5)	37/77 (48)	. . .	77/249 (31)
Haemophilus influenzae	2/28 (7)	3/28 (11)	23/28 (82)	. . .	28/249 (11)
Streptococcus pyogenes	1/1 (100)	. . .	. . .	. . .	1/249 (0.4)
Others‡	10/29 (34)	7/29 (24)	12/29 (41)	. . .	29/249 (12)
Legionella species	. . .	. . .	. . .	29/29 (100)	29/249 (12)
Chlamydia pneumoniae	. . .	. . .	. . .	43/43 (100)	43/249 (17)
Mycoplasma pneumoniae	. . .	. . .	. . .	10/10 (100)	10/249 (4)
Coxiella burnetii	. . .	. . .	. . .	9/9 (100)	9/249 (4)
Chlamydia psittaci	. . .	. . .	. . .	1/1 (100)	1/249 (4)
Mycobacterium tuberculosis§	2/2 (100)	. . .	. . .	. . .	2/249 (1)
Fungi‖	1/4 (25)	2/4 (50)	. . .	1/4 (25)	4/249 (2)
Viruses¶	. . .	. . .	. . .	16/16 (100)	16/249 (6)
All	**52/249** (21)	**16/249** (6)	**72/249** (29)	**109/249** (44)	**249** (100)

*Percentages have been rounded and may not sum 100. TTP indicates transthoracic puncture; BAL, bronchoalveolar lavage; PSB, protected specimen brush; TBAS, tracheobronchial aspirate; and ellipses, not diagnostic or not applicable. Other abbreviations are explained in the first footnote to Table 1.

†Includes *Proteus* species, *Serratia* species, and *Morganella morganii*.

‡Includes *Streptococcus milleri, Staphylococcus aureus*, and *Moraxella catarrhalis*.

§Diagnosis was made by means of lung tissue culture.

‖Inclues *Candida albicans* detected in blood culture (n = 1), *Histoplasma capsulatum* detected in BAL (n = 1) and in results of serologic testing (n = 1), and *Aspergillus fumigatum* in TBAS (n = 1).

¶Includes influenzavirus, parainfluenza virus, respiratory syncytial virus, and adenovirus.

sporin with antipseudomonal activity in combination with an aminoglycoside (n=3 [5%]) and additional clindamycin hydrochloride (n=1 [2%]); a cephalosporin with antipseudomonal activity in combination with a quinolone (n=2 [3%]); a cephalosporin with antipseudomonal activity in combination with other antibiotic drugs (n=1 [2%]); third-generation cephalosporins in combination with clindamycin (n=6 [10%]), antifungal drugs (n=1 [2%]), a macrolide (n=23 [38%]), or an aminoglycoside (n=1 [2%]); third-generation cephalosporins with at least 2 other drugs (n=3 [5%]); and imipenem and an aminoglycoside with clindamycin (n=1 [2%]) or a macrolide (n=1 [2%]).

PREDICTORS OF CAP DUE TO GNB

Table 3 summarizes the results of the univariate statistics for the presence of GNB. Probable aspiration, previous hospital admission, previous antimicrobial use, and the presence of a pulmonary comorbidity were more frequent in the population with CAP due to GNB ($P<.10$). Factors that were also independently predictive in the multivariate analysis included probable aspiration (adjusted OR, 2.3; 95% CI, 1.0-5.2; $P=.04$), previous hospital admission (adjusted OR, 3.5; 95% CI, 1.7-7.1; $P<.001$), previous antimicrobial treatment (adjusted OR, 1.9; 95% CI, 1.0-3.7; $P=.049$), and the presence of a pulmonary comorbid illness (adjusted OR, 2.8; 95% CI, 1.5-5.5; $P=.02$).

INDIVIDUAL RISK FOR CAP DUE TO GNB FOR PATIENTS WITH MORE THAN 1 RISK FACTOR

Among the 559 patients undergoing analysis in this study, 161 (29%) had 0, 280 (50%) had 1, 96 (17%) had 2, and 22 (4%) had 3 or more risk factors for gram-negative etiology present on admission. The frequencies of pneumonia due to gram-negative microorganisms are summarized in the **Figure**. Frequencies increased with increasing numbers of risk factors and reached 50% in patients with at least 3 risk factors (linear trend $\chi^2=44.3$; $P<.001$). The ORs compared with the baseline value (patients with no risk factor present) were 4.2 (95% CI, 1.4-16.7) for 1, 9.1 (95% CI, 2.8-37.2) for 2, and 39.3 (95% CI 9.3-188.3) for 3 or more risk factors present on admission.

OUTCOME

The 30-day in-hospital mortality of patients was 63 (11%) of 559. Patients with GNB had a significantly higher mortality when compared with the non-GNB group (19/60 [32%] vs 44/499 [9%]; $P<.001$). **Table 4** summarizes univariate and multivariate associations with outcome. In the univariate analyses, current smoking, admission from a nursing home, probable aspiration, previous hospital admission, acute respiratory failure, severe sepsis or septic shock, and CAP due to GNB

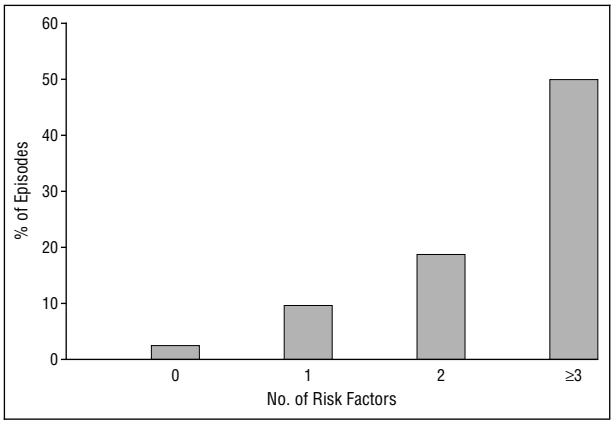
Table 3. Univariate and Multivariate Analyses of Individual Risk Factors for CAP Due to GNB*

Risk Factors, No. (%)	Univariate Analysis				Multivariate Analysis	
	Other Pneumonia	GNB	Odds Ratio (95% CI)	*P* Value†	OR (95% CI)	*P* Value‡
Age ≥65 y	329/499 (66)	43/60 (72)	1.3 (0.7-2.5)	.37	. . .	. . .
Alcohol abuse	67/499 (13)	8/60 (13)	1.0 (0.4-2.3)	.98	. . .	. . .
Current smokers	134/499 (27)	12/60 (20)	0.7 (0.3-1.4)	.25	. . .	. . .
Nursing home residence	40/490 (8)	5/59 (8)	1.0 (0.4-2.9)	>.99	. . .	. . .
Probable aspiration	40/459 (9)	11/59 (19)	2.4 (1.1-5.2)	.02	2.3 (1.02-5.2)	.04
Previous hospital admission	41/492 (8)	19/60 (32)	5.1 (2.6-10.0)	<.001	3.5 (1.7-7.1)	<.001
Previous use of antibiotics	99/484 (20)	18/57 (32)	2.1 (1.1-4.1)	.054	1.9 (1.01-3.7)	.049
H_2 blockers	30/490 (6)	3/57 (5)	0.9 (0.2-3.1)	>.99	. . .	. . .
Pulmonary comorbid illness	250/492 (51)	45/59 (76)	3.1 (1.6-6.1)	<.001	2.8 (1.5-5.5)	.02
Oral corticosteroids, <20 mg/d	17/499 (3)	4/60 (7)	2.0 (0.6-6.7)	.27	. . .	. . .

*Patients with absence of the described risk factor are used as the reference category for calculation of ORs. Ellipses indicate that those factors were not included in multivariate analysis because they did not reach significance in univariate analysis. Abbreviations are explained in the first footnote to Table 1.

†Determined by means of the χ^2 test. Number of patients varies in univariate analyses.

‡Total number of patients entered in logistic regression analysis was 492, including 55 (92%) of 62 with GNP and 437 (88%) of 499 with other pneumonia (OR, 1.6; 95% CI; 0.6-4.6; *P* = .49).



Incidence of causative gram-negative bacteria in community-acquired pneumonia according to the number of risk factors present. Independent risk factors identified in multivariate analyses (probable aspiration, previous hospital admission, previous antimicrobial treatment, and the presence of pulmonary comorbidity) were added as 0, 1, 2, and 3 or more. We used χ^2 analysis for linear trends to assess differences relative to baseline (no risk factor present; *P*<.001). Odds ratios and 95% confidence intervals are described in the "Results" section.

were associated with death. However, in multivariate analysis, only GNB (RR, 3.4; 95% CI, 1.6-7.4; *P*=.002), acute respiratory failure (RR, 4.1; 95% CI, 1.5-11.3; *P*<.001), severe sepsis or septic shock (RR, 9.2; 95% CI, 4.6-18.3; *P*<.001), and probable aspiration (RR, 3.3; 95% CI, 1.5-7.5; *P*=.004) were independent predictors of death. Pulmonary comorbidity was equally distributed between survivors and nonsurvivors; therefore, this variable was not selected for the multivariate approach (Table 4).

Of 18 patients with GNB who had received ambulatory antimicrobial treatment, 15 (83%) had an inadequate regimen. Initial empirical in-hospital antimicrobial treatment was rated inadequate in 35 (58%) of the 60 patients with GNB. Mortality included 7 (28%) of 25 patients receiving adequate and 12 (34%) of 35 receiving inadequate initial empirical in-hospital antimicrobial treatment (*P*=.60).

SUBANALYSES FOR PATIENTS WITH *P AERUGINOSA* PNEUMONIA

In 39 (13%) of the 309 patients with a definite cause, *P aeruginosa* was recovered. No differences in mean age (72±12 vs 69±18 years; *P*=.35), duration of symptoms (4.9±3.9 vs 5.4±6.8 days; *P*=.43), or respiratory rate on admission (33.3±9.1 vs 30.5±9.1 breaths/min; *P*=.07) could be found when average values were compared with those of patients without *P aeruginosa*. The proportion of men was higher in the group of patients with *P aeruginosa* (34/39 [87%] vs 343/520 [66%]; *P*=.006). A previous hospital admission (12/39 [31%] vs 48/513 [9%]; *P*<.001), pulmonary comorbidity (33/38 [87%] vs 262/513 [51%]; *P*<.001), and the requirement of ICU admission (12/39 [31%] vs 60/520 [12%]; *P*<.001) or of mechanical ventilation (9/39 [23%] vs 45/520 [9%]; *P*=.008) were also more frequently observed in the group of patients with *P aeruginosa* pneumonia. The initial antimicrobial treatment was adequate in 11 (28%) of the 39 cases.

Data of 544 patients (97%) were entered in the multivariate analysis, and a pulmonary comorbidity (adjusted OR, 5.8; 95% CI, 2.2-15.3; *P*<.001) was the strongest predictor of *P aeruginosa* pneumonia together with a previous hospital admission (adjusted OR, 3.8; 95% CI, 1.8-8.3; *P*=.02).

Mortality was significantly higher in patients with CAP due to *P aeruginosa* compared with the group without *P aeruginosa* (11/39 [28%] vs 52/520 [10%]; *P*=.002). However, pneumonia due to *P aeruginosa* was not an independent risk factor for death in the logistic regression analysis.

Inadequate initial empirical in-hospital antimicrobial treatment was associated with a nonsignificant trend toward a higher mortality compared with adequate treatment (10/31 [32%]) vs 1/8 [13%]; *P*=.27).

COMMENT

In this study, we assessed the incidence and prognosis of and the risk factors for CAP in hospitalized patients

Table 4. Univariate and Multivariate Analyses of Factors Associated With Survival in Patients With CAP Due to GNB*

	Univariate Analysis				Multivariate Analysis	
No. (%) of Patients	Survivors	Nonsurvivors	RR (95% CI)	*P* Value†	RR (95% CI)	*P* Value‡
Descriptive data						
Age ≥65 y	325/496 (66)	47/63 (75)	1.1 (1.0-1.3)	.15	. . .	. . .
Alcohol abuse	65/496 (13)	10/63 (16)	1.2 (0.7-2.2)	.54	. . .	. . .
Current smokers	137/496 (28)	9/63 (14)	0.5 (0.3-1.0)	.02	. . .§	. . .§
Nursing home residence	31/486 (6)	14/63 (22)	3.5 (2.0-6.2)	<.001	. . .§	. . .§
Probable aspiration	35/463 (8)	16/55 (29)	3.9 (2.3-6.5)	<.001	3.3 (1.5-7.5)	.004
Previous hospital admission	49/491 (10)	11/61 (18)	1.8 (1.0-3.3)	.057	. . .§	. . .§
Previous use of antibiotics	101/481 (21)	16/60 (27)	1.3 (0.8-2.0)	.32	. . .	. . .
Pulmonary comorbid illness	264/489 (54)	31/62 (50)	0.9 (0.7-1.2)	.553	. . .	. . .
Acute respiratory failure on admission	275/496 (55)	55/63 (87)	1.6 (1.4-1.8)	<.001	4.1 (1.0-11.3)	.005
Severe sepsis or septic shock on admission	89/496 (18)	46/63 (73)	4.1 (3.2-5.2)	<.001	9.2 (4.6-18.3)	<.001
Etiologic factor						
Streptococcus pneumoniae	72/496 (15)	5/63 (8)	0.6 (0.2-1.3)	.15	. . .	. . .
Legionella species	27/496 (5)	2/63 (3)	0.6 (0.1-2.4)	.44	. . .	. . .
Viruses	16/496 (3)	0/63 (0)	‖	.15	. . .	. . .
Atypical bacterial pathogens¶	61/496 (12)	2/63 (3)	0.3 (0.1-1.03)	.03	. . .§	. . .§
GNB	41/496 (8)	19/63 (30)	3.7 (2.3-5.9)	<.001	3.4 (1.6-7.4)	.002

*Patients with absence of the described risk factor are used as the reference category for calculation of RRs. RR indicates risk ratio; ellipses, not included in multivariate analysis because they did not reach significance in univariate analysis. Other abbreviations are explained in Table 1.

†Determined by the χ^2 test. Number of patients varies in univariate analyses.

‡Total number of patients entered in logistic regression analysis was 505, including 53 (84%) of 63 with GNP and 452 (91%) of 496 with other pneumonia (OR, 0.8; 95% CI; 0.3-2.0; *P* = .13).

§Indicates items that were eliminated by the multivariate model as potential predictors during stepwise forward calculation.

‖Not calculated due to zero count in 1 cell.

¶Includes *Chlamydia pneumoniae, Mycoplasma pneumoniae, Coxiella burnetii,* or *Chlamydia psittaci.*

with CAP due to GNB and *P aeruginosa* to provide evidence about the role of these pathogens as a basis for the ongoing validation of current management guidelines. The main findings are that (1) the incidence of these etiologic pathogens was 11%; (2) independent risk factors included the presence of a pulmonary comorbidity, previous antimicrobial treatment, previous hospitalization, and probable aspiration to the lower airways; (3) risk factors identified in multivariate analysis were additive and the risk for gram-negative etiology increased with the increasing numbers of risk factors on admission; (4) the associated mortality was 32% and significantly higher compared with that for other causes of CAP (9%), and CAP due to GNB represented an independent risk factor for death; and (5) the incidence of CAP due to *P aeruginosa* was 7% and the associated mortality was 28%. Independent predictors were pulmonary comorbidity and previous hospital admission.

The role of GNB has been subject to considerable debate. In the general population of patients with CAP, only 4 recent studies had a proportion of greater than 3% of CAP due to GNB,[5,6,13] the highest reaching 9%.[5] The incidence of GNB in severe CAP was about 15%, which is 2- to 3-fold higher than that of the general hospitalized population. Similarly, of 10 recent studies consisting of more than 250 patients, 6 did not find any case due to *P aeruginosa*,[6,13-16] and the incidence in the remaining 4 was only 1% to 5%.[7,17,18] Again, in severe CAP, the incidence was higher, reaching 12%.[8,19-21] In our study, the incidence of GNB was 3% and within the range expected. However, with an incidence of 7%, *P aeruginosa* was the third most common pathogen. This incidence is, to our knowledge, the highest reported so far in a general population. Possible explanations for this particularly high incidence include a higher proportion of patients with severe CAP and with structural lung disease. However, the proportion of patients requiring ICU admission was 12% in our series, which is not higher than that of other reports,[14,22] making it unlikely that an increased proportion of patients with severe pneumonia accounted for the higher incidence of pseudomonal CAP. On the other hand, the proportion of patients with structural lung disease in our series was very high (52%). This is especially true for bronchiectasis (8%). Other large recent series of more than 300 patients included 31% to 35% with structural lung disease,[6,14,18] and patients with bronchiectasis were not specified. Since the severity of structural lung disease is difficult to assess in acutely ill patients, comparisons with other series are difficult.

A critical issue consists in the criteria for an etiological diagnosis of GNB. A definite proof for the involvement of these pathogens, such as growth of the pathogen in usually sterile media (blood, pleural fluid, transthoracic aspirate, and lung tissue homogenate), can be obtained only in a minority of cases. In our study, GNB was diagnosed in usually sterile media in only 6 patients (1%), and *P aeruginosa* in only 9 (2%). On the other hand, the value of sputum, tracheobronchial aspirates, and even bronchoscopically retrieved samples may be seriously questioned, especially in patients with structural lung disease such as COPD or bronchiectasis or even in patients with heavy cigarette use. Gram-negative bacteria may easily colonize the tracheobronchial tree in the presence of any alterations or damage of the respiratory epithelium. It has been repeatedly shown that the bacterial load found in respiratory secretions of patients with GNB and/or

P aeruginosa may readily reach or surpass amounts usually present in pneumonia ($\geq 10^5$ cfu/mL).[23,24] Therefore, the isolation of pseudomonads in the culture of any respiratory secretion and its quantification cannot independently establish a definite etiologic diagnosis of CAP due to GNB or pseudomonads. Nevertheless, in view of the potential continuum of bronchitis and pneumonia and of the adverse prognostic potential of these pathogens, it seems to be prudent to consider any corresponding isolate in valid cultures of lower respiratory tract secretions at least as a probable underlying pathogen. This view, although debatable, must be realized when comparing our results with those of other studies.

It has long been recognized that colonization of the upper airways by GNB (and to a lesser extent, by *P aeruginosa*) increases with increasing age, care in a nursing home, and hospitalization.[25] Therefore, CAP due to GNB has often been reported to be more frequent in the elderly population, especially by American authors in the 1970s.[26-28] A corresponding high incidence of 16% was found in a series of severe CAP in the elderly.[29] However, this view has been challenged by 2 recent European studies addressing CAP in the elderly, which did not find significant amounts of corresponding pathogens in this population (0% and 2%).[4,29] Similarly, in a recent Canadian study, the proportion of infections due to GNB was not different in patients admitted from a nursing home compared with that in the control group.[14] In the present study, we did not find a significant association between age and CAP due to GNB or *P aeruginosa*, corroborating the view that age does not represent an independent risk factor for these pathogens. Residence in a nursing home failed to be associated with these etiologic factors.

We could, however, confirm the crucial importance of previous hospitalization for CAP due to GNB. Community-acquired pneumonia due to these pathogens (especially *P aeruginosa*) after a previous hospitalization may be regarded as late-onset sequelae of nosocomial colonization with corresponding pathogens. Similar to nosocomial pneumonia, antimicrobial treatment may represent a major risk factor for a corresponding colonization. Our findings suggest that in-hospital and ambulatory previous antimicrobial treatment may predispose to a colonization of the airways with GNB. In patients who received antimicrobial treatment for a lower respiratory tract infection, CAP due to GNB may represent a superinfection, ie, an adverse effect of previous antimicrobial treatment. If this point of view can be confirmed in prospective studies designed to clarify the sequence of colonization and infection with GNB in CAP, new prevention strategies may evolve.

As expected, pulmonary comorbidity was an independent risk factor for GNB. The main comorbid pulmonary conditions predisposing to these pathogens were COPD and bronchiectasis. A previous Spanish multicenter study of CAP in patients with COPD found a much lower incidence of GNB of only 4%.[30] Apart from differences in diagnostic evaluation, severity of airflow obstruction may account for this discrepancy, since at least during acute exacerbation GNB have been shown to be significantly more frequently involved in patients with a forced expiratory volume in 1 second that is less than 35% of the predicted volume.[31] Therefore, an attempt should be made to assess the severity of airflow limitation in a patient presenting with CAP and COPD.

A further independent risk factor was aspiration to the lower airways. Gram-negative pathogens are known to frequently colonize the upper airways and the stomach of elderly patients or those with significant comorbidity.[32] However, aspiration is more likely to occur in severely disabled patients. Thus, GNB aspiration pneumonia may simply reflect the association of GNB and disability or severe comorbidity.

The prevalence of a pulmonary comorbidity as a risk factor in this study (251/551 [46%]) was very high. This finding strengthens the statistical approach, because patients with and without this risk factor were almost equally represented. However, this fact may limit the applicability of our finding to other less severely affected populations. Therefore, we also analyzed individual risks according to the number of risk factors present on admission to the hospital. We found a clear association between the likelihood of finding a gram-negative etiology and the number of risk factors. The frequency of etiologic GNB increased from 2.5% to 50% in the last group, and the ORs—using patients without any of the 4 risk factors as a reference category—ranged from 4.2 to 39.3. Thus, this study showed that in addition to structural pulmonary comorbidity, other risk factors should be evaluated to assess the risk for CAP due to GNB.[3]

In this carefully defined patient population, severe immunosuppression was an exclusion criterion, since we believe that immunosuppressed patients do not form part of the concept of CAP and that their disease should be managed as an entity of its own. Classifying as immunosuppressed those patients who receive oral corticosteroids in doses of at least 20 mg/d of a prednisone equivalent may have precluded us from detecting a significant association of corticosteroid use with GNB. Since we found a nonsignificant trend for corticosteroids in lower doses ($<$20 mg/d) to be more frequent in patients with GNB (7% vs 3%), we argue that patients receiving oral corticosteroids should at least undergo careful evaluation for these pathogens.

Our study confirms the adverse prognostic potential of GNB in patients with CAP. Mortality in patients with CAP due to these pathogens was 32%, compared with 9% in the non-GNB group. Other reports found mortality ranging from 29% to 45%.[13] In particular, *Klebsiella pneumoniae* and *P aeruginosa* have been reported to be associated with a worsened prognosis.[33,34] In our study, mortality due to *P aeruginosa* pneumonia was 28%. Again, data in the literature available for comparison are scarce, especially for a general population with CAP. In severe CAP, the outcome was explicitly reported in only 27 patients, and of these, 59% died.[35] This proportion is well within the range of the mortality rates reported in patients with ventilator-associated pseudomonal pneumonia (40%-70%).[35] Since comorbidity in patients with and without GNB was comparable, it is likely that excess mortality observed in the GNB group is directly attributable to these pathogens. Nevertheless, since we were unable to assess chronic disease severity, we cannot fully ex-

clude that the severity of comorbidity to some extent may represent a confounder. As expected, there was a clear, albeit nonsignificant, trend for inadequate initial empirical in-hospital antimicrobial treatment to have prognostic bearing in patients with GNB. This trend was more obvious when we analyzed the subgroup of patients with *P aeruginosa*. Overall, 83% of ambulatory and 58% of in-hospital antimicrobial treatment regimens were rated as being inadequate. These numbers seem logical, because GNB and in particular *P aeruginosa* were not the expected pathogens. The detection of 4 independent risk factors should help to identify patients who require a different initial empirical antimicrobial treatment covering GNB.

In multivariate analysis, an etiology due to GNB was an independent predictor of death, together with well-known adverse prognostic factors such as acute respiratory failure, septic shock, and aspiration to the lower airways. Other etiologic factors were not associated with death, and atypical bacterial pathogens (excluding *Legionella* species) turned out to be protective factors. Consistent with our findings, at least 1 study[36] of a general population showed that GNB were independent predictors of death, and another confirmed this finding in patients with severe CAP.[37] *Pseudomonas aeruginosa* failed to be an independent predictor of death in our study, but this may simply have been due to a limited number of cases. In fact, in 1 study evaluating prognostic factors of community- and hospital-acquired pneumonia requiring ICU admission, *P aeruginosa* was found to represent an independent prognostic factor.[8]

Overall, these data are in accordance with the view of the American Thoracic Society guidelines that GNB and *P aeruginosa* form an important part of the microbial pattern in patients with severe CAP.[1] In addition to previous work from our group, which already confirmed an independent association of these pathogens with severe CAP,[7] the present data provide independent risk factors for these pathogens that allow us to predict the patient particularly at risk and, therefore, to select individual initial empirical antimicrobial treatment more judiciously.

CONCLUSIONS

Our study bears significant implications for the management of CAP that might influence future updates of management guidelines. Gram-negative bacteria and *P aeruginosa* form a relevant part of the microbial pattern of CAP that must be taken into account in patients who require hospitalization, particularly those with severe CAP. An initial empirical antimicrobial coverage of these pathogens should be seriously considered in patients with pulmonary comorbidity (particularly COPD or bronchiectasis), previous hospitalization, previous antimicrobial treatment, and probable aspiration.

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Correction

Error in Text. In the Original Investigation by Rahme et al titled "Association Between Naproxen Use and Protection Against Acute Myocardial Infarction," published in the May 27 issue of the ARCHIVES (2002;162:1111-1115), an error occurred in the "Comment" section on page 1115. The last sentence of the third paragraph on that page should have read as follows: "However, *Santé Québec* (a government public health agency [written communication, 1992-1993]) reports that, during the years of the study, older Quebecois acquired the following agents over the counter (given as proportions of the total numbers of those who used the agents): acetaminophen (5.5%), NSAIDs (0.5%), and aspirin (0.3%)." The journal regrets the error.