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H. Georges
O. Leroy
C. Vandenbussche
B. Guery
S. Alfandari
L. Tronchon
G. Beaucaire

Epidemiological features and prognosis of severe community-acquired pneumococcal pneumonia

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H. Georges (✉) · O. Leroy · B. Guery · S. Alfandari · G. Beaucaire
Service de Réanimation Médicale et Maladies Infectieuses,
Lille University Medical School,
Centre Hospitalier,
135 Rue du Président Coty,
F-59208 Tourcoing, France
e-mail: bguery@compuserve.com
Tel. + 33.3.20.69.44.30
Fax + 33.3.20.69.44.39

C. Vandenbussche
Service de Réanimation Médicale,
Centre Hospitalier, Arras, France

L. Tronchon
Service de Réanimation Médicale,
Centre Hospitalier, Lens, France

Abstract *Objective*: To describe risk factors of severe pneumococcal community-acquired pneumonia and to study variables influencing outcome.
Design: Retrospective (1987–1992) and prospective (1993–1995) study.
Setting: Three participating ICUs from primary care hospitals.
Patients: Five hundred and five patients (mean age: 63 ± 17 years) with severe community-acquired pneumonia (CAP). Three groups of patients were defined: pneumococcal CAP (group 1), CAP with microbial diagnosis other than *Streptococcus pneumoniae* (group 2), CAP from group 2 and CAP without microbial diagnosis (group 3).
Measurements and results: Admission data and data on the disease's course were recorded. The mean Simplified Acute Physiologic Score (SAPS) was 12.5 ± 5.4. On admission 288 (57 %) patients were mechanically ventilated (mv) and 82 (16.2 %) required inotropic support. A microbial diagnosis was established for 309 (61.2 %) patients. *S. pneumoniae* was isolated in 137 (27.1 %) patients. Severe pneumococcal CAP was independently associated with male sex ($p = 0.01$), lack of antibiotics use before admission ($p = 0.0001$), non-aspiration pneumonia ($p = 0.01$) and septic shock ($p = 0.0001$). The overall mortality rate was 27.5 % (29.2 % in group 1). In patients with severe pneumococcal CAP, multivariate analysis showed that leukopenia less than 3,500/mm^3 ($p = 0.0004$), age over 65 years ($p = 0.01$), septic shock ($p = 0.01$), sepsis related complications ($p = 0.0001$), ICU complications ($p = 0.001$) and inadequacy of antimicrobial therapy ($p = 0.002$) worsened the prognosis.
Conclusions: Few features facilitate the identification of pneumococcal CAP on ICU admission. The prognosis is mostly related to severity of illness (leukopenia, septic shock) while comorbidities do not seem to influence outcome. Sepsis-related disorders, ICU complications and adequate antimicrobial chemotherapy are the major variables affecting the outcome during an ICU stay.

Key words Severe CAP · Pneumococcal pneumonia · Prognosis on ICU

Introduction

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality worldwide, accounting for 2.8 % of all hospital admissions [1]. Approximately 18–36 % of patients with CAP needing hospitalization require intensive care unit (ICU) treatment [2, 3]. Among different pathogens, *Streptococcus. pneumoniae* is a major cause of CAP. In a recent American Thoracic Society guideline, *S. pneumoniae* was the

most prevalent pathogen in each of the four defined patient categories: young outpatients without comorbidity, outpatients with comorbidity and/or 60 years of age or older, hospitalized patients with CAP and severe CAP [4]. Initial adequate and/or effective antimicrobial therapy, initiated before definitive etiological diagnosis, is associated with a good prognosis [5]. Many authors have pointed out the difficulty of determining pneumococcal etiology during the first 48 h after admission [6, 7]. Consequently, the awareness of correct empirical antimicrobial strategies can only be achieved through periodical epidemiological studies. To our knowledge there are few prospective studies with multivariate analysis, assessing epidemiological parameters and prognostic factors in severe community-acquired pneumococcal pneumonia. The goals of our study were: 1) to describe the epidemiological features and risk factors of severe community-acquired pneumococcal pneumonia and 2) to determine prognostic factors of severe community-acquired pneumococcal pneumonia.

Methods

Patients and definitions

We performed a multicenter, retrospective (1987–1992) and prospective study (1993–1995) recording all patients admitted for severe CAP in the three participating ICUs in the North of France. Some patients in this study ($n = 299$) have already formed part of a previous study assessing the prognoses of patients with severe CAP whatever the microbial diagnoses [8]. People with CAP were identified according to previously defined criteria [9]. Patients admitted from home or a nursing-home to the general medical wards for pneumonia and then admitted to the ICU within 2 days were also included. The presence of at least one of the following conditions justifies classifying the pneumonia as severe: respiratory frequency more than 30 breaths/min on admission; severe respiratory failure defined by a PaO_2/FIO_2 ratio lower than 250 mmHg; the requirement of mechanical ventilation (MV); chest radiograph showing bilateral involvement or involvement of multiple lobes or an increase in the size of the opacity by 50 % or greater within 48 h of admission; shock (systolic blood pressure below 90 mmHg or diastolic blood pressure below 60 mmHg); the need for vasopressors for more than 4 h; urine output lower than 80 ml in 4 h or acute renal failure requiring dialysis [4].

Patients were excluded from the study if they had been hospitalized 30 days before developing pneumonia, had radiographic evidence of abnormalities attributed solely to pulmonary embolus, lung carcinoma or congestive heart failure, or had a clinical diagnosis of AIDS or were known to be HIV positive.

Data collection

Within 24 h of admission, the following data were recorded: age, sex, origin (home, nursing home), underlying clinical characteristics (chronic obstructive pulmonary disease (COPD), alcohol intake, immunosuppression), prior antibiotic use (within 1 week before admission) chest radiographic features (unilateral or bilateral involvement and number of lobes involved), mechanisms of lung contamination (aspiration or not), initial vital signs (arterial blood pressure, heart rate, urine output, mental status), and hematological and biochemical tests (total leukocyte count, creatinine, total serum protein). All these variables were collected for the two periods studied (retrospective and prospective).

Aspiration pneumonia was diagnosed in patients with altered mental status, swallowing disorders and infiltrates on chest X-ray involving the superior or basilar segments of the lower lobes or the posterior segments of the upper lobes [9]. The underlying clinical conditions were classified according to the criteria proposed by McCabe and Jackson [10]. Preexisting COPD was diagnosed according to previously described criteria [11]. Immunosuppression was defined as a leukocyte count of less than $1000/mm^3$, recent use of systemic corticosteroids or cytotoxics drugs, radiation treatment or asplenia [7].

Vital sign abnormalities were assessed by the Simplified Acute Physiologic Score (SAPS I) [12] and the Acute Organ System Failure (OSF) scoring system [13]. Septic shock was defined by a systolic blood pressure lower than 90 mmHg, urine output less than 30 ml/h or the need for vasopressors for more than 4 h, after standardized fluid replacement [14]. Neurological status and changes in mental state were stratified according to the Glascow Coma Score [15]. Pneumococcal vaccine status was documented for less than 5 % of the records and this was not included in the analysis.

Microbiological investigations

Microbiological examination included two serial blood cultures taken on admission, culture of pleural effusion, microscopy and culture of sputum collected on admission or tracheal aspirates taken immediately on intubation and processed routinely in the laboratory. Protected specimen brush (PSB) was performed in some patients when immediate plating of a PSB specimen could be obtained. Finally, serological tests for *Mycoplasma pneumoniae*, *Chlamydia*, *Legionella pneumophila* and *Rickettsia* were performed on all patients.

A positive microbiological diagnosis was defined by any of the following criteria [2, 5] : a) a positive blood culture for a pulmonary pathogen without another apparent source, except for *Staphylococcus sp*., which was additionally required to be isolated from the bronchopulmonary sample; b) a positive pleural fluid culture for a pulmonary pathogen; c) a positive quantitative culture of endotracheal aspirate or sputum specimens with a bacterial count of 10^5 or more colony forming unit (cfu) /ml. This specimen was considered for culture only if it had more than 25 neutrophils and fewer than 5 squamous epithelial cells per low power field; d) a positive quantitative culture of specimens obtained by PSB or bronchoalveolar lavage, with respective thresholds of 10^3 cfu/ml and 10^5 cfu/ml; e) serum specimens were tested for evidence of complement-fixing antibody to *M. pneumoniae*, *Chlamydia psittaci* and *Coxiella burnettii* on ICU admission. The fluorescent antibody technique was used to detect antibodies against *Chlamydia pneumoniae* or *L. pneumophila*. Blood samples for follow-up serological studies were collected 3 weeks later for patients still hospitalized in ICU. A four-fold rise in antibody titer was accepted as evidence of infection due to *L. pneumophila* serogroups 1–4, *Chlamydia sp.*, *M. pneumoniae* or *C. burnettii.* All strains of S. pneumoniae were screened for susceptibility to antimicrobial agents. Resistance to antimicrobial agents was defined according to the criteria of the National Committee for Clinical Laboratory Standards [16].

In order to assess epidemiological features and prognostic factors of severe pneumococcal pneumonia, three groups of patients were defined: pneumococcal pneumonia (group 1), pneumonia with microbiological diagnosis other than *S. pneumoniae* (group

2), pneumonia with microbiological diagnosis other than *S. pneumoniae* and pneumonia without microbiological diagnosis (group 3).

Therapy and assessment of evolution

The following therapeutic data were recorded for each patient : MV on admission or within 12 h following admission, use of systemic corticosteroids or vasoactive drugs and initial antimicrobial therapy. Antimicrobial therapy was started as soon as microbiological samplings were performed. The choice of antibiotic(s) was left to the discretion of each attending physician. Clinical status was re-evaluated 72 h after the initiation of antimicrobial agents. Initial antimicrobial chemotherapy was considered effective if the clinical conditions improved and fever lessened within the first 72 h of treatment, and was considered adequate if the causative pathogen was susceptible according to antibiotic susceptibility reports. Patients were followed by the medical staff throughout their hospitalization in the ICU until discharge from the ICU or death. During the patient's stay in the ICU, the occurrence of complications was recorded. We characterized:

Pneumonia-related complications. Sepsis-related complications (septic shock, acute respiratory distress syndrome (ARDS) or development of multiple organ failure (MOF)) or occurrence of septic metastasis (i. e., meningitis). MOF and ARDS were defined according to the usual criteria [14, 17].

ICU-related complications. Upper gastrointestinal bleeding, catheter-related infection, deep venous thrombosis and pulmonary embolism, cerebral hemorrhage, cholecystis, pneumothorax.

ICU-acquired bronchopneumonia. The appearance of new and persistent infiltrates during the ICU stay on chest radiograph and at least one clinical criteria associated with PSB of 10^3 cfu/ml or more. (Clinical criteria: temperature > 38.5 °C or hypothermia < 36.5 °C, leukocytosis > 10×10^9 /l or neutropenia < 4×10^9 /l, purulent tracheal aspirates).

Complications due to underlying medical conditions. Preexisting diseases such as chronic congestive heart failure and chronic respiratory failure.

Statistical analysis

In order to assess the characteristics of patients exhibiting pneumococcal pneumonia, group 1 vs 2 and, then, group 1 vs 2 and 3 were compared, at baseline, for the epidemiological and clinical data as well as laboratory results collected within 24 h of presentation. The qualitative variables were compared by the Fischer's exact (two-tailed) and the chi-square tests with Yates' correction when necessary. When appropriate, continuous variables were analyzed as categorical variables using clinically meaningful cut-off points. Continuous variables were compared using Student's *t* test. To study the relationship between the etiology of pneumonia and baseline data, taking the significant variables into account, we performed a multivariate analysis using a stepwise logistic regression technique. A probability level of 0.2 or less was chosen for covariate retention. Each independent variable identified by this analysis was assigned a regression coefficient directly proportional to its magnitude in the multivariate canonical regression.

To study the prognostic factors of pneumococcal pneumonia, all variables collected within 24 h of admission and during the ICU stay were analyzed to compare survivors and non-survivors. Univariate analysis was performed using the previously described statistical tests. Moreover, to study the relationship between the outcome and any predictor, taking the significant variables into account, we performed three stepwise logistic regressions: the significant variables collected within 24 h of admission were used for a first analysis, the significant variables collected during the ICU stay were used for a second analysis and, finally, all significant variables were entered into a third stepwise analysis. The level for covariate retention and technique use for the determination of regression coefficient were similar to those previously described.

Table 1 Microbiological diagnosis in patients from group 2, which includes patients with microbial diagnosis other than *S. pneumoniae*

Etiology of pneumonia	No. of patients who had this organism isolated*
Streptococcus sp.	21
S. aureus	54
M. catarrhalis	10
E. coli	27
K. pneumoniae	17
Proteus sp.	11
H. influenzae	37
P. aeruginosa	10
C. pneumoniae	7
Rickettsia	1
Anaerobes	3
M. pneumoniae	2

* includes 28 patients with polymicrobial etiologies

Results

General characteristics

Five hundred and five consecutive CAP patients (283 patients during the retrospective period) were enrolled in the study. The mean age of the patients was 63.4 ± 17.7 years (16–95) and 335 were male. Mean SAPS was 12.5 ± 5.4. On admission, 288 patients needed intubation and MV, 82 required inotropic drugs for hemodynamic support, 184 had a decreased level of consciousness. COPD was observed in 210 patients. Twenty-eight patients presented with immunosuppression, but no patient exhibited asplenia. Seventy-four patients had received one or more antibiotics prior to hospital admission. Chest radiograph showed bilateral involvement in 118 patients. *S. pneumoniae* was isolated in 137 (27.1 %) patients (87 patients during the retrospective period and 50 patients during the prospective period). Blood samples for follow-up serological studies were performed in 60 patients 3 weeks after ICU admission and, overall, a microbiological diagnosis was made for 172 (34.0 %) other patients (Table 1).

Etiology and antibiotic regimens

S. pneumoniae was isolated from blood cultures in 39 patients, from tracheal aspirates in 52 patients, PSB in 10 patients, pleural fluid in 1 patient, bronchoalveolar lavage in 1 patient and from sputum specimens in 34 patients. *S. Pneumoniae* was associated with other pathogen(s) in 46 patients (multiple sputum isolates) : *S. aureus* ($n = 17$), *H. influenzae* ($n = 20$), *M. catarrhalis* ($n = 10$), *E. coli* ($n = 3$), *P. mirabilis* ($n = 2$), *K. pneumoniae* ($n = 1$), *S. epidermidis* ($n = 1$), *Streptococcus sp.* ($n = 1$), *C. psittaci* ($n = 1$). Five of 137 (3.6 %) pneumococci exhibited intermediate resistance to penicillin (four during the prospective study) and noone exhibited high resistance to penicillin. Twelve (8.7 %) were resistant to macrolides (5 during the prospective period). All pneumococci were susceptible to third-generation cephalosporin during the two periods studied.

Four patients in group 1 and one in group 2 died before initiation of the antimicrobial therapy from rapidly refractory septic shock. Antibiotics administered in group 1 were a monotherapy in 56 cases, bitherapy in 68 and triple therapy in 9 cases. Monotherapy was amoxicillin ($n = 15$), amoxicillin-clavulanic acid ($n = 14$), third-generation cephalosporin ($n = 11$), ureidopenicillin ($n = 6$), quinolones ($n = 6$), carbapenem ($n = 4$). Bitherapy combined penicillin and aminoglycosides ($n = 28$), third-generation cephalosporin and aminoglycosides ($n = 17$), penicillin and quinolones ($n = 12$), aminoglycosides and quinolones ($n = 5$), carbapenem and aminoglycosides ($n = 2$), third-generation cephalosporin and quinolones ($n = 2$), third-generation cephalosporin and fosfomycin ($n = 2$). Triple therapy associated penicillin, quinolones and aminoglycosides ($n = 4$), penicillin, aminoglycosides and glycopeptides ($n = 2$), third-generation cephalosporin, quinolones and imidazol ($n = 1$), quinolones, aminoglycosides and glycopeptides ($n = 1$), quinolones, aminoglycosides and imidazol ($n = 1$). In group 2, monotherapy was used in 63 patients, bitherapy in 95 patients and triple therapy in 13 patients. In group 3, monotherapy was used in 82 patients, bitherapy in 93 patients and triple therapy in 21 patients.

In group 1, initial antimicrobial therapy was adequate in 125 patients (91.2 %), and effective in 91 patients (68.4 %). Failure occurred in 39 patients (29.3 %) and 3 patients were unappraised due to death within 48 h. Initial antimicrobial therapy was, respectively, adequate and effective in 141 (81.9 %) and 94 (54.6 %) patients from group 2 and effective in 135 (68.8 %) patients from group 3.

Characteristics of severe community-acquired pneumococcal pneumonia

Table 2 compares comorbidities, clinical, biological and radiological data on ICU admission in patients with pneumococcal CAP and patients with non-pneumococcal CAP. Stepwise logistic regression showed that male sex, lack of antimicrobial agents before ICU admission, septic shock and non-aspiration pneumonia were independently predictive of pneumococcal pneumonia (Table 3).

Comparison of groups 1 and 2 showed the same significant factors in univariate analysis, except septic shock (Table 2). Polymicrobial infections were more important in group 1. Moreover, pneumococcal pneumonia was characterized by more adequate and effective initial antimicrobial therapy: respectively, 91.2 % vs 81.9 % ($p < 0.001$) and 68.4 % and 54.6 % ($p < 0.02$). Non-aspiration pneumonia ($p < 0.007$), lack of previous antibiotics use ($p < 0.04$), and male sex ($p < 0.02$) were independently predictive of pneumococcal pneumonia.

Outcome

Table 4 compares outcome in patients with pneumococcal CAP and non-pneumococcal CAP. One hundred thirty-nine (27.5 %) of 505 patients died. Mortality was 29.2 % in group 1, 33.7 % in group 2 and 20.9 % in group 3. Mortality in group 3 was significantly lower than in the other groups ($p < 0.008$). Fifteen patients died of ICU complications: digestive hemorrhage in three patients, pulmonary embolism in two patients, catheter-related bacteremia with septic shock in three patients, cholecystis with acute renal failure in two patients, cerebral hemorrhage in five patients. Nine patients died of complications due to preexisting disease: heart or vascular diseases in six patients, chronic respiratory failure in three patients.

Prognosis of patients with severe pneumococcal pneumonia

One hundred thirty-four patients with pneumococcal pneumonia were evaluable for prognosis. Among these patients, 37 (27.6 %) died. Epidemiological, clinical, radiological and biological data, and data on the disease's course of surviving or deceased patients are compared in Table 5. The results of the stepwise logistic regression concerning prognosis are reported in Table 6.

Table 2 Characteristics of 505 patients with severe community-acquired pneumonia who were admitted to three intensive care units during the study period (*COPD* chronic obstructive pulmonary disease, *SAPS* simplified acute physiologic score, *OSF* organ system failure)

Characteristics	No. (%) of patients				
	Group 1 (n = 137)	Group 2 (n = 172)	p* value	Group 3 (n = 368)	p** value
Demographical					
Sex: male	103 (75.2%)	108 (62.8%)	0.02	232 (63.1%)	0.01
Age > 65 years	72 (52.5%)	100 (58.1%)	0.32	206 (55.9%)	0.47
Nursing home	3 (2.2%)	11 (6.4%)	0.07	21 (5.7%)	0.09
Underlying conditions					
Immunosuppression	8 (5.8%)	9 (5.2%)	0.84	20 (5.4%)	0.85
Preexisting COPD	60 (43.8%)	72 (41.9%)	0.73	150 (40.7%)	0.53
Alcohol ingestion	12 (8.8%)	12 (7.0%)	0.56	23 (6.3%)	0.32
Anticipated death within 5 years	55 (40.1%)	85 (49.4%)	0.10	167 (45.3%)	0.29
Prior antibiotic use	10 (7.3%)	32 (18.6%)	0.004	64 (17.4%)	0.004
Pneumonia					
Bacteremia	40 (29.2%)	34 (19.8%)	0.05		
Aspiration	22 (16.0%)	48 (27.9%)	0.01	94 (25.5%)	0.02
Septic shock	32 (23.4%)	33 (19.1%)	0.37	50 (13.6%)	0.008
Mechanical ventilation	94 (68.6%)	123 (71.5%)	0.57	227 (61.7%)	0.15
MV within 12 h following admission	84 (61.3%)	111 (64.5%)	0.55	204 (55.4%)	0.89
Bilateral lung involvement	35 (25.5%)	42 (24.4%)	0.81	83 (22.5%)	0.47
Number of lobes involved > 2	31 (22.6%)	29 (16.9%)	0.2	62 (16.8%)	0.13
Polymicrobial infection	47 (34.3%)	28 (16.2%)	0.001		
SAPS > 12	70 (51.1%)	85 (49.4%)	0.72	154 (41.1%)	0.06
Glascow scale > 12	96 (70.1%)	94 (54.6%)	0.005	225 (61.2%)	0.06
OSF score < 2	92 (67.1%)	121 (70.3%)	0.53	277 (75.5%)	0.06
Laboratory value results					
PaO_2/FIO_2 < 300	104 (78.2%)	123 (72.8%)	0.27	256 (71.5%)	0.13
Serum creatinine > 14 mg/l	54 (39.4%)	77 (44.7%)	0.34	150 (40.7%)	0.78
Total serum protein $\leq$ 45 g/l	7 (6.4%)	7 (4.8%)	0.59	12 (4.1%)	0.33
Leukocyte count < 3.500/mm^3	9 (6.7%)	8 (4.7%)	0.45	19 (5.2%)	0.52
Platelets count < 75.000 × 10^9/l	10 (7.9%)	14 (8.6%)	0.82	27 (7.9%)	0.99

Group 1: pneumococcal pneumonia
Group 2: pneumonia with microbiological diagnosis other than *S. pneumoniae*
Group 3: pneumonia with microbiological diagnosis other than *S. pneumoniae* + pneumonia without microbiological diagnosis
p* value: comparison between group 1 and group 2
p** value: comparison between group 1 and group 3

Table 3 Independent predictors of pneumococci in 505 patients with community-acquired pneumonia

Variable	Regression coefficients	p
Septic shock	+ 0.499	0.0001
Male sex	+ 0.483	0.01
Aspiration	– 0.424	0.01
Prior antibiotic use	– 0.537	0.0001

Discussion

Five hundred and five patients were included in the study representing, to our knowledge, the largest published series of severe CAP. A causative pathogen was found in 61.2% of the patients. A major concern of our study relates to the specificity of the etiology. Some results could appear surprising; first, our series with no *Legionella sp* episodes contrasts with previous studies [5, 10, 18]. However, this pathogen predominates essentially in Southern Europe. On the other hand, the absence of this pathogen could be due to incomplete search. Most patients left the ICUs 3 weeks after admission, i.e., before a second serological sample could be performed. Second, *S. aureus* represents 10.7% of our pneumonias. Generally sputum cultures yielding *S. aureus* are considered to show upper airway contamination in CAP culture [19]. However community-acquired *S. aureus* pneumonia exists and is readily a complication of viral pneumonia, particularly influenza A. Viral serologies were not performed in our study and the incidence of patients with recent viral infection can not be specified. In our report, *S. aureus* was isolated from blood cultures in 3 patients, from tracheal aspirates in 45 patients, PSB in 6 patients, pleural fluid in 2 patients and from sputum specimens in 5 patients. Our samples are probably reliable. Indeed blood cultures (two posi-

Table 4 Outcome of 505 patients with community-acquired pneumonia. Comparison of patients with pneumococcal pneumonia and other patients (*ARDS* acute respiratory distress syndrome, *ICU* intensive care unit, *CAP* community-acquired pneumonia)

Characteristics	*S. pneumoniae* ($n = 137$)	Other etiologies ($n = 368$)	p value
ARDS	3 (2.2%)	7 (1.9%)	0.53
Multiple organ failure	4 (2.9%)	19 (5.1%)	0.28
Delayed septic shock > 12 h	6 (4.4%)	14 (3.8%)	0.76
ICU-acquired bronchopneumonia	18 (13.1%)	48 (13.0%)	0.97
Died	40 (29.2%)	99 (26.9%)	0.6
Died due to CAP	28 (70%)	68 (68.7%)	0.61
Died due to ICU-acquired broncho-pneumonia	7 (5.1%)	14 (3.8%)	0.51
Died due to ICU complications	4 (2.9%)	11 (2.9%)	0.61
Died due to underlying clinical status	3 (2.1%)	6 (1.6%)	0.45

Table 5 Prognosis factors associated with severe community-acquired pneumococcal pneumonia in 134 patients (*MV* mechanical ventilation, *NF* non fatal, *UF* ultimately fatal, *RF* rapidly fatal, *COPD* chronic obstructive pulmonary disease, *SAPS* simplified acute physiologic score, *OSF* organ system failure scoring system, *ICU* intensive care unit)

Factor	No. (%)		
	Alive $n = 97$	Died $n = 37$	p
Sex: male/female	71/26	30/7	0.34
Age > 65 years: yes/no	46/51	24/13	0.07
Nursing home: yes/no	2/95	0/37	0.52
Aspiration: yes/no	17/80	3/34	0.17
Mc Cabe: NF/UF/RF	62/32/3	19/18/0	0.16
Immunosuppression: yes/no	5/92	3/34	0.51
Alcohol ingestion: yes/no	7/90	5/32	0.25
Prior antibiotic use: yes/no	7/90	2/35	0.7
COPD preexisting: yes/no	37/60	22/15	0.02
Bilateral radiological involvement: yes/no	22/75	13/24	0.14
Number of lobes involved > 2: yes/no	19/78	12/25	0.11
Septic shock: yes/no	16/81	14/23	0.008
MV: yes/no	59/38	33/4	0.002
MV within 12 h following admission: yes/no	54/43	28/9	0.03
Delayed MV: yes/no	5/92	5/32	0.09
$PaO_2/FIO_2 > 300$: yes/no	23/72	6/29	0.39
Serum creatinine (mg/l) > 14: yes/no	37/60	17/37	0.41
Platelet count < 75.000×10^9/l: yes/no	4/85	6/28	0.04
Leukocytes < 3500/mm^3: yes/no	3/94	6/29	0.005
Total serum protein $\leq$ 45 g/l: yes/no	4/73	3/27	0.36
Bacteremia: yes/no	24/73	15/22	0.07
Polymicrobial infection: yes/no	33/64	13/24	0.9
Antimicrobial agents: monotherapy: yes/no	43/54	12/21	0.42
Penicillin susceptible *S. pneumoniae:* yes/no	94/3	31/2	0.44
Adequacy of antimicrobial therapy: yes/no	94/3	31/6	0.01
Vasoactive drug use: yes/no	29/68	22/15	0.002
Use of steroids: yes/no	16/81	6/31	0.96
Clinical improvement after 72 h: yes/no	87/10	15/19	0.001
SAPS < 12: yes/no	50/47	9/28	0.005
OSF score $\geq$ 2: yes/no	26/71	17/20	0.03
Nosocomial bronchopneumonia: yes/no	13/84	5/21	0.45
Septis-related complications: yes/no	1/96	12/25	0.001
ICU complications: yes/no	11/86	13/24	0.001

tive cultures with the same pathogen), PSB and pleural fluid cultures are gold standard methods. Tracheal aspirates were restricted to the first tracheal aspirates obtained immediately post intubation. Third, the incidence of gram negative rods, most particularly *P. aeruginosa* (10 patients), seems important. However this pathogen can lead to CAP in COPD patients with bronchiectasis [19].

In our report *S. pneumoniae* is the most frequent causative pathogen, accounting for 27.1% of the patients. The diagnosis of pneumococcal pneumonia was made on respiratory specimens in 97 patients. Most studies only include bacteremic pneumonia [20–22]. A definition of pneumococcal pneumonia requiring positive blood cultures seems to us to be restrictive. It excludes numerous non-bacteremic patients with other

Table 6 Factors selected by multiple logistic regression as independently increasing the risk of mortality in patients with severe pneumococcal pneumonia

	Regression coefficients	*p*
Admission data		
Leukocytes < 3500/mm^3	+ 0.731	0.0004
Septic shock	+ 0.555	0.01
Age > 65 years	+ 0.378	0.01
Data on disease's course		
Sepsis-related complications	+ 0.820	0.0001
ICU complications	+ 0.480	0.001
Adequacy of antimicrobial therapy	− 0.410	0.002
Total data		
Sepsis-related complications	+ 0.772	0.0001
Leukocytes < 3500/mm^3	+ 0.491	0.005
ICU complications	+ 0.452	0.002
Septic shock	+ 0.373	0.0007

features of pneumococcal pneumonia. Involvement of *S. pneumoniae* is also strongly suggested, on sputum examination, by the demonstration of areas with at least 15–20 WBCs and less than five epithelial cells in a standard microscopic field under × 1,000 magnification and a culture of *S. pneumoniae* [23].

Male sex, lack of the use of antibiotics before hospital admission, non-aspiration pneumonia and shock were individually predictive of pneumococcal pneumonia. Some of these factors have been previously reported [24, 25]: community surveys have already suggested that men are at increased risk for pneumococcal infections. However, to our knowledge, no previous study has mentioned the role of prior antibiotic use in the epidemiological features of CAP. Even if indication, duration and type of prior antibiotics is not specified, we can present a hypothesis for this: antibiotic regimens prescribed by physicians in outpatients focus essentially on *S. pneumoniae,* thus (i) decreasing hospital admissions, (ii) eliminating pneumococcus from cultures and (iii) selecting gram negative rods accountable for severe CAP in some patients. In the same way, severe pneumococcal pneumonia could require hospital admission more rapidly than other bacterial pneumonia before the initiation of antibiotic regimen. The etiological diagnosis of aspiration pneumonia has been the subject of few reports. In our study *S. pneumoniae* was found in 19% of aspiration pneumonia, including 38% documented aspiration pneumonia. Mier et al. reported *S. pneumoniae* to be only the 4th leading causative agent of aspiration pneumonia [26]. In the group of 309 patients with defined microbiological diagnosis (groups 1 and 2), only lack of prior antibiotic use, male sex and absence of aspiration pneumonia are predictive of pneumococcal etiology. Septic shock is no longer significant and is thereby more characteristic of bacterial pneumonia whatever the microbiological diagnosis. One can suggest that documented pneumonias are due to higher inoculum levels which could explain a more aggressive course. Among all the epidemiological data that we studied no attention was paid to pneumococcal vaccination. Indeed, pneumococcal vaccination is not very widespread in our area and therefore not recorded systematically in our unit. Thus, we can not assess if those patients who received pneumococcal vaccination developed pneumococcal pneumonia, although it would be interesting data.

Mortality in group 3 (20.9%) is significantly lower than in the other two groups (31.7%). We suggest that, in this group, most pneumonia was due to bacterial pathogens partly eradicted by previous antimicrobial therapy, anaerobes or atypical pathogens. Atypical pathogens are responsible for 20–30% of CAP in the literature and cause less severe pneumonia with lower mortality [5, 9, 27]. The overall mortality rate reported in patients with severe pneumococcal pneumonia has remained unchanged over the past four decades around 25%, which is close to our 29.2% mortality [28–30].

Among admission data, the most significant prognostic factor was leukopenia . A WBC count of lower than 4,000/μl occurs in 5–10% of hospitalized patients (6.7% in our study) and has already been described as an indicator of poor prognosis [31]. It reflects the accumulation of available WBCs at the infected site and suggests overwhelming sepsis and/or decreased marrow granulocyte reserves. Age over 65 years is an indicator of poor prognosis, as recently described for patients with severe CAP requiring MV [32]. However, comorbidities such as alcoholism, COPD and McCabe's criteria do not influence the prognosis. Surprisingly, multivariate analysis shows that severity of initial respiratory failure, defined by bilateral radiological involvement, number of involved lobes, PaO_2/FIO_2 ratio and requirement for MV, is not an indicator of poor prognosis. The prognosis of these patients depends essentially on infectious disorders (septic shock) rather than respiratory injury.

Among the data on the disease's course, prognosis was dependent on sepsis-related complications, ICU complications and adequacy of antimicrobial therapy. Sepsis-related complications depend on the severity of pneumonia. To decrease the mortality in these patients, improvements in the management of sepsis, ARDS and MOF are required. Improving ICU management essentially involves measures like prevention of deep venous thrombosis and pulmonary embolism, optimal stress ulcer prophylaxis and the early diagnosis of intraabdominal surgical procedures such as cholecystis. Adequacy of antimicrobial therapy improves the prognosis. This could represent an interesting challenge for physicians at a time when the problem of penicillin resistance has become worrying throughout the world. In our study,

only a few patients with pneumococcal pneumonia exhibited strains with a decreased susceptibility to penicillin G (3.7%) or resistance to macrolids (8.7%). This low resistance occurrence is due to the long study period, resistant pneumococci having become more frequent in recent years, and, in addition, a particularly low prevalence of resistance in our area compared with other geographical areas. Resistance to penicillin in patients with severe pneumococcal pneumonia is not associated with increased mortality as long as antimicrobial therapy is adequate initially [33]. The population of patients with decreased susceptibility is well described nowadays [33, 34]. We think that the initial empirical therapy of severe pneumococcal CAP must include amoxicillin (50 mg/kg BW per day) in patients without risk factors for decreased susceptibility to penicillin and ceftriaxone, or cefotaxime if those risks factors are present. Carbapenems must be used in geographical areas where cephalosporin resistance is a concern. In all cases antimicrobial therapy must be reconsidered with the minimal inhibitory concentrations (MICs) of penicillin and cephalosporin in order to prescribe the antimicrobial agent with the narrowest spectrum. In our view, macrolides, with variable activity for *S. pneumoniae*, must be avoided when severe pneumococcal pneumonia is suspected.

Analysis of the global database using stepwise logistic regression individualize only a few parameters as predictors of outcome (Table 6). Among admission data, only leukopenia and septic shock are significant. Surprisingly, the occurrence of nosocomial bronchopneumonia does not influence prognosis. Nosocomial bronchopneumonia is a frequent complication among mechanically ventilated patients, with a substantial mortality. However the question of whether nosocomial pneumonia or the host setting is the crucial factor responsible for death has not been clearly defined. Our study is consistent with a recent report showing that ventilator-associated pneumonia did not increase mortality [35].

In summary, few features facilitate the identification of *S. pneumoniae* in patients with severe CAP on admission. Leukopenia, septic shock and age over 65 years impair outcome while comorbidities do not seem to influence the prognosis. Antimicrobial chemotherapy must combat *S. pneumoniae* efficiently. The presence of septic and ICU complications are the major variables affecting the outcome during ICU stay. Progress in the management of sepsis is necessary to improve prognosis.

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