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Severe pneumococcal community-acquired pneumonia admitted to medical Tunisian ICU

**Khairallah Belkhouja · Kaïs Ben Romdhane ·
Asma Ghariani · Afef Hammami · Emna M'hiri ·
Leila Slim-Saidi · Jalila Ben Khelil · Mohamed Besbes**

Abstract *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia (CAP). There are no available data about this disease in Tunisian intensive care patients. The objective of this study is to describe the clinical and microbiological features of pneumococcal CAP and determine the prognostic factors. This is a retrospective cohort study of all pneumococcal CAP cases hospitalized in the medical intensive care unit (ICU) of Hospital A. Mami of Ariana (Tunisia) between January 1999 and August 2008. Included were 132 patients (mean age, 49.5 years; 82.6% males); 30 patients had received antimicrobial treatment before hospital admission. The mean of the Simplified Acute Physiology Score II was 32.9. All patients had an acute respiratory failure; 34 patients (25.8%) had pneumococcal bacteremic CAP. Among the isolated strains, 125 antimicrobial susceptibility tests were performed. The use of the new Clinical and Laboratory Standards Institute breakpoints for susceptibility when testing penicillin against *S. pneumoniae* showed that all isolated strains were susceptible to penicillin. The mortality rate was 25%. The need of mechanical ventilation at admission [odds ratio (OR), 3.4; 95% confidence interval (CI), 1.67–6.94; $P = 0.001$), Sepsis-related Organ Failure Assessment (SOFA) score at admission ≥4 (OR, 3.1; 95% CI, 1.56–6.13; $P = 0.001$), and serum creatinine at admission ≥102 μmol/l (OR, 1.8; 95% CI, 1.02–3.17; $P = 0.043$) were independent factors related to ICU mortality. In conclusion, pneumococcal CAP requiring hospitalization in the ICU is associated with high mortality. All isolated stains were susceptible to penicillin.

Keywords Community-acquired pneumonia ·
Streptococcus pneumoniae · Intensive care · Prognosis

Introduction

Community-acquired pneumonia (CAP) remains a major cause of morbidity and mortality in developed countries [1]. Approximately 10–20% of hospitalized patients with CAP required admission to an intensive care unit (ICU), with increased morbidity, mortality, and costs [2–4]. The mortality rates reported in these patients ranged from 20% to 50% [2, 5].

The identification of the causal CAP microorganism varies from 40% to 60% for patients admitted in a general ward [6, 7] and can reached 78% for those admitted in an ICU [8]. The leading cause of CAP is *Streptococcus pneumoniae*, whatever the age and comorbidities of patients and the site of care (outpatient, medical ward, or ICU) [6–11]. During the past 35 years, the global emergence of drug-resistant *Streptococcus pneumoniae* (DRSP) has been reported [12, 13]. This resistance is particularly

K. Belkhouja · K. Ben Romdhane · A. Hammami ·
J. Ben Khelil · M. Besbes
Department of Intensive Care Medicine,
Abderrahmen Mami Hospital, Ariana, Tunisia

K. Belkhouja · K. Ben Romdhane · A. Hammami ·
J. Ben Khelil · M. Besbes
Faculty of Medicine, University of Tunis El-Manar,
Tunis, Tunisia

Present Address:
K. Belkhouja (✉)
Department of Intensive Care Medicine,
Abderrahmen Mami Hospital, Ariana, Tunisia
e-mail: belkhouja2000@yahoo.fr

A. Ghariani · E. M'hiri · L. Slim-Saidi
Department of Microbiology,
Abderrahmen Mami Hospital, Ariana, Tunisia

documented to β-lactams, and the prevalence of penicillin-nonsusceptible *S. pneumoniae* (PNSSP) has been reported in several regions of the world [14–17]. In Tunisia, there are no available data about the epidemiological characteristics and prognostic of pneumococcal CAP admitted in ICUs. The aim of this study was to describe the clinical and microbiological features of pneumococcal CAP and to determine its prognostic factors.

Patients and methods

Design and study population

A retrospective cohort study was carried out in the Hospital Abderrahmen Mami of Ariana, Tunisia. Approval was obtained from the hospital ethics committee. Included were all consecutive cases of CAP admitted to the ICU (22-bed medical adult ICU) between January 1, 1999 and August 31, 2008, in patients more than 15 years old in whom *S. pneumoniae* was isolated. All patients with severe immunosuppression [solid organ transplant, current chemotherapy, human immunodeficiency virus (HIV) diagnosis] were excluded.

Diagnostic criteria

Pneumonia was defined as the presentation of acute onset of symptoms suggestive of lower respiratory tract infection at hospital admission (cough, sputum production, pleural chest pain, fever >38.3°C or hypothermia, pulmonary consolidation at examination, abnormal leukocyte counts) and radiographic evidence of a new pulmonary infiltrate. The definitive diagnosis of pneumococcal pneumonia was considered if there was clinical and radiologic pneumonia with one of the following conditions: (1) blood cultures positive for *S. pneumoniae*; (2) pleural fluid cultures yielding *S. pneumoniae*; (3) validated sputum at direct examination (≥25 leucocytes per field and <10 epithelial cells per field) and cultures with ≥10^7 colony-forming units (cfu)/ml *S. pneumoniae*; (4) endotracheal aspirate (ETA) cultures with ≥10^6 cfu/ml *S. pneumoniae*; (5) bronchoalveolar lavage (BAL) cultures with ≥10^4 cfu/ml *S. pneumoniae*; (6) plugged telescoping catheter (PTC) cultures with ≥10^3 cfu/ml *S. pneumoniae*; and (7) positive pneumococcal urinary antigen test result (Binax NOW-test; Binax, Portland, ME, USA). Diagnosis of atypical microorganisms was performed by means of paired serology at admission and at the third week thereafter: these microorganisms included *Chlamydia pneumoniae* (diagnosis in the case of fourfold increase in IgG titers and/or initial single IgM titer ≥1:32), *Mycoplasma pneumoniae* (diagnosis in the case of fourfold increase in IgG titers and/or any initial positive IgM titer), as well as *Legionella pneumophila*

serotypes 1–6 and *Coxiella burnetii* (diagnosis in the case of fourfold increase in IgG titer). The diagnosis of *L. pneumophila* serotype 1 was also performed by positive urinary antigen. Pneumonia was considered as CAP if it was diagnosed within the first 48 h of hospitalization and the patient had been discharged from an acute care facility within 14 days of hospital admission.

Data collection

The following data were collected at the time of ICU admission: age, gender, current smoking, comorbid illness, antimicrobial treatment instituted within 1 month before hospital admission, Simplified Acute Physiology Score II (SAPS II) [18], sepsis-related organ failure assessment (SOFA) score [19], the pneumonia severity index (PSI) and the CURB-65 score [20, 21], Glasgow Coma Score (GCS), and signs of severity at admission as defined below: mechanical ventilation (MV) requirement, septic shock, acute lung injury or acute respiratory distress syndrome (ALI/ARDS), coma, acute renal failure (ARF), multiple organ failure (MOF), chest radiograph pattern (alveolar, interstitial, or mixed infiltrate, multilobar involvement, bilateral involvement, presence of cavity, pleural effusion), blood analysis (leukocyte count, serum creatinine, C-reactive protein, lactate, serum glucose, PCO_2, PO_2, and arterial pH), bacteriological identification procedure, and empiric antimicrobial treatment.

During hospital admission, the following information was recorded: antimicrobial susceptibility testing of *S. pneumoniae* isolates and any associated organism, any complication of stay (need for MV, shock, ARDS/ALI, ARF, nosocomial infections, MOF, arrhythmia, etc.), ICU length of stay, and ICU mortality.

Susceptibility testing

Susceptibility testing of *S. pneumoniae* isolates was performed using the disk-agar diffusion method. The following antibiotics were tested for antimicrobial susceptibility: penicillin, amoxicillin, cefotaxime, erythromycin, lincomycine, pristinamycine, tetracycline, levofloxacin, trimethoprim–sulfamethoxazole, chloramphenicol, rifampicin, and vancomycin.

The minimum inhibitory concentration (MIC) was not tested for all antimicrobials against *S. pneumoniae* isolates. The susceptibility of *S. pneumoniae* to β-lactams was determined with an oxacillin disk charged to 5 μg. For all strains including oxacillin of diameter smaller than 26 mm, the determination of the MIC for penicillin, amoxicillin, and cefotaxime was performed by the E test method. The MIC_{90} and MIC_{50} were not performed in this study. Before 2008, the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints for penicillin for treatment of

S. pneumoniae infection were defined as susceptible, ≤0.06 μg/ml; intermediate, 0.12–1 μg/ml; and resistant, ≥2 μg/ml. In January 2008, the CLSI published revised breakpoints for susceptibility when testing penicillin against *S. pneumoniae* [22]. The revised breakpoints for nonmeningeal infections treated with parenteral penicillin were defined as susceptible, ≤2 μg/ml; intermediate, 4 μg/ml; and resistant, ≥8 μg/ml. The term nonsusceptible refers to both resistant and intermediate stains. We compared the rate of PNSSP between pre-2008 and the new 2008 revised breakpoints for nonmeningitis intravenous administration.

Definitions

Acute respiratory failure at ICU admission was defined as PaO_2 <60 mmHg and/or $PaCO_2$ >45 mmHg while the patient was breathing room air, or the need for an increase in inspired oxygen concentration or MV. ALI and ARDS were defined in concordance with the American-European consensus conference [23]. Shock was defined as systolic blood pressure <90 mmHg not corrected after fluid administration or if patients needed vasopressor drug support for >4 h. Coma was defined as GCS ≤8. ARF was defined as a rapidly rising serum creatinine ≥120 μM/l or oliguria (urine output as measured, <20 ml/h or <80 ml/4 h). MOF was defined as the dysfunction of two or more of the six evaluated organ systems accorded to the definition by Fagon et al. [24].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or as median (extreme) when the variables were not normally distributed. Discrete variables are expressed as counts (percentage). Categorical variables were compared using chi-square test or Fisher's exact test correction, when chi-square was not appropriate. Continuous variables were compared using Student's *t* test or the Mann–Whitney *U* test when the variables were not normally distributed.

All the statistically significant variables in the univariate analysis were included in the multiple logistic regression analysis model with a stepwise forward selection. A two-tailed *P* value <0.05 was considered statistically significant for all analyses.

Results

Patient description

During the study period, 273 patients were hospitalized for CAP. The microorganism was identified in 187 patients

(68.5%), of whom 132 had *S. pneumoniae* (48.3%). The mean age was 49.5 ± 21.6 years; 109 patients (82.6%) were men. Thirty-nine (29.5%) patients had received some antibiotic treatment before ICU admission. The mean SAPS II was 32.9 ± 18.6 and the median SOFA score and CURB-65 were 3 and 2, respectively; 72 patients (54.5%) had PSI class IV or V. All patients had an acute respiratory failure. Oxygen tension in arterial blood (PaO_2)/inspiratory oxygen fraction (FiO_2) index was <300 mmHg in 97 patients (73.5%). At admission, 84 patients had one or more signs of severity, and MV was needed in 62 patients (47%). Pneumonia was bilateral and multilobar in 39.4% and 48.5% of patients, respectively (Table 1).

Microbiological investigation and data

A least one blood culture was collected for all patients: 34 (25.8%) had a positive blood culture result. BAL and plugged telescoping catheter (PTC) were carried out in 116 patients and identified the organism in 103 (88.8%). Endotracheal aspiration (ETA) was performed in 84 patients and identified the organism in 54 (64.3%). Sputum samples were performed in 30 patients and identified the organism in 10 (33.3%). Urine detection antigen for *S. pneumoniae* and *L. pneumophila* was performed in 34 patients (25.7%) and identified the *S. pneumoniae* in 9 samples (26.5%) and *L. pneumophila* in 1 sample. Microbiological diagnosis was made only by urine antigen detection in 7 patients. Pleural fluid was performed in 25 patients and identified the organism in 7 (28%). Serological analyses for atypical microorganisms were performed in 65 patients (49.2%) and identified *L. pneumophila* and *M. pneumoniae* in 1 case.

S. pneumoniae was associated with another organism in 37 patients (28%), mainly *Haemophilus influenzae* in 25 cases, followed by *Staphylococcus aureus* (5 cases), *Escherichia coli* (2 cases), *Enterobacter cloacae* (2 cases), and *Klebsiella pneumoniae*, *L. pneumophila*, and *M. pneumoniae* (1 case each).

Of the 132 strains, 125 susceptibility tests were performed. Thirty-one of isolated strains had an oxacillin diameter smaller than 26 mm; the median MIC was 0.75 μg/ml, ranging between 0.125 and 2 μg/ml. When applying the old CLSI penicillin breakpoints, the rate of PNSSP was 24.8%. When applying the new CLSI penicillin breakpoints, however, all isolated stains were susceptible to penicillin. Forty-five (36%) isolated strains were fully resistant to erythromycin (Table 2).

Initial antibiotic treatment

The median time for first antibiotic dose administration was 5.5 h (range, 1–168 h). Initial empiric antibiotic

Table 1 Baseline characteristics of 132 patients with pneumococcal community-acquired pneumonia (CAP)

Variables	Value
Age (years)	49.5 ± 21.6
Gender ratio (male/female)	4.7 (109/23)
Comorbidities	81 (61.4)
Pulmonary disease	67 (54.5)
Chronic obstructive pulmonary disease	51 (38.6)
Heart disease	27 (20.5)
Diabetes mellitus	21 (16)
Current smoking	79 (60)
Prior antibiotherapy	39 (29.5)
SAPS II	32.8 ± 18.6
SOFA	2 (0–22)
CURB-65	2 (0–5)
PSI class II and III	60 (45.5)
PSI class IV	35 (26.5)
PSI class V	37 (28)
Signs of severity at admission	
Acute renal failure	63 (47.7)
Septic shock	35 (26.5)
ALI/ARDS	30 (22.7)
Mechanical ventilation	62 (47)
Multiple organ failure	19 (14.4)
Leukocyte count ($\times 10^9$/l)	17.3 ± 8.4
C-reactive protein (mg/l)	163.3 ± 89.4
Serum glucose (mmol/l)	8.9 ± 5.6
Serum creatinine (μmol/l)	122.3 ± 94.3
Serum lactate (mmol/l)	6.9 ± 7.1
Arterial pH	7.35 ± 0.13
PaO_2/FiO_2	244 ± 82.6
Chest radiograph at admission	
Alveolar infiltrates	132 (100)
Interstitial infiltrates	34 (25.8)
Bilateral involvement	52 (39.4)
Multilobar involvement	64 (48.5)
Pleural effusion	31 (23.5)

Data are presented as number (%) or mean ± SD or median (extreme)

SAPS Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment, *PSI* pneumonia severity index, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *PaO2* partial pressure of oxygen in arterial blood, *FiO2* fraction of inspired oxygen

therapy was monotherapy in 71 patients (53.8%), as follows: amoxicillin/clavulanic acid in 53 (40.1%), cefotaxime in 9 (6.8%), and levofloxacin in 9 (6.8%). Different combinations of β-lactams (cefotaxime or amoxicillin/clavulanic acid) and erythromycin or quinolones (ofloxacin or levofloxacin) were used in the remaining 61 patients (46.2%).This antibiotic has been secondarily simplified, after the results of susceptibility testing, to amoxicillin alone in 103 patients (78%).

Outcome and prognosis factors

During their stay, 49 patients (37.1%) had at least one complication, mainly dominated by septic shock (25 cases) and MOF (18 cases). The median length of stay in the ICU was 9.5 days (range, 1–68 days). The overall ICU mortality rate was 25% (33 patients) (Table 3). The univariate analysis recorded variables related to death are listed in Table 4 for continuous variables and in Table 5 for categorical variables. Neither the empiric monotherapy [odds ratio (OR), 0.5; 95% confidence interval (CI), 0.22–1.11; $P = 0.08$] nor bacteremia (OR, 1.36; 95% CI, 0.57–3.25; $P = 0.491$) were predictors of mortality in univariate analysis.

The logistic regression demonstrated that need of MV at admission, SOFA score ≥4, and serum creatinine ≥102 μmol/l were the only independent factors related to death (Table 6).

Discussion

The incidence of pneumococcal CAP in our study was 48.3%. In the literature, the incidence varies between 15.2% and 42% [4, 8, 11], which is explained mainly by the variation of diagnostic procedures in these studies. Indeed, in the study by Restrepo et al. [4], where invasive diagnostic procedures were not used, this incidence was low. In the studies by Paganin et al. [8] and Rello et al. [11], as in our study, fiberoptic technique was used for lower respiratory tract secretions sampling in nonintubated patients.

The orientation of a patient with CAP to a site of care (outcome, hospital ward, or ICU) was a major concern of the authors. Fine et al. [20] developed the PSI score. Initially designed for a prognosis evaluation, this score has become a tool for deciding CAP hospitalization. However, several limitations are noteworthy. First, hypoxemia, whose "weight" is only 10, remains an important factor of severity, while a 71-year-old man passes immediately to IPS class III only by the "weight" of his age. Second, its use in other populations or in countries with different health system needs validation. Finally, socioeconomic condition and psychological and digestive disorders are not taken into account. In our study, the decision for ICU hospitalization was based mainly on the clinical judgment of the physician, taking into account the socioeconomic condition of the patient. Another prognostic score is the CURB-65, widely used and adopted by the British Thoracic Society [21, 25]. This score is much easier to use and

Table 2 Susceptibility testing of 125 isolated pneumococci stains

Antimicrobial	Susceptible	Intermediate	Resistant
Penicillin[a]	125 (100)	0	0
Erythromycin	80 (64)	0	45 (36)
Lincomycine	82 (65.6)	0	43 (34.4)
Pristinamycine	118 (94.4)	1 (0.8)	6 (4.8)
Chloramphenicol	111 (88.8)	2 (1.6)	12 (9.6)
Tetracycline[b]	50 (65.8)	2 (2.6)	24 (31.6)
Levofloxacin[c]	74 (100)	0	0
Trimethoprim–sulfamethoxazole[d]	53 (45.7)	23 (19.8)	40 (34.5)
Rifampicin	125 (100)	0	0
Vancomycin	125 (100)	0	0

Data are presented as number (%)

[a] According to current Clinical and Laboratory Standards Institute [29] susceptibility breakpoints for penicillin for treatment of *Streptococcus pneumoniae* infection

[b] Susceptibility testing to tetracycline was performed in 76 isolated stains

[c] Susceptibility testing to levofloxacin was performed in 74 isolated stains

[d] Susceptibility testing to trimethoprim–sulfamethoxazole was performed in 116 isolated stains

Table 3 Outcome data of 132 patients with pneumococcal CAP

Variable	Value
Complication	49 (37.1)
Septic shock	25 (19)
MOF	18 (13.6)
ARDS	8 (6.1)
Nosocomial pneumonia	12 (9.1)
Arrhythmias	7 (5.3)
Acute renal failure	7 (5.3)
Pneumothorax	6 (4.5)
Length of stay (days)	9.5 (1–68)
ICU mortality	33 (25)

Data are presented as number (%) or median (extreme)

MOF multiple organ failure, *ARDS* acute respiratory distress syndrome, *ICU* intensive care unit

more practical than that of the IPS score. For the ICU admission criteria of patients with CAP, the American Thoracic Society (ATS) recommends admission to intensive care if the patient has two minor signs or one major sign [26]. The ATS criteria seem more practical and easy to use. Indeed, the majority of our patients had at least one criterion of the ATS (acute respiratory failure in 94% of cases, MV in 47% of cases, bilateral radiologic involvement in 39.4%, multilobar involvement in 48.5% of patients, and septic shock in 26.5% of cases).

The incidence of mixed CAP varies from 13% to 38% [6, 27], and *S. pneumoniae* is the pathogen most often associated with another infectious agent, particularly *Haemophilus influenzae* [6], as in our series, but also with atypical bacterial pathogens and viruses [28]. This large variation is the result of the variation of microbiological tests carried out in various studies. In our work, the search for atypical pathogens is very inadequate, and no respiratory viruses have been searched. Serological analyses for atypical microorganisms were performed in 49.2% of patients and urine antigen detection in 25.7% of patients, mainly because of lack of available resources.

For more than two decades, the global emergence of in vitro antibiotic resistance among *S. pneumoniae* has been reported. This resistance is of special interest for the β-lactams, with a variable frequency from one country to another, ranging from 18% to 53% [12–17]. After 2008, when CLSI revised the breakpoints, the rate of PNSSP was decreased significantly. Recently, Mera et al. have compared the rates of susceptibility of *S. pneumoniae* to penicillin before and after the 2008 revised CLSI breakpoint. In this study, the penicillin susceptibility level was 92.2% in 2008 (11,185 strains), if the new breakpoints for intravenous antibiotic use and nonmeningitis syndromes such as bacteremia or pneumonia are applied, whereas using the old definition, the proportion was 58.8% [29]. In our study, the PNSSP rate was 24.8% if the old breakpoints are applied, whereas all stains were susceptible to penicillin if we referred to the present CLSI breakpoints. The resistance of *S. pneumoniae* to macrolides is markedly increasing worldwide, exceeding 50% in some studies [12, 13].

For treatment of severe CAP, all international scientific societies recommended the use of combination therapy [25, 26, 30, 31], which will include an anti-pneumococcal β-lactam agent and additional coverage for "atypical" pathogens with a respiratory fluoroquinolone or a macrolide. This association has some drawbacks and criticisms.

Table 4 Univariate analysis of prognostic factors: continuous variables

Factor	Nonsurvivors, 33	Survivors, 99	P
Age (years)	60.7 ± 14.7	45.7 ± 22.4	<0.001
SAPS II	48.2 ± 20.3	27.8 ± 14.9	<0.001
SOFA at admission	6 (1–14)	2 (0–22)	<0.001
CURB-65	3 (2–5)	2 (0–5)	<0.001
Serum glucose at admission (mmol/l)	11.4 ± 7	8 ± 4.8	0.01
Serum creatinine at admission (μmol/l)	161.3 ± 104.3	109.3 ± 87.6	0.013
Arterial pH at admission	7.28 ± 0,14	7.37 ± 0.12	0.001
PaO_2/FiO_2 at admission	184 ± 86.9	262.1 ± 75.9	<0.001

Data are presented as mean ± SD or median (range)

SAPS Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment, *PaO2* partial pressure of oxygen in arterial blood, *FiO2* fraction of inspired oxygen

Table 5 Univariate analysis of prognostic factors: categorical variables

Factor	Nonsurvivors, 33	Survivors, 99	OR	95% CI	P
PSI class ≥IV	30/72 (71.7)	3/60 (5)	13.6	3.88–47.46	<0.001
Heart disease comorbidities	11/27 (40.7)	22/83 (21)	2.6	1.05–6.3	0.03
Chronic obstructive pulmonary disease	18/51 (35.3)	15/66 (18.5)	2.4	1.07–5.35	0.03
Diabetes mellitus	9/21 (42.9)	24/111 (21.6)	2.7	1.02–7.2	0.039
Bilateral pneumonia	20/52 (38.5)	13/80 (16.3)	3.2	1.42–7.28	0.004
Multilobar pneumonia	23/64 (35.9)	10/68 (14.7)	3.3	1.4–7.56	0.005
Septic shock at admission	14/35 (40)	19/97 (19.6)	2.7	1.2–6.35	0.017
ALI/ARDS at admission	14/30 (46.7)	19/102 (18.6)	3.8	1.6–9.15	0.002
MOF at admission	14/19 (73.7)	19/113 (16.8)	13.8	4.5–43.1	<0.001
MV required at admission	30/62 (48.4)	3/70 (4.3)	20.9	5.9–73.7	<0.001

Data are presented as number (%)

OR odds ratio, *CI* confidence interval, *PSI* pneumonia severity index, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *MOF* multiple organ failure, *MV* mechanical ventilation

Table 6 Multivariate analysis of prognostic factors

Factor	OR	95% CI	P
MV required at admission	3.4	1.67–6.94	0.001
SOFA at admission ≥4	3.1	1.56–6.13	0.001
Serum creatinine at admission ≥102 μmol/l	1.8	1.02–3.17	0.043

SOFA Sequential Organ Failure Assessment, *MV* mechanical ventilation

The first is the significant risk of emergence of resistant strains. The second is the absence of clear epidemiological data and obvious impact of atypical pathogens in the CAP. The third and most important is that the impact of monotherapy on mortality is not clearly proven. Finally, the combination results in increased cost of care. In our study, more than half of the patients received empiric monotherapy, explained, first, by the fact that the choice of initial antibiotic therapy has not been guided throughout the study period by any rigorous protocol and, second, that combination therapy has been conducted mainly in the presence of shock and/or the need for VM.

The mortality rate in our report was 25%. In a recent meta-analysis including 10 studies conducted between 1984 and 2001 and including 3,430 patients hospitalized with pneumococcal CAP, the short-term mortality ranged from 10.9% to 36.4% [31]. This study raises the problem of the important heterogeneity between studies and the extensive period of these works (17 years).

Concerning the empirical treatment of pneumococcal CAP, some studies have evaluated the efficacy of monotherapy versus combination therapy and its mortality impact [32, 33]. The report of the most recent study showed that in a group of nonsevere patients, there is no difference in mortality between monotherapy versus combination therapy. In contrast, in a group of patients with septic shock, there is a significant reduction in

mortality in favor of the combination therapy (23.4% vs. 55%; $P = 0.001$) [33]. In our results, we did not observe any significant difference in mortality between patients treated with monotherapy and those treated by combination therapy. Because the initial treatment included at least one antibiotic effective against *S. pneumoniae* (amoxicillin/clavulanic acid or cefotaxime and/or levofloxacin), the impact of this factor on the prognosis cannot be analyzed.

Our study revealed that pneumococcal bacteremic CAP did not significantly increase mortality compared to nonbacteremic pneumococcal CAP. The impact of pneumococcal bacteremia on mortality remains controversial [34–36]. Bordon et al. have reported a larger sample size, including 1,847 cases of nonbacteremic CAP and 125 pneumococcal bacteremic CAP. Among these, 284 patients were cared for in intensive care (39 patients with pneumococcal bacteremia). The authors showed no significant differences between the two groups in either overall mortality or mortality attributable to CAP [36].

There are some limitations to our study. First, this is a retrospective cohort study, and there are inherent problems related to this design, including selection bias. However, several similar studies, including epidemiological studies, have provided relevant data to the medical scientific community. Second, the study period is very wide (January 1999–August 2008). However, during this period the epidemiology of bacterial CAP and the acquisition of antibiotic resistance have evolved and changed over time. Our diagnostic and therapeutic strategy may also have changed in this long period. Third, the antimicrobial susceptibility testing used the E test method and not the broth microdilution test, which is now considered the gold standard method. The MIC was not performed for all antimicrobial against *S. pneumoniae* isolates. Also, the MIC_{50} and MIC_{90} were not performed for any antimicrobial. Investigation to detect atypical pathogens was insufficient. All these limits are mainly the result of the lack of resources in a developing country such as ours. Finally, this is a single-center study. Indeed, the epidemiology and management of CAP, particularly those cases requiring hospitalization in intensive care, vary from one country to another and within a country could vary from one region to another. So, the results of this study cannot be extrapolated to other regions of Tunisia and other countries nearby.

In conclusion, this first Tunisian study, with a relatively large size, of pneumococcal CAP hospitalizations in an adult medical ICU, can provide interesting prognostic and epidemiological data. A prospective, multicenter study seems necessary to better know our national epidemiology of severe CAP in general and, more specifically, that of pneumococcal CAP.

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