Severe pneumococcal community-acquired pneumonia admitted to medical Tunisian ICU

Khairallah Belkhouja · Kais Ben Romdhane · Asma Ghariani · Afef Hammami · Emma M’hiri · Leila Slim-Saidi · Jalila Ben Khelil · Mohamed Besbes

Received: 8 June 2011 / Accepted: 19 October 2011 / Published online: 2 November 2011
© Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases 2011

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
documented to $\beta$-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 character-
istics 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 med-
ical 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 $\geq$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 ($\geq$25 leucocytes per field and $<$10 epithelial
cells per field) and cultures with $\geq 10^{5}$ colony-forming
units (cfu/ml) $S. pneumoniae$; (4) endotracheal aspirate
(ETA) cultures with $\geq 10^{6}$ cfu/ml $S. pneumoniae$; (5)
broncho-alveolar lavage (BAL) cultures with $\geq 10^{4}$ cfu/ml
$S. pneumoniae$; (6) plugged telescoping catheter (PTC)
cultures with $\geq 10^{3}$ cfu/ml $S. pneumoniae$; and (7) positive
pneumococcal urinary antigen test result (Binax NOW-test;
Binax, Portland, ME, USA). Diagnosis of atypical micro-
organisms was performed by means of paired serology at
admission and at the third week thereafter: these microor-
ganisms included *Chlamydia pneumoniae* (diagnosis in the
case of fourfold increase in IgG titers and/or initial single
IgM titer $\geq 1:32$), *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
doubling 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
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-react-
tive 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 antibi-
otics were tested for antimicrobial susceptibility: penicillin,
amoxicillin, cefotaxime, erythromycin, lincomycin, pristin-
amycine, tetracycline, levofloxacin, trimethoprim–sulfameth-
oxazole, 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 $\beta$-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 PaO2 <60 mmHg and/or PaCO2 >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 (PaO2)/inspiratory oxygen fraction (FiO2) 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
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 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 (×10³/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 |
| PaO₂/FiO₂ | 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.
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 strains 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 2 Susceptibility testing of 125 isolated pneumococci stains

| Antimicrobial                  | Susceptible | Intermediate | Resistant |
|-------------------------------|-------------|--------------|-----------|
| Penicillin*                   | 125 (100)   | 0            | 0         |
| Erythromycin                  | 80 (64)     | 0            | 45 (36)   |
| Lincomycin                    | 82 (65.6)   | 0            | 43 (34.4) |
| Pristinamycin                 | 118 (94.4)  | 1 (0.8)      | 6 (4.8)   |
| Chloramphenicol               | 111 (88.8)  | 2 (1.6)      | 12 (9.6)  |
| Tetracyclineb                 | 50 (65.8)   | 2 (2.6)      | 24 (31.6) |
| Levofloxacinc                 | 74 (100)    | 0            | 0         |
| Trimethoprim–sulfamethoxazoled| 53 (45.7)   | 23 (19.8)    | 40 (34.5) |
| Rifampicin                    | 125 (100)   | 0            | 0         |
| Vancomycin                    | 125 (100)   | 0            | 0         |

Data are presented as number (%)

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

* Susceptibility testing to tetracycline was performed in 76 isolated stains

* Susceptibility testing to levofloxacin was performed in 74 isolated stains

* 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
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 mono-therapy 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 mono-therapy, 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

| 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 |
| PaO2/FiO2 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
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 levofoxacin), 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 pneumococcal CAP. 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.

Acknowledgments We are indebted to the doctors and nurses with the Intensive Care Medicine Service who provided care for the patients included in the study and to all the personnel in the microbiology laboratory. We also thank Dr. Nozha Brahmi for his help.

References

1. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med. 2002;162:1059–64.
2. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. JAMA. 1996;275:134–41.
3. Rello J, Catalan M, Diaz E, Bodí M, Alvarez B. Associations between empirical antimicrobial therapy at the hospital and mortality in patients with severe community-acquired pneumonia. Intensive Care Med. 2002;28:1030–5.
4. Restrepo MI, Mortensen EM, Velez JA, Frei C, Anzueto A. A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. Chest. 2008;133:610–7.
5. Angus DC, Marrie TJ, Obrosky DS, Clermont G, Dresnizov TT, Coley C, et al. Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. Am J Respir Crit Care Med. 2002;166:717–23.
6. De Roux A, Ewig S, Garcia E, Marcos MA, Mensa J, Lode H, et al. Mixed community-acquired pneumonia in hospitalised patients. Eur Respir J. 2006;27:795–800.
7. Van Der Eerden MM, Vlaspolder F, de Graaff CS, Groot T, Jansen HM, Boersma WG. Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis. 2005;24:241–9.
8. Paganin F, Lilienthal F, Bourdin A, Lugagne N, Tixier F, Génin R, et al. Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. Eur Respir J. 2004;24:779–85.
9. Ruiz M, Ewig S, Marcos MA, Martínez JA, Arancibia F, Mensa J, et al. Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med. 1999;160:397–405.
10. Zalacain R, Torres A, Celis R, Blanquer J, Aspa J, Esteban L, et al. Community-acquired pneumonia in the elderly: Spanish multicenter study. Eur Respir J. 2003;21:294–302.
11. Rello J, Bodi M, Mariscal D, Navarro M, Díaz E, Gallego M, et al. Microbiological testing and outcome of patients with severe community-acquired pneumonia. Chest. 2003;123:174–80.
12. Adam D. Global antibiotic resistance in Streptococcus pneumoniae. J Antimicrob Chemother. 2002;50:1–5.
13. Jacobs MR, Felsingham D, Appelbaum PC, Grunberg RN, Alexander Project Group. The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. J Antimicrob Chemother. 2003;52:229–46.
14. Baquero F. Pneumococcal resistance to beta-lactam antibiotics: a global geographic overview. Microb Drug Resist. 1995;1:115–20.
15. Low DE, de Azavedo J, Weiss K, Mazzulli T, Kuhn M, Church D, et al. Antimicrobial resistance among clinical isolates of Streptococcus pneumoniae in Canada during 2000. Antimicrob Agents Chemother. 2002;46:1295–301.
16. Song JH, Jung SI, Ki HK, Shin MH, Ko KS, Son JS, et al. Clinical outcomes of pneumococcal pneumonia caused by antibiotic-resistant strains in Asian countries: a study by the Asian network for surveillance of resistant pathogens. Clin Infect Dis. 2004;38:1570–8.

17. Castanheira M, Gales AC, Mendes RE, Jones RN, Sader HS. Antimicrobial susceptibility of Streptococcus pneumoniae in Latin America: result from five years of the SENTRY Antimicrobial Surveillance Program. Clin Microbiol Infect. 2004;10:645–51.

18. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North America multicenter study. JAMA. 1993;270:2957–63.

19. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med. 1998;26:1793–800.

20. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community acquired pneumonia. N Engl J Med. 1997;336:243–50.

21. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377–82.

22. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: 18th informational supplement. CLSI document M100-S18. Wayne: Clinical and Laboratory Standards Institute; 2008.

23. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS: definition, mechanism, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149:818–24.

24. Fagon JY, Chastre J, Novara A, Medioni P, Gibert C. Characterization of intensive care unit patients using a model based on the presence or absence of organ dysfunctions and/or infection: the ODIN model. Intensive Care Med. 1993;19:137–44.

25. British Thoracic Society Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults. Thorax 2001;56(suppl 4):I1–44.

26. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44:S27–72.

27. Lieberman D, Schlaeffer F, Boldur I, Lieberman D, Horowitz S, Friedman MG, et al. Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one-year prospective study of 346 consecutive patients. Thorax. 1996;51:179–84.

28. Gutierrez F, Masia M, Rodriguez JC, Mirete C, Soldán B, Padilla S, et al. Community-acquired pneumonia of mixed etiology: prevalence, clinical characteristics, and outcome. Eur J Clin Microbiol Infect Dis. 2005;24:377–83.

29. Mera RM, Miller LA, Amrine-Madsen H, Saum DF. Impact of new Clinical Laboratory Standards Institute Streptococcus pneumoniae penicillin susceptibility testing breakpoints on reported resistance changes over time. Microb Drug Resist. 2011;17:47–52.

30. Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortwist A, et al. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J. 2005;26:1138–80.

31. SPLIFF. 15th consensus conference about management of lower respiratory tract infections in immunocompetent adults. Med Mal Infect 2006;36:235–244.

32. Martínez JA, Horcajada JP, Almeda M, Marco F, Soriano A, García E, et al. Addition of a macrolide to a β-lactam based empirical regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis. 2003;36:389–95.

33. Baddour LM, Yu VL, Klugman KP, Feldman C, Ortwist A, Rello J, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med. 2004;170:440–4.

34. Mushrif DM, Alexandraki I, Graviss EA, Yanheig N, Eid A, Inderias LA, et al. Bacteremic and nonbacteremic pneumococcal pneumonia: a prospective study. Medicine (Baltim). 2000;79:210–21.

35. Marrie TJ, Low DE, de Carolis E, Canadian Community-Acquired Pneumonia Investigators. A comparison of bacteremic pneumococcal pneumonia with nonbacteremic community-acquired pneumonia of any etiology: results from a Canadian multicenter study. Can Respir J. 2003;10:368–74.

36. Bordon J, Peyrani P, Brock GN, Blasi F, Rello J, File T, et al. The presence of pneumococcal bacteremia does not influence clinical outcomes in patients with community acquired pneumonia: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort study. Chest. 2008;133:618–24.