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Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor

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Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. F. Paganin, F. Lilienthal, A. Bourdin, N. Lugagne, F. Tixier, R. Génin, J-L. Yvin. ©ERS Journals Ltd 2004.

ABSTRACT: Community-acquired pneumonia (CAP) remains a major cause of mortality. The aetiology of CAP has rarely been identified as a mortality risk factor. A prospective study was conducted to assess the prognostic factors of CAP patients admitted to the intensive care unit (Centre Hospitalier Departmental Félix Guyon, St Denis de la Réunion, France), with a special emphasis on microbial aetiology.

All variables assessing severity were collected, with a special emphasis on microbial investigations. Among 112 immunocompetent patients (mean±SD age 54.7±15.1 yrs), 84% were male. Severity of CAP was demonstrated by mortality rate (43%), shock (48%), simplified acute physiology score (SAPS; 46.4±21.6) and mechanical ventilation support (82%). Mean risk factor score was 2.2±1.2. Microbiological identification was obtained in 78.6% of cases, with positive blood culture in 33%. Most frequently, microbial agents were *Streptococcus pneumoniae* and *Klebsiella pneumoniae* (42% and 22%, respectively).

The univariate analysis recorded the usual mortality variables: age, alcohol consumption, SAPS, shock, mechanical ventilation, positive end expiratory pressure level, positive blood culture, multilobar infiltrates on chest radiograph, neutropenia, and acidosis, and found *K. pneumoniae* (*versus S. pneumoniae*, and all CAP) as a mortality factor. The multivariate analysis demonstrated that septic shock (relative risk (RR) 141), *K. pneumoniae* CAP (RR 27), SAPS (RR 10.7) and positive blood culture (RR 2.7) were independent factors related to death.

In conclusion, the present study found that the microbial aetiology, *Klebsiella pneumoniae*, was an independent risk factor for mortality in severe community-acquired pneumonia.

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Despite advances in the management of severe infectious diseases, community-acquired pneumonia (CAP) remains the major cause of mortality in developed countries [1, 2]. Approximately 10% of hospitalised patients with CAP require admission to an intensive care unit (ICU), where 20–50% of them will ultimately die [3, 4].

Many studies have investigated CAP prognosis factors [1–12], and guidelines have been proposed by several medical societies to define the optimal management of patients with CAP [13–17].

The aetiology of CAP is now well known and of worldwide use. However, specific studies suggest a higher frequency of certain pathogens in some geographical areas: *Legionella* are more common in countries bordering the Mediterranean, *Coxiella burnetii* in north-west Spain and Canada, Gram-negative bacilli (GNB) in Italy, *Burkholderia pseudomallei* in South East Asia and Northern Australia, *Klebsiella pneumoniae* in South Africa, and *Mycobacterium tuberculosis* in nonindustrialised countries [14]. The knowledge of these particularities is of great importance for physicians dealing in these areas, but also for the medical community, who can be faced everywhere with the diagnosis and prognostic challenges of CAP patients with uncommon pathogens.

In many studies, the rate of microbial identification, even in the ICU, remains extremely low, ranging 10–30% [2–5, 18–20].

In the majority of published studies, the aetiology of CAP has not been identified as a risk factor (RF) for mortality [2–8, 10, 11, 21, 22]. Although specific CAP aetiologies, such as *K. pneumoniae*, are frequently suspected of being associated with a higher mortality rate, these aetiologies have not been shown to constitute a prognostic factor for mortality [23–26].

A large prospective study was conducted in order to assess the prognostic factors for mortality of severe CAP patients admitted to the ICU, with a special emphasis on microbial aetiology.

Methods

Patients

The 475-bed (16 ICU beds) Centre Hospitalier Departmental Félix Guyon (St Denis de la Réunion, France), where the present study was conducted, is a tertiary institution of a French overseas territory located in the Indian Ocean 2,500 km east from the South African coast. The island population is estimated to be 750,000. The medical system and accessibility to medical care is no different to that of France.

The present study prospectively studied 146 consecutive

patients admitted to the ICU for CAP from September 1995 to December 2000.

All patients had symptoms suggestive of lower respiratory tract infection as generally accepted. Briefly, diagnosis for CAP was a new chest radiological infiltrate and symptoms consistent with pulmonary infection (cough, sputum production, fever >38.3°C or hypothermia, pulmonary consolidation at examination, abnormal leukocytes counts, pleural chest pain). All patients with severe immunosuppression were excluded (known HIV diagnosis, solid organ transplant, current chemotherapy).

Generally, patients were admitted to the emergency room (ER) of the Centre Hospitalier Departmental Félix Guyon. Patients were, secondary, directly admitted to the ICU according to the attending physician's clinical judgement and criteria defining severe CAP [12, 13, 27]. The current authors considered only initial CAP, and excluded progressive pneumonia and early nosocomial pneumonia. All the patients were secondary classified according to the criteria of FINE *et al.* [28]. When possible, a follow-up visit was performed with clinical parameters analysis, chest radiograph and serological analysis.

Data collection

In all cases, the following variables were carefully recorded: age, sex, simplified acute physiology score II (SAPS II), prior illness and concomitant conditions, initial signs and symptoms of CAP, alcohol habits, chest radiograph features, arterial blood gases measurements, mechanical ventilation (MV) requirement, and level of positive end expiratory pressure (PEEP). Regarding biological parameters, only initial values were used.

Bacteriological identification procedure

At least one blood culture was collected for all patients. Serological analysis included the following determination: immunoglobulin (Ig)G *versus Mycoplasma pneumoniae, Chlamydia psittaci* and IgG, and IgM *versus C. pneumoniae* by indirect immunofluorescence. *Legionella pneumophila* serotypes 1–6 were diagnosed using the indirect immunofluorescence technique for antibodies detection. ELISA was used to detect IgM in *M. pneumoniae*. When possible, a second serum sample was obtained on the follow-up visit at 21 days. Urine detection for Legionella antigens was not routinely performed in the ICU.

Pleural fluid culture was performed for patients with significant pleural effusion on chest radiograph. A fibreoptic bronchoscopy with a bronchoalveolar lavage (BAL) was performed, when it was possible, in most patients as a routine procedure in the ICU. No sputum or endotracheal aspiration analysis was performed to obtain bacterial identification.

For BAL, a direct examination (DE) was immediately performed with a cellular differential count (polynuclear, macrophages, lymphocytes, bronchial cells). The absence of bronchial cells or <5% was considered as satisfactory for the BAL. For typical pathogens, the authors choose arbitrarily the $\geqslant 1\times10^4$ cfu·mL^{-1} cut-off (recommended for the diagnosis of nosocomial pneumonia) to enhance specificity.

All samples (BAL and pleural fluid) were cultured in adequate media that allowed optimal results (blood agar, chocolate agar, Sabouraud agar, and medium for anaerobes). A microorganism was considered the aetiological agent when blood or pleural fluid cultures were positive and/or if it could be isolated with a cut-off point $\geqslant 1\times10^4$ cfu·mL^{-1} for the BAL. Serologies were considered positive under the following conditions: 1) four-fold increase in IgG titres with final titres for *C. pneumoniae* (IgG $\geqslant$512), *C. psittaci* (IgG $\geqslant$64), *L. pneumophila* (IgG $\geqslant$128); 2) increase of IgM titres for *C. pneumoniae* (IgM $\geqslant$32), any positive titre for *M. pneumoniae*; and 3) a single titre $\geqslant$128 for *L. pneumophila*.

Definitions

Shock was defined if initial systolic blood pressure was $\leqslant$80 mmHg after fluid administration or if patients needed vasopressor drug support for >4 h. Alcohol abuse was considered present when consumption was $\geqslant$120 g·day^{-1}.

For data obtained in the laboratory, the following criteria were used: hyponatraemia (sodium level <136 mmol·L^{-1}), hyperkaliaemia (potassium level >5 mmol·L^{-1}), acidosis (arterial pH $\leqslant$7.35), neutropenia (polynuclear cells $\leqslant$1000·mL^{-1}), renal failure (creatinine >200 μmol·L^{-1} and/or blood urea nitrogen >30 mg·dL^{-1}), hypoxaemia at room air (arterial oxygen tension <60 mmHg), liver disease (aspartate aminotransferase, alanine aminotransferase >4-fold normal value).

Generally, admitted RFs (diabetes mellitus, liver disease, chronic renal failure, cardiac disease, chronic obstructive pulmonary disease (COPD), neurological disease, age $\geqslant$65 yrs) were recorded in order to obtain a RF score. Each RF was considered as equal.

Statistical analysis

Prognostic factors were analysed using the Chi-squared test with Fisher's exact test correction, when necessary. For the comparison of means, the Mann-Whitney U-test was used when the variables were not normally distributed; otherwise, the unpaired t-test was used. A p-value <0.05 was considered statistically significant. The relative risk for outcome was defined according to the following variables: age (>65 or <65 yrs), alcoholism (>120 or <120 g·day^{-1}), presence of RF (yes/no), number of RF ($\geqslant$2/<2), SAPS (<40 or >40), shock (yes/no), MV requirement (yes/no), initial MV (yes/no), level of PEEP (>10 or <10 mmHg), positive blood culture (yes/no), bilateral involvement on chest radiograph (yes/no), number of lobes involved (<2 or >2), microbiological identification (yes/no), type of bacteriological identification (all *versus K. pneumoniae*, all *versus Streptococcus. pneumoniae*, *S. pneumoniae versus K. pneumoniae*), and all of the biological variables, as previously defined.

All of the variables attaining α-values <0.05 in the univariate analysis were included in the multiple logistic regression analysis model with a stepwise forward selection. All of the first level interactions were tested, excluding all of the variables presenting interaction in the analysis. All reported p-values are two-tailed and the level of significance was set at 5%.

Results

Patient characteristics

Among the 146 patients, 34 were excluded as they did not meet a definite diagnosis of CAP (25 pulmonary oedema, one pulmonary embolism, and four patients with a normal chest radiograph; five patients had a secondary diagnosis as they were HIV infected with *Pneumocystis carinii* pneumonia and were subsequently excluded from the analysis). A total of 112 patients (84% male, mean age 54.7±15.1 yrs) were included in

the study. The main baseline patient characteristics and underlying conditions are listed in table 1.

Patients were transferred from the ER to the ICU after only 4.0±2.4 h (time necessary to confirm the CAP diagnosis and evaluate severity). A total of 42 patients (62%) did not receive antibiotics during their ER stay because of rapid orientation to the ICU as a definite diagnosis of CAP was obtained. The present authors did not observe a statistical difference in the delay for antibiotic administration in the patients that were initially treated in the ER compared with those treated in the ICU (3.6±3.6 h *versus* 3.2±3.1 h, respectively)).

According to FINE *et al*. [28], 55 patients in groups 1–3 and 57 in groups 4–5 were found with a statistical difference regarding mortality between these two groups ($p<0.0045$, relative risk (RR; 95% confidence interval) 1.92 (1.2–3.09)).

Alcohol abuse was recorded in 62% of cases and was found to be the most frequent and only RF associated with mortality.

Table 1. – Patient characteristics and underlying conditions

Patients	112 (100)
Sex	
Male	94 (84.0)
Female	18 (16.0)
SAPS	46.4±21.6
Risk factors	2.2±1.2
Alcohol abuse	70 (62.5)
Smoking habit	49 (44.0)
COPD	32 (28.5)
Diabetes mellitus	22 (19.6)
Cardiac disease	16 (14.2)
Chronic renal failure	10 (8.9)
Neurologic disease	7 (6.2)
Immunosuppression	0
Neoplasia	0
Temperature at admission °C	38.0±1.4
Polymorphonuclear neutrophils cell count	9936±7781 (100–36400)
Serum pH	7.35±0.15 (6.66–7.55)
P_{a,O_2} mmHg	
At room air	53±10 (32–71)
With nasal O_2 4±2 L	73±16 (42–120)
Under MV, F_{I,O_2} 65±20%	96±46 (42–290)
Overall P_{a,CO_2} mmHg	38±13 (14–71)
Serum sodium mmol·L^{-1}	133±5.4 (112–155)
Serum potassium mmol·L^{-1}	3.2±1.2 (2.4–6.1)
Serum urea mmol·L^{-1}	7.4±2.8 (2.1–35)
Serum creatinine µmol·L^{-1}	108±42 (52–650)
Patients with initial MV required	46 (41.1)
Patients with MV required	92 (82.1)
Days of MV	7.1±7.1
Shock at admission	54 (48.2)
Chest radiograph at admission	
Unilateral involvement	83 (74.1)
Bilateral involvement	29 (25.9)
Interstitial	7 (6.2)
Alveolar	33 (29.5)
Consolidated	72 (64.3)
Positive blood culture	37 (33.0)
Fine's Score (n, % deceased)	
Group 1	7 (3, 47)
Group 2	14 (2, 14)
Group 3	34 (11, 32)
Group 4	47 (26, 55)
Group 5	10 (6, 60)
Overall mortality	48 (43)

Data are presented as n (%), mean±SD or mean±SD (range), unless otherwise stated. SAPS: simplified acute physiology score; COPD: chronic obstructive pulmonary disease; P_{a,O_2}: arterial oxygen tension; MV: mechanical ventilation; F_{I,O_2}: inspiratory oxygen fraction; P_{a,CO_2}: carbon dioxide arterial tension.

Radiological and biological findings

A total of 74% of patients had a chest radiograph with unilateral involvement. The mean number of lobes involved was 1.8±0.9. Consolidated (64%) and alveolar (28%) features were most frequently observed, and were consistent with bacteriological results. No radiological features suggesting a specific aetiology of CAP were observed. Significant pleural effusion was observed in only two cases (1.7%). Initial biological values are listed in table 1.

Bacteriological diagnosis

Fibreoptic bronchoscopy with BAL was performed in 85 (76%) patients and a DE result was obtained in 67 (60%) cases, *i.e.* presence of Gram-positive cocci, GNB or both.

Microbiological identification was obtained in 88 cases (78.6%). A positive BAL culture was obtained in 73 (65%) cases. When BAL was negative, a positive blood culture was recorded in 13 (11.6%) cases and significant positive serology in two cases. BAL and blood cultures were both positive in 24 (21%) of the cases. No pleural effusion analysis was positive.

The most frequently isolated aetiological agents were *S. pneumoniae* and *K. pneumoniae* (42% and 22% of patients, respectively). Other microbial agents (*Escherichia coli*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *L. pneumophila*, *H. influenzae*, *Morganella morgani*) were found in <3% of cases, and are listed in table 2. Only three cases (2.6%) were found of *S. pneumoniae* CAP associated with *Haemophilus influenzae*. Due to predominant pathogen, these cases of CAP were considered as *S. pneumoniae* CAP. One case of aspergillosis was recorded by a positive BAL and corresponded to subacute necrotising pneumonia.

Overall, a positive blood culture was obtained in 37 (33%) of patients, and in 48% and 36% of patients with *S. pneumoniae* CAP and *K. pneumoniae* CAP, respectively. MV support was required for 88% of *K. pneumoniae* patients and 76% of *S. pneumoniae* patients (nonsignificant).

The high rate of klebsiella pathogens is strongly related to alcoholism. A significant specific distribution of CAP related to *K. pneumoniae* was found in the group of alcoholic patients compared to nonalcoholic patients (88% *versus* 12%, RR (95% confidence interval) 4.5 (1.45–14.35), $p<0.002$). However, this finding is not very discriminatory, as a high percentage of alcoholic patients with a *S. pneumoniae* CAP

Table 2. – Microbial identification

Aetiology		Positive blood culture	Mortality rate
Identified	88 (78.6)	37 (33)	41 (36.7)
Streptococcus pneumoniae	48 (42.9)	23 (48)	17 (35.4)
Positive DE on BAL	39 (81)		
Klebsiella pneumoniae	25 (22.4)	9 (36)	18 (72)
Positive DE on BAL	21 (84)		
Escherichia coli	3 (2.6)	1 (33.3)	2 (66.7)
Moraxella catarrhalis	3 (1.8)	0	0
Staphylococcus aureus	2 (1.8)	1 (50)	1 (50)
Pseudomonas aeruginosa	2 (1.8)	2 (100)	2 (100)
Legionella pneumophilia	2 (1.8)	NA	0
Haemophilus influenzae	1 (0.9)	0	0
Morganella morganii	1 (0.9)	1 (100)	0
Aspergillus niger	1 (0.9)	NA	1 (100)
None identified	24 (21.4)	0	7 (29)

Data are presented as n (%). DE: direct examination; BAL: bronchoalveolar lavage fluid; NA: not available.

(64%) was also found, but with no significant statistical correlation.

Antibiotic regimens for treatment of pneumonia

All patients were treated with adequate *i.v.* antibiotics depending on the physician's judgment. All patients received at least a third-generation cephalosporin in 70 cases (62.5%), or amoxicillin/clavulanic acid in 42 cases (37.5%). Monotherapy was administrated in 43 cases (38%) as follows: third-generation cephalosporin in 33 (77%) and amoxicillin/clavulanic acid in 10 (23%). Aminoglycosides were added in 33 cases (29.5%), macrolide or quinolone (ofloxacin) in 29 cases (26%) and multiple regimens (β-lactam+aminoglycoside+quinolone) in seven cases (6%). Addition of antibiotics was guided by microbiological results (*i.e.* DE), and occurred within the first 24 h after admission.

A total of 42 (37.5%) patients received antibiotics before admission in the ICU (initial antibiotics). Among the 15 patients that were treated by their general practitioner before ER admission, antibiotic regimen was continued in seven cases (*i.v.* third-generation cephalosporin) and modified in eight cases (*i.v.* antibiotic administration: amoxicillin/clavulanic acid in six cases, and *i.v.* third-generation cephalosporin in two cases, in substitution of macrolides in seven cases and cyclines in one case). The 70 (62.5%) other patients received antibiotics at admission in the ICU. Among patients treated with antibiotics in the ER, it was possible to obtain a microbial identification in 20 cases (47%), as it was obtained in 68 (97%) of the 70 remaining patients that received antibiotics in ICU. The results of bacteriological procedures (positive DE or positive BAL), and the administration of antibiotics before admission in ICU did not influence mortality (table 3). The authors did not observe differences in outcome for patients that received monotherapy *versus* multiple antibiotic regimens (RR 0.76, p=0.33). However, the decision of administrating antibiotic treatment was different for patients that received antibiotics in the ER (monotherapy in 8%) compared with the group that received antibiotics in the ICU (monotherapy in 31%; p<0.008).

The resistance of *S. pneumoniae* to penicillin was observed in only two cases (4%), with one case of intermediate resistance and one case of high-level resistance. All of the *K. pneumoniae* had an *in vitro* sensitivity to third-generation cephalosporin, amoxicillin/clavulanic acid, aminoglycosides and quinolones. None of the strains expressed extended-spectrum β-lactamases.

Prognostic factors

The severity of the CAP diagnosed in this study was demonstrated by a high mortality rate (43%), a high percentage of patients with initial shock (48%), and initial MV support at admission (41%). All the patients, except two, who were discharged from the ICU survived. The univariate analysis recorded variables related to death and are listed in table 4.

Table 5 shows the results of the multivariate analysis of prognosis factors. The logistic regression demonstrated that septic shock (RR 141), CAP with a Klebsiella aetiology (RR 27), SAPS II score >40 (RR 10.7) and positive blood culture (RR 2.7) were the only independent factors related to death.

Table 6 presents clinical, radiological and biological data on Klebsiella CAP compared with CAP of other aetiology.

Discussion

A large prospective study of nonimmunocompromised patients, presenting with severe CAP, is herein reported. A special emphasis was given to the microbiological identification, in order to assess the microbial aetiology as a potential prognostic factor for mortality.

Two important findings were drawn from this study. *K. pneumoniae* was identified as the causative pathogen in 22% of cases, second to *S. pneumoniae*. Moreover, *K. pneumoniae* was identified as an independent mortality factor for CAP.

The study population was characterised by a large percentage of males. Unlike most severe CAP studies, classical RFs, such as COPD, renal failure, heart diseases and diabetes mellitus, were present in only a minority of patients [2, 4, 6, 9, 29]. Alcohol abuse was the only RF correlated with death, but was also found to be more frequent in *K. pneumoniae* CAP compared with other CAPs (table 6). In the literature, alcoholism is generally associated with severe CAP and, particularly, with *K. pneumoniae* CAP [30, 31]. However, the current authors found about half of patients with alcohol abuse in the non-*K. pneumoniae* group. Alcoholism was correlated with death (table 3), but did not appear to be an independant mortality factor in the multivariate analysis, as alcoholism was widely distributed in the studied patients. Alcohol abuse cannot be a factor, suggesting a specific microbial aetiology for CAP. The relatively young age and the low representation of RFs were in contrast with the high severity of the population that was reflected by a high rate of required MV and septic shock, a high-severity SAPS score and, finally, a high crude mortality rate of 43%.

Radiological features were consistent with the microbiological epidemiology. A large proportion of unilateral, alveolar and consolidated infiltrates reflected the high incidence of *S. pneumoniae* and *K. pneumoniae*. Bilateral involvement was found in 26% of cases, with half of them caused by *S. pneumoniae* and *K. pneumoniae*. Bilateral infiltrates appeared to result from the rapid extension of a typical pneumonia. Of the 24 CAP without a microbial diagnosis, 17 had a unilateral infiltrate, suggesting a pathogen related to a

Table 3. – Influence of antibiotic therapy and identification technique

	Survivors#	Nonsurvivors¶	Relative risk	95% CI	p-value
Initial AB					
Administered by GP	9 (14)	6 (12.5)	1.0	0.67–1.65	1.00 NS
Administered in ER	23 (20.5)	19 (17)	1.06	0.65–1.71	0.84 NS
AB regimen (use of monotherapy)	27 (24)	16 (14)	0.76	0.46–1.24	0.33 NS
Monotherapy (for *S. pneumoniae*)	17 (26.5)	8 (16)	0.83	0.45–1.5	0.55 NS
Examination of BAL (positive DE)	34 (30)	33 (29.5)	1.28	0.94–1.74	0.12 NS
Positive culture of BAL	37 (33)	36 (32)	1.20	0.92–1.57	0.23 NS

Data are presented as n (%), unless otherwise stated. CI: confidence interval; AB: antibiotics; GP: general practitioner; ER: emergency room; *S. pneumoniae*: *Streptococcus pneumoniae*; BAL: bronchoalveolar lavage fluid; DE: direct examination. NS: nonsignificant. #: n=64; ¶: n=48.

Table 4. – Univariate analysis of prognostic factors

	Survivors#	Nonsurvivors¶	Relative risk	95% CI	p-value
Age >65 yrs	0	8 (7)	2.6	2.03–3.31	0.0008
Alcoholism	29 (26)	40 (36)	3.11	1.61–6.00	0.0001
Presence of RF	27 (51)	46 (41)	2	0.58–6.95	0.29 NS
Number of RF >2	44 (39)	34 (30)	0.93	0.5–1.6	0.83 NS
Fine′s score 1–3/4–5	39/25	16/32	1.92	1.2–3.09	0.0045
SAPS II score >40	16 (14)	40 (36)	2.93	1.91–4.51	0.0001
Septic shock	9 (8)	43 (39)	12.08	46–31.4	0.0001
MV	42 (38)	49 (44)	11.3	1.65–77.3	0.0001
Initial MV	23 (21)	23 (21)	1.26	0.83–1.92	0.33 NS
PEEP >10 mmHg	7 (8)	25 (28)	2.18	1.47–3.25	0.0002
Positive blood culture	15 (13)	23 (21)	1.72	1.15–2.57	0.015
Initial chest radiograph					
Bilateral infiltrate	18 (16)	11 (10)	0.80	0.48–1.35	0.5 NS
Multilobar infiltrate+	8 (7)	15 (13)	1.7	1.14–2.54	0.03
Neutropenia <1000 cells·mm^3	5 (4)	20 (18)	2.48	1.72–3.57	0.0001
Acidosis pH <7.35 mmol·L^{-1}	13 (12)	36 (32)	2.20	1.49–3.24	0.0001
Sodium level <136 mmol·L^{-1}	28 (25)	30 (27)	0.9	0.67–1.36	0.8 NS
Potassium level >5 mmol·L^{-1}	6 (5)	12 (11)	1.56	1.04–2.34	0.07 NS
Renal failure	8 (7)	2 (1.8)	0.32	0.07–1.44	0.18 NS
Hypoxaemia	17 (15)	21 (19)	1.51	1.0–2.29	0.07 NS
No microbial identification	16 (14)	8 (7)	0.71	0.38–1.31	0.3 NS
Aetiology of CAP					
S. pneumoniae versus all	30 (27)	17 (15)	0.75	0.48–1.19	0.2 NS
Klebsiella *versus* all	7 (6)	18 (16)	2.02	1.39–2.93	0.0025
Klebsiella *versus S. pneumoniae*	7 (10)	18 (25)	1.99	1.26–3.12	0.006

Data are presented as n (%), unless otherwise stated. Percentages in parentheses indicate values calculated from the total of patients, except the positive end expiratory pressure (PEEP, n=88) and aetiology Klebsiella *versus Streptococcus pneumoniae* (*S. pneumoniae*, n=72). CI: confidence interval; RF: risk factor; SAPS: simplified acute physiology score; MV: mechanical ventilation; CAP: community-acquired pneumonia. NS: nonsignificant. #: n=64; ¶: n=48; +: >2 lobes.

Table 5. – Multivariate analysis of prognostic factors

	Survivors#	Nonsurvivors¶	Relative risk	95% CI	p-value
Septic shock	9 (8)	43 (39)	141	28–704	0.0001
Klebsiella *versus* all	7 (6)	18 (16)	27	25–149	0.0001
SAPS II score >40	16 (14)	40 (36)	10.7	3.1–3.7	0.0001
Positive blood culture	15 (13)	23 (21)	2.7	0.8–8.9	0.0002

Data are presented as n (%), unless otherwise stated. CI: confidence interval; SAPS: simplified acute physiology score. #: n=64; ¶: n=48.

Table 6. – Characteristics of Klebsiella community-acquired pneumonia (CAP) patients compared to CAP of other aetiology

	Klebsiella CAP#	Other CAP¶	p-value
Male:female	24:1	75:12	NS
Age yrs	56±13	54±15	NS
Alcohol abuse	21 (84)	49 (56)	<0.001
Temperature at admission °C	37.5±1.3	38.1±1.4	NS
Polymorphonuclear cells	8412±7294	10357±7898	NS
Chest radiograph			
Number of lobes involved	1.7±0.8	1.7±0.9	
Unilateral involvement	19 (76)	64 (82)	
Bilateral involvement	6 (24)	23 (26)	NS
Interstitial	0	7 (8)	
Alveolar	5 (20)	28 (32)	
Consolidated	14 (56)	58 (66)	
SAPS II score	55.3±26.9	43.9±19	NS
Shock	15 (60)	39 (45)	NS
Mortality	18 (72)	30 (34)	<0.002

Data are presented as n, n (%) or mean±SD. SAPS: simplified acute physiology score. NS: nonsignificant. #: n=25; ¶: n=87.

typical CAP. Some radiological features were attributed to *K. pneumoniae*. Radiographical description for the *Friedlander pneumoniae* focused on the bulging fissure sign, highly suggesting *K. pneumoniae* species when present. Unfortunately, this fissure sign was not found, except in one case. The present authors, at least, did not find any radiographical features that could predict a specific aetiology (table 6).

A microbial diagnosis was established in 78.6% of patients due to the frequent utilisation of fibreoptic techniques routinely used by chest physicians and trained anaesthesiologists in the ICU. At least, microbial identification was more frequent in patients that did not receive antibiotics before admission into the ICU. BAL was performed in 85 (76%) patients, along with blood cultures, and serologies were systematically performed in all patients. No complications were experienced in any patients that underwent BAL. *S. pneumoniae* was isolated in 43% of patients. This result is consistent with those reported in severe [2–11, 18, 19–23] and nonsevere CAP [12, 32, 33]. However, the high frequency of isolated *K. pneumoniae* (22%) is in contrast with the low percentage reported in most published CAP series, with the exception of studies conducted by FELDMAN *et al.* [30, 31] in South Africa. The current authors have no hypothesis to

explain these similarities, except the location in the south hemisphere region, 2,500 km east of South Africa. The type of alcohol abuse is specific on Reunion Island (high-proof agricol rum), but no data was found to support a relation with high *K. pneumoniae* incidence. Alcoholism and poor underlying conditions are known predisposing factors of CAP caused by either *K. pneumoniae* or *S. pneumoniae*, and are frequently reported in similar proportion in published studies [6, 34].

Surprisingly, only two patients were diagnosed with an atypical pathogen. Both cases were caused by Legionella and were imported from Europe. The diagnosis of atypical pathogens may have been underestimated, as a second serology could not be obtained in most patients who died within the first 2 weeks after admission. However, the knowledge of the local epidemiology does not support the fact that Legionella is a common pathogen in Réunion, France.

A univariate analysis identified several prognostic RFs for mortality: age, alcoholism, SAPS II (>40), septic shock, mechanical ventilation, PEEP (>1.33 kPa (>10 mmHg)), multilobar infiltrate, positive blood cultures, neutropenia and acidosis. A multivariate analysis of these factors only found septic shock, SAPS II and positive blood cultures to be independently associated with mortality. All these findings were consistent with those reported in the literature [2–12].

The major objective of this study was to assess whether the microbiological aetiology could be a factor associated with fatal outcome. *K. pneumoniae* was shown to be a prognostic factor for mortality in a univariate analysis, but also in the multivariate analysis (RR 27). In the literature, GNB were identified as a mortality factor for CAP [9]. However, among 14 cases of GNB, they found six cases with *K. pneumoniae* and seven cases with *E. coli*, with a mortality of 33% and 43%, respectively. A high percentage (72%) of microbiological aetiology could explain these results. In the present study, the rate and the mortality of *K. pneumoniae* was extremely high (72%), and this subgroup was not matched with other GNB. It is important to notice that *S. pneumoniae* was not found to be associated with fatal outcome in the univariate analysis, whether with a positive blood culture or not. In the current study, the results of MOINE *et al.* [9] could not be confirmed that found *S. pneumoniae* associated with death. It is noteworthy to point out that the crude mortality of *S. pneumoniae* was equal in the study by MOINE *et al*. [9] and the present study (35%). Some authors have focused on the potential severity of some bacteriological species (*Pseudomonas aeruginosa*) in nosocomial pneumonia [35, 36], or in CAP [6, 37] when structural lung diseases are present (bronchiectasis) [38]. In CAP, the pathogens generally implicated in severe cases have failed to demonstrate a role in poor outcome.

The potential influence of antibiotic regimen is important for the outcome [39]. The choice of antibiotic regimen administrated at admission in the ICU was effective regarding the bacterial results recorded throughout the study. A total of 15 (13%) patients received antibiotics by their general physician before admission to the hospital. Most patients (62%) did not receive any antibiotic treatment during their brief ER stay and rapidly underwent microbiological procedures upon their ICU admission. No differences were seen in the outcome for patients that received antibiotics in the ER and those that received antibiotics after admission in the ICU. For the group of patients that were not given antibiotic, the mean time from admission to diagnosis in the ICU was 3.2±3.1 h, compared with the pretreated group in the ER (3.6±3.6 h). This result supports the fact that a direct admission in the ICU without antibiotic therapy did not influence patient outcome, but improved the possibility to obtain a microbial identification. A rapid result with a positive DE of the BAL was helpful for antibiotic therapy decision, as recently pointed out [37]. GNB observed on the BAL DE highly suggested a *K. pneumoniae* CAP, as Gram-positive cocci suggested *S. pneumoniae* CAP. Guided by a positive DE of the BAL, monotherapy (third-generation cephalosporin or amoxicillin/clavulanic acid) was administrated in 25 (52%) of patients with *S. pneumoniae*. This decision did not influence outcome, as shown in table 3. The knowledge of high antibiotic sensitivity of the strains of *S. pneumoniae* recorded in the area, and the chest radiograph presentation (inconsistent with atypical pathogens), supported the choice of monotherapy in some patients of the *S. pneumoniae* group. The use of two antibiotics (β-lactam + macrolide or quinolone) is generally indicated to extend the antibiotic spectrum against atypical pathogens [13–15]. Moreover, the addition of an aminoglycoside can be recommended in case of severe CAP [13–15]. The addition of an aminoglycoside in some CAP patients of the *S. pneumoniae* group and in other patients with non-*S. pneumoniae* aetiologies did not modify survival. In all cases of GNB, observed at DE of the BAL, an aminoglycoside was immediately administrated in association with a β-lactam antibiotic. According to this antibiotic strategy and the overall bacterial sensitivity, the poor outcome in CAP patients in this study cannot be explained by the antibiotic treatment [40].

In summary, this large prospective study showed that *Klebsiella pneumoniae* was not only a frequent aetiology of severe community-acquired pneumonia patients, but also an independent risk factor for mortality in this population. The high rate of patients with a microbial diagnosis (~80%) significantly contributed towards demonstrating these findings, but *a contrario* represented a limit of the study, as bronchoscopic procedures are not routinely performed everywhere. As *Klebsiella pneumoniae* is certainly more frequent in Réunion than in other countries, this aetiology can be found worldwide in patients with some underlying conditions, such as alcohol abuse. However, the authors failed to find some clinical and radiological particularities, suggesting this aetiology in patients at admission. Further studies on the epidemiology and prognostic risk factors of severe community-acquired pneumonia are warranted to assess if early recognition of microbial aetiology can modify the outcome of these severe community-acquired pneumonias.

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