37. SEVERE COMMUNITY-ACQUIRED PNEUMONIA

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Introduction

Pneumonia remains a common illness and a major cause of morbidity and mortality in the United States. In 1995, 82,900 deaths were caused by pneumonia [1]. The incidence of community-acquired pneumonia (CAP) is about 2 to 4/1000 persons/year, about 20% of whom require hospitalization [2].

The steady increase in the number of senior citizens and immunocompromised patients (those receiving corticosteroids, organ transplant recipients, HIV infection) and the better survival rates of patients affected by chronic illness are reasons that justify research in this field. Current investigations focus on improving diagnosis, defining risk factors that influence outcome, and assessing new therapies.

In the last decade, a number of medical societies have sought to broaden our understanding of pneumonia by producing and publishing sets of guidelines. The first set of guidelines that avoided the traditional classification into "typical and atypical" pneumonia was published in 1993 by the American Thoracic Society (ATS) [3]. These guidelines classify patients into four categories on the basis of the most probable etiology: a) community-acquired pneumonia in patients younger than 60, without chronic associated illness; b) community-acquired pneumonia in patients older than 60 or patients with chronic associated conditions; c) pneumonia that requires hospitalization and d) pneumonia that requires ICU admission. In Europe similar guidelines have been produced, seeking to identify patients at risk of death or complications [4]. This chapter focuses on the subgroup of CAP patients that are admitted to the ICU – approximately 10% of patients hospitalized for CAP [5] – and reviews the most important factors regarding etiology, prognosis, diagnostic tools and treatments.

Definition

No consensus has been reached among researchers as regards the definition of severe pneumonia. Obviously, the condition of patients admitted to the ICU for control of vital constants, shock correction or mechanical ventilation can be considered severe, but criteria for ICU admission may differ from hospital to hospital. Therefore percentages of hospitalized patients requiring admission to the ICU obtained in different studies fluctuate between 5% and 35% [6], and may well reflect differences not only in clinical criteria, but in infrastructure as well. Some authors have tried to define criteria of severe pneumonia. In 1987 the British Thoracic Association [7] published the first guidelines based on a survey of 453 patients admitted to hospital for CAP. Using multivariate analysis the study concluded that three variables were associated with an increased risk of mortality: respiratory rate $\geq$30 breaths/min, blood urea >7 mmol/l and diastolic blood pressure $\leq$60 mmHg. The association of at least two of these variables increased the mortality risk 21

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times. Subsequent studies have identified other factors that are related to mortality. The ATS guidelines, only recently validated, suggested 10 items for definition of severity (shown in Table 1); patients presenting any of them were diagnosed as cases of severe pneumonia. In a study conducted in Barcelona, Ewig *et al.* [8] studied 331 hospitalized CAP and 64 severe CAP admitted to the ICU. The presence of at least one of 10 criteria was 98% sensitive but only 32% specific, and the positive predictive value was as low as 24%. Moreover, both factors reflecting respiratory failure (respiratory rate >30 and PaO_2/FiO_2 <250 mm Hg) were found to be poorly sensitive and specific regarding to pneumonia severity. The authors suggested that definition of severity would need a "major" criterion (requirement of vasopressors >4 hours or requirement of mechanical ventilation) or at least two minor criteria (systolic blood pressure <90 mm Hg, PaO_2/FiO_2 <250 mm Hg, involvement of >two lobes in chest radiograph). These criteria had a sensitivity of 78% and specificity of 94%. Positive predictive value was 75% and negative predictive value 95%.

Aside from the need to validate these rules, there is no doubt that considering pneumonia as a dynamic process (which in the first 24–48 hours may worsen and require ICU admittance) can improve our approach to, and management of, this clinical entity. In a study of the influence of adherence to British guidelines on mortality, Hirani and Macfarlane [9] reported that 7% of CAP admitted in ICU were in cardiac arrest. In a previous study, cardiac arrest was present in 25% of cases [10]. In our own experience [11], pneumonia was documented in 24% of patients admitted to the ICU by cardiac arrest. This emphasizes the need for careful follow-up and respiratory monitoring of patients hospitalized by CAP.

TABLE 1. Criteria of severity in CAP

Respiratory rate >30/minutes
Severe respiratory failure (PaO_2/FiO_2 < 250)
Requirement for mechanical ventilation
Bilateral involvement in chest radiograph
Increase in the size of the opacity by 50% or greater within 48 hours
Systolic blood pressure <90 mmHg
Diastolic blood pressure <60 mmHg
Requirement of vasopresors >4 hours
Urine output lower than 20 ml/h, or total urine output lower than 80 ml in 4 hours
Acute renal failure requiring dialysis

Etiology and Risk Factors

The spectrum of causative agents of severe CAP is similar to that found in hospitalized patients or outpatients with CAP. The main difference is the relative importance of each microorganism. Table 2 [9, 12–17] shows that *S. pneumoniae* and *Legionella spp* account for 50% of cases with etiologic diagnosis. Likewise, Gram-negative microorganisms are the third most frequent cause in most series in the ICU. Interestingly, in some countries, ICU admission for tuberculosis may reach 10% of total cases [14].

The most important risk factors for *S. pneumoniae* infection are chronic hepatic disease, alcoholism, influenza, cigarette smoking and COPD [18]. In patients with HIV infection, the risk of pneumococcal infection correlates with the CD4 count. CD4 count below 200 or AIDS diagnosis significantly increases the risk of pneumococcal pneumonia. As many as 25% of these infections can produce bacteremia; the diagnosis of pneumococcal bacteremia should alert us to the possibility of HIV infection.

Pneumonia caused by *Legionella spp* is the second most frequent etiology, though there are significant regional variations. It is more common in Mediterranean countries and the US than in the north of Europe or South America.

The most important risk factors are smoking and corticotherapy. El-Ebiary *et al.* [19] reported COPD to be a more frequent risk factor in nosocomial pneumonia than in CAP caused by *Legionella pneumophila* (64% versus 41%). Infection in previously healthy patients has also

TABLE 2. Causative agents of severe CAP

Author	Pachón	Torres	Rello	Moine	Leroy	Rello	Hirani
Year	1990	1991	1993	1994	1995	1996	1997
Episodes	(n = 67)	(n = 92)	(n = 58)	(n = 132)	(n = 229)	(n = 95)	(n = 57)
Ref.	12	13	14	15	16	17	9
Intubation	–	61	87.5	61	50	87.3	96.4
Etiological diagnosis	48	52	60.3	72	66	39	67
S. pneumoniae	37.5	15	37	45	30.8	29.4	18
Legionella spp.	22	14	22.8	4.2	–	3.1	16
Enterobacteriaceae	25	4	11.4	14.7	18.1	6.3	–
H. influenzae	6	–	–	14.7	10	–	–
P. aeruginosa	–	5	–	–	3	–	1.7
Staphylococci	3	–	–	5.2	22**	1	12
Atypical pathogens*	–	6	–	7.3	3	3.1	5.2
P. carinii	–	–	8.5	–	–	1	5.2
M. tuberculosis	–	–	11.4	–	–	–	1.7
Virus	3	–	2.8	7.3	–	1	7
Others	–	5	5.6	10.5	12.7	–	1.7

* *M. pneumoniae, C. psitacci, C. pneumoniae, Rickettsia conorii, Coxiella burnetti.*
** Coagulase-negative staphylococci obtained from endotracheal aspirates that suggest contamination.
Values are presented as percentages.

been reported, even in cases of nosocomial acquisition.

H. influenzae accounts for between 6% and 15% [9, 12–17] of pneumonia that require ICU admission. COPD, elderly and HIV patients are mainly affected. Pneumonia caused by *S. aureus* is usually a severe infection, requiring ventilatory support in up to 90% of cases. The infection can occur after epidemic influenza or via bloodstream spread. Enterobacteriaceae are usually involved in nosocomial pneumonia and in some studies of CAP, are the third most important cause (25%) [12]. The microorganism most frequently involved is *Klebsiella pneumoniae*, which mainly affects COPD patients, alcoholics and in general patients suffering from consuming diseases. Blood isolation is reported in up to 38% of cases, especially in alcoholic patients.

Among Gram-negative bacteria, *P. aeruginosa* stand out on account of their extreme virulence. Fortunately the incidence in the community setting is low. In our opinion, this etiology should be considered only in patients with structural lung disease (bronchiectasis and cystic fibrosis), patients with neutropenia due to chemotherapy and HIV patients.

Finally, in a high percentage of patients the causative agent is impossible to determine even after extensive research. New microorganisms such as *C. pneumoniae* do not seem to play a role in severe pneumonia. A recent study [20] using PCR techniques confirmed that in the subgroup of patients with unknown etiology *S. pneumoniae* was the most probable cause.

Diagnosis

Empiricism is the usual approach in patients suffering from CAP. Indeed, some guidelines strongly recommend it [3]. However, a knowledge of causative agent is useful, given the possibility of adjusting antibiotic treatment on the basis of the antibiogram. Despite intensive etiologic research, the causative agent is not isolated in as many as 40% of cases. However, no study has concluded that outcome may be influenced by microorganism isolation.

From our point of view, the knowledge of etiology is useful, either for epidemiological purposes or to improve management in cases with poor clinical evolution. In severe CAP we recommend obtaining (at least) blood cultures and respiratory samples for cultures and Gram stain. However, it is extremely difficult to obtain a good sputum sample for the Gram stain from these patients (more than 25 neutrophils and ≤10 epithelial cells per microscopic field (×100)). In severe CAP a respiratory sample is available in only 40% of patients and in only 50% of these is it considered good enough for analysis [21].

Sputum induced by hypertonic saline serum has proved to be a good tool for *Pneumocystics carinii* and tuberculosis research, especially in AIDS patients. The success of this approach depends on the skill of the nurse and patient cooperation; an accuracy between 40–80% has been reported [22]. The usefulness of this method in the detection of other pulmonary pathogens has not been established.

The proper interpretation of Gram stain can be affected by staff training and by previous use of antibiotics; that is to say, previous antibiotic use may sterilize cultures, particularly in cases due to *H. influenzae* and *S. pneumoniae*. Furthermore, the interpretation of results in populations with high levels of bacterial colonization, such as COPD patients, can be difficult.

Blood cultures are positive in around 10–30% of patients with SCAP [2]. In spite of low sensitivity, the convincing nature of the isolation of a respiratory pathogen from blood, the opportunity to test the antimicrobial sensitivity of the isolate and the relative simplicity of drawing blood for cultures are all arguments in favor of the practice of obtaining blood cultures in patients requiring hospital admission. At least two cultures should be drawn by direct venopunction at separate sites. The main drawback is the time required, which means that the results are of no use in guiding initial treatment.

Other noninvasive techniques are based on antigen detection of some microorganisms in urine, plasma or sputum. The most useful is antigen detection of *Legionella spp* in urine. Sensitivity is around 50% and specificity is near to 100%. Likewise, this test is not influenced by previous use of the right antibiotic and can still remain positive for a long time after pulmonary infection has occurred (usually several weeks). The main drawback is that only serogroup 1 can be detected, though this serogroup accounts for >70% of *Legionella* infection [23]. More recently a colorimetric technique has been validated, allowing antigen detection at the bedside [24].

Other useful diagnostic tools that can be applied in etiologic investigation are based on invasive tests. Among these, fiberoptic bronchoscopy and transthoracic needle aspiration (TNA) are the most frequently used. Bronchoscopy is easy to perform when a patient is intubated, but it tends to be little used, because of the absence of laboratory equipment and well-trained bronchoscopic staff. Furthermore, in non-intubated patients, respiratory failure constitutes a relative contraindication, given the possibility of speeding up urgent intubation. In order to avoid this complication, a method that makes bronchoscopy safer in patients treated with CAP has recently been described [25]. This approach avoids the decline of positive end expiratory pressure and maintains correct levels of PaO_2.

The few studies undertaken in severe CAP have reported that the reliability of bronchoscopic tests is high. In one study, the authors reported isolation of causative agents in up to 70% of cases [26]. Likewise, correlation between bronchoalveolar lavage (BAL) and protected specimen brush (PSB) was good. In that study, none of the patients was receiving antibiotic treatment. In another study [27] performed in 193 patients affected by CAP of different degrees of severity, diagnosis was achieved in 71% of cases; the most reliable test was PSB. Other authors have tried to define the role of bronchoscopy as a rescue tool for pneumonia with poor clinical evolution. Örtqvist *et al.* [28]

evaluated the role of bronchoscopic techniques in patients with therapeutic failure. The authors considered failure to be early if it occurred before 72 hours, and late if it occurred after 72 hours. 277 patients were included in the study. Early failure was identified in 6% of cases and late failure in 7%. In 41% of these patients the performance of bronchoscopy gave useful information.

In the context of immunocompromise (HIV infection, stepidal therapy, transplantation) or high suspicion of atypical microorganism, performance of bronchoscopy with bronchoalveolar lavage (BAL) is the first step in the diagnostic approach. The accuracy of this test to detect *Pneumocystis carinii* is close to 90% [22].

Another invasive technique is TNA. Although few studies have evaluated its role in CAP, good results have been reported in nosocomial pneumonia and immunocompromised patients. In patients requiring ICU admission, the need for ventilatory support may preclude the performance of this technique, due to the high risk of barotrauma. Respiratory failure and severe bleeding diathesis are contraindications for this test. In general, sensitivity is around 40–50% and specificity is near to 100%. The prior use of antibiotic treatment and the size of pulmonary infiltrate are the main factors that can affect the diagnostic yield of this technique [29]. Pneumothorax and hemoptysis are the main complications; utilization of G25 needles reduces the number of adverse events.

Currently, it is possible to increase sensitivity of this procedure by means of techniques based on polymerase chain reaction (PCR) and agglutination latex, especially in the case of *S. pneumoniae* [30]. Procedures based on PCR techniques can be applied to noninvasive samples; sensitivity remains high, in spite of antibiotic treatment. In addition, the results are available in only a few hours. The high cost of these procedures and the lack of well-prepared laboratories preclude their world-wide use.

In our view, in severe CAP, a basic etiologic investigation should be performed, including at least two blood cultures, a respiratory sample (obtained by means of bronchoscope or simple trackeal aspirate) and urinary antigen detection for *Legionella*. Other tests can be performed depending on the equipment available at the center in question. In our opinion, establishing the etiology is recommended whenever possible.

Mortality – Prognostic Factors

In spite of advances in antibiotic treatments and the technical improvements in ICU, severe CAP mortality remains unacceptably high. In different studies of SCAP that require ICU admission, crude mortality is around 20–54% [9, 12–17]. In a recent meta-analysis undertaken by Fine *et al.* [31] these data on mortality are confirmed. In that study 33,148 patients were evaluated from 127 publications. Thirteen of these studies were of patients admitted to ICU. Mortality in hospitalized patients was 14%, and 36.5% in those admitted to ICU.

Mortality from respiratory infection is due to a combination of microbial virulence, bacterial burden and the patient's defensive system. For its part the immune system is conditioned by underlying disease, immunosuppressive treatments and other factors. In this section we will review the factors associated with worse outcome.

HOST CHARACTERISTICS

Age: This factor has been considered for a long time as a risk factor for the development of pneumonia and a factor associated with worse outcome. Mufson *et al.* [32], reported that the incidence of pneumococcal bacteremia increased with advancing age. In the 34–44 year-old group the incidence was 1/100,000, whereas in the 65–74 year group it was 25/100,000. Furthermore, in a study from Canada undertaken by Marrie [33] in a population older than 65, it was concluded that the mortality rate increased with the age, reaching 61% in those over 71.

Although it is true that pneumonia incidence and mortality rate are higher in senior citizens,

the population older than 65 years is a mixture of healthy people and others with devastating underlying diseases. Age itself is not a factor of bad prognosis. In a case-control study (older than 65) performed in 101 pneumonia patients, Riquelme *et al.* [34] concluded that risk factors for CAP in this group of people were gastric aspiration and malnutrition (albumin less than 30 mg/dl) (the two groups were similar in relation with age, gender, and day of admittance). The significant prognostic factors were bedridden patients (RR 10.7), deglutition impairment (RR 7.3), lack of fever (RR 10.5), respiratory rate >30/min (RR of 5.2) and bilateral and multilobar involvement in chest radiography (more than three lobules) (RR 2.33).

In a study performed in patients older than 65 requiring ICU admission for SCAP [17], the mortality rate was 40%; however, in patients younger than 65 it was 31%. Nonetheless, in multivariate analysis, of the 23 variables studied, only the initial degree of severity of pneumonia, radiologic progression, septic shock and immunosuppression (corticoids included) were significantly related with bad outcome.

Underlying diseases: In most studies of severe pneumonia, a significant percentage of patients are reported to be affected by one or several underlying diseases. COPD is the most prevalent disease, reaching 50% of patients [12–17]. Furthermore, in epidemiological studies of pneumonia performed in general population [35], 39% of patients had some comorbidity, COPD accounting for 40% of them. In another study undertaken in the general population by Lange *et al.* [36], age and low FEV_1 were related with increased risk of death and hospital admittance. In view of these results, it is not surprising that COPD is a risk factor of poor outcome, and hospital admission is recommended in most guidelines. However, in a prospective multicenter study performed in COPD patients admitted for CAP [37], mortality was only 23% in the 22 patients who required ICU admission. This percentage of mortality is similar to the rate in COPD patients undergoing intubation for exacerbation.

In a multicenter study performed in ICUs in the USA [38], crude mortality in exacerbated COPD patients was 24%. This level of mortality was not related to COPD status but to multiorganic failure. When mortality was evaluated at 180 days, underlying disease was clearly related with mortality; severe COPD patients had fewer possibilities of survival than less severe COPD patients.

In another prospective study performed in the ICU (including patients with SCAP and severe nosocomial pneumonia) Almirall *et al.* [39] evaluated 127 patients, finding no relationship between mortality and underlying disease. The most closely related variables were age older than 70, a *simplified acute physiology score* (SAPS) higher than 12, septic shock, radiological bilateral involvement and *Pseudomonas aeruginosa* infection.

Likewise, in the meta-analysis by Fine *et al.* [31], neither COPD nor alcoholism were among the eleven prognostic significant factors. These findings agree with Rello *et al.*'s findings in elderly patients [17]; in that study, comorbidities were not related with pneumonia outcome, excepting immunosupresion.

Although patients affected by AIDS, transplantation or chemotherapy are excluded in most studies, their relative importance is growing. In a general population study, 57% of 385 evaluated patients were affected by some degree of immunocompromise (mainly HIV infection). This is why *S. pneumoniae* and *Pneumocystis carinii* were the most isolated microorganisms [40].

The type of underlying disease clearly affects the prognosis of these patients. For example, HIV infected patients suffering from pneumococcal bacteremia are six times more likely to die than HIV infected patients without pneumonia [41]. In severe neutropenia (<500 cells) due to chemotherapy, bacteremia is frequent, the most commonly isolated microorganisms being *P. aeruginosa* and *S. pneumoniae* [42].

RADIOLOGIC AND LABORATORY FACTORS

Septic shock, infiltrate progression, need for mechanical ventilation and multilobar involvement in initial chest x-ray are well established prognostic factors. In contrast, hypoxemia *per se* is not a risk factor, although it is mentioned in most guidelines.

MICROBIAL CHARACTERISTICS

The isolation of a microorganism in blood has been considered as a factor of poor prognosis. The most frequently isolated microorganism is *S. pneumoniae*. In spite of the use of newer antibiotics, mortality due to pneumococcal bacteremia remains unchanged (20–45%), reflecting perhaps the existence of a subgroup of patients with frail immunological defense. Marfin *et al.* [43] tried to identify risk factors of mortality in 102 patients with pneumococcal pneumonia and bacteremia. By means of multivariate analysis they found that age >50 years, lack of fever and nosocomial acquisition were the most important factors. Hypothermia is probably a marker of WBC activity or of reduced interleukin production.

In several studies, the isolation of *Pseudomonas aeruginosa* has been identified as a risk factor for death. The mortality rate was 100% in one study [13], although the incidence was only 1%. Fine *et al.* [31] reported *P. aeruginosa*-attributable mortality to be 63%, the highest among a range of causative agents.

Treatment

Treatment of SCAP involves a number of aspects that will be reviewed in this section: adequate antibiotic spectrum, shock management, and ventilatory support. It is important to remember that mortality is due to septic shock (particularly within the first four days) and refractory hypoxemia (ARDS and MOF) despite adequate antibiotic treatment [14].

IMPACT OF TREATMENT ON MORTALITY

Several studies using multivariate analysis have shown that inadequate antibiotic treatment is associated with a significant increase in mortality [12, 13, 16]. In a multicenter, retrospective study [44] of more than 14,000 patients older than 65 years with CAP, the authors reported that delay in starting antibiotic treatment (>8 hours) and non-performance of blood cultures in the first 24 hours were associated with increased mortality at 30 days of admission. In spite of these findings, other studies specifically addressed to SCAP in ICU admissions reported that the correct adherence to guidelines did not increase survival. In one study of 57 SCAP patients, mortality was 58%, the most frequently isolated microorganisms being *S. pneumoniae*, *Legionella pneumophila* and *Staphylococcus aureus*. Ten years earlier (before guidelines were extensively used), the same authors reported a similar level of mortality (54%) [9, 10]. These findings suggest that some unknown host-dependent factor of severity is present. Perhaps improvement of ICU management with newer therapies and identification of new prognostic factors would lower the mortality rate.

SHOCK MANAGEMENT

Hemodynamic instability is defined by the need for vasoactive drugs, once the hydroelectrolytic dysfunction has been corrected, in order to achieve an arterial blood pressure sufficient to preserve peripheral perfusion. 25–50% of patients meet shock septic criteria when admitted to ICU. Currently, management of these patients is based on adequate hydration followed by norepinephrine administration. The specific approach of patients with pneumonia and septic shock does not differ from the general population with septic shock and it is discussed in detail in Chapter 6. Rescue therapy with vasopresine is a promising alternative in patients with refractory shock.

TREATMENT OF REFRACTORY HYPOXEMIA

Among patients admitted to the ICU for SCAP, between 58–88% need mechanical ventilation [21]. In patients undergoing mechanical ventilation, the goal is to improve gas interchange

maintaining plateau pressures low in order to avoid acute lung injury.

The main drawback of intubation is that it increases the possibility of superinfections. New forms of ventilation that avoid intubation have been promoted in recent years, known generically as noninvasive ventilation. Noninvasive forms of ventilation have been tested in several diseases, and are very useful in COPD patients. As regards respiratory failure in SCAP, Confalonieri *et al.* [45] concluded that noninvasive ventilation was associated with a significant reduction in the rate of endotracheal intubation and duration of ICU stay. In more than 50% of enrolled patients (33/56 patients), COPD was the main underlying disease. Moreover, in this subgroup, a significant reduction of mortality was achieved when noninvasive ventilation was applied.

In general, our policy is to implement noninvasive ventilation whenever possible in order to avoid endotracheal intubation. When the level of consciousness is depressed or the ability to clear secretions is impaired, we avoid their use. The success of this approach depends mainly on training of nurses and respiratory therapists. Regardless of the population evaluated, the performance of these techniques seems to be useful to reduce the rate of nosocomial respiratory infection, to shorten hospital stay and to reduce mortality rate [46].

SCAP is associated with ARDS in about 10% of cases [21]. In general, when ARDS is developed, mechanical ventilation is needed, requiring high level O_2 delivery as well as high levels of PEEP, to ensure venous oxygen saturation of 90%. Two important goals in this context are the maintenance of low FiO_2 and tidal volume. In general, it is desirable to achieve a level of PEEP that maintains FiO_2 below 0.6 whenever possible. A protective ventilatory strategy using tidal volume below 6 ml/kg improves survival in patients with ARDS and increases the number of days without ventilator use [47].

In very severe cases, nitric oxide (NO), alveolar recruitment maneuvers and placement of patient in prone position as rescue adjunctive therapy have all been tested. The two last maneuvers are employed for alveolar reopening of collapsed areas of lung. Sometimes these approaches can achieve a dramatic reduction in the level of FiO_2 and PEEP.

ANTIBIOTIC TREATMENT

Usually, antibiotic treatment is started empirically, trying to cover the most frequent microorganisms and taking into account the risk factors for specific microorganisms. For an accurate treatment, it is critical to identify whether the pulmonary infection is due to *P. aeruginosa*, *Legionella* or penicillin-resistant pneumococci (PRP). Given that clinical differentiation is usually inaccurate, most guidelines recommend expanded-spectrum antibiotherapy. A combination of two antibiotics is generally preferred. For example, the ATS guidelines [3] recommend in 1993 a combination of a third generation cephalosporine with antipseudomonal activity plus a macrolide. This recommendation is based on the high mortality level reported for *P. aeruginosa*, but it does not take into account the low incidence of this pathogen in the community. Furthermore, activity of cefoperazone or ceftazidime against PRP is poor [48]. When it is necessary to expand coverage to *P. aeruginosa* (for example, in a patient with bronchiectasis), beta-lactam antibiotics such as cefepime or carbapenems are suitable because they maintain good activity against PRP. Table 3 shows some antibiotics with a good alveolar penetration and

TABLE 3. Antibiotics with acceptable activity against PRP and good alveolar penetration

a)	Cephalosporines
	Ceftriaxone
	Cefotaxime
	Cefepime
b)	Beta-lactam/beta-lactamase inhibitors
c)	Third generation fluoroquinolones
d)	Linezolid
e)	Carbapenems

Modified from [49–52].

activity against PRP. Among new fluoroquinolones, none have greater antipseudomonal activity than ciprofloxacin. As for aminoglycosides, their poor lung penetration, the fact that they can be inactivated when pH is low and the risk of severe renal toxicity all advise against their use.

In the IDSA guidelines [23] for ICU patients, third generation cephalosporine such as cefotaxime or ceftriaxone (or beta-lactam/beta-lactamase inhibitors) plus a macrolide or a fluoroquinolone are recommended. The use of a macrolide is due to the high incidence of *Legionella* infection. Although the standard treatment has classically included erythromycin, the need for large volume infusion, the better *in vitro* activity and the uncomfortable side effects (epigastric pain, transitory deafness) has led to the progressive introduction of newer macrolides. Both fluoroquinolones and newer macrolides present better activity against *Legionella* than erythromycin. Table 4 presents the different MIC of most significant macrolides and other antibiotics against *Legionella sp*. When *Legionella sp* infection is confirmed, combination therapy with rifampin is recommended in the first three days of treatment.

In some geographic areas PRP has become an important problem. In a multicenter Spanish study [54], 95 isolates of *S. pneumoniae* were analyzed. Half showed penicillin resistance, 24% intermediately resistant (MIC: 0.1–1 μgr/ml) and 25.2% highly resistant (MIC >1 μgr/ml). All isolates were susceptible to ceftriaxone and cefotaxime. The prior use of beta-lactam antibiotics (OR 2.8; 95% CI 1.4–1.9) and alcohol consumption (OR 5.2 95% CI 0.9–8.2) were independent risk factors for penicillin resistance. The same study reported that 30% of PRP strains were resistant to macrolides. Using multivariate analysis, it was detected that age under five years (OR 16.7, 95% CI 1.6–176.3) or above 65 (OR 4.3; CI 1.4–13.2), as well as previous use of beta-lactam antibiotics in patients with non-invasive pneumococcal infection (OR 7.9; 95% CI 1.8–34) were associated with a higher risk of multiple antibiotic resistance.

TABLE 4. Activities of antimicrobial agents against *Legionella spp.*

Antimicrobial	MIC 90 (μg/ml)
Rifampin	0.002–0.008
Erythromycin	0.12
Roxithromycin	0.03–0.12
Clarithromycin	<0.004
Linezolid	4–8
Ciprofloxacin	≤0.01–0.06
Grepafloxacin	≤0.01
Trovafloxacin	≤0.01

Modified from [49, 53].

Whether or not these strains are associated with increased mortality remains a controversial issue. In a study reported in 1995, 504 pneumococcal episodes of pneumonia were evaluated [55]. Although in the univariate analysis mortality rate in patients affected by PRP was 38% and 24% in PSP, the multivariate analysis did not show any significant differences. In another study conducted by Einarrson *et al.* [56], no differences in mortality were shown, but hospital stay and pharmacy costs were both increased. In contrast, in another study [57], although no differences in mortality were observed between PRP and PSP, the authors found no differences in pharmacy costs or hospital stay either. Moreover, a further study [58] reported an excess of mortality among patients suffering from CAP by PRP. More important in clinical practice is that cefixime, cefoperazone, ceftazidime or macrolides alone, must be ruled out as first line therapy for SCAP.

Due to the world-wide increase in PRP and the high incidence of *Legionella sp* infection in SCAP, new antibiotics have been developed in order to cover both microorganisms. New fluoroquinolones (levofloxacin, grepafloxacin, moxifloxacin and trovafloxacin) seem to offer good coverage against PRP and *Legionella*, and excellent lung tissue levels have been reported. These antibiotics could be a good alternative to the combination therapy mentioned above.

Clinafloxacin, moxifloxacin and trovafloxacin are the most active against *S. pneumoniae*. Trovafloxacin has an expanded spectrum to anaerobes. The lack of clinical trials in SCAP patients admitted to ICU and the risk of emergence of resistances, makes the use of fluoroquinolones advisable only in patients allergic to beta-lactam antibiotics.

Finally, the new oxazolidines, such as lizenolid, may become an interesting alternative for resistant Gram-positive respiratory infections [59]. In contrast, the poor alveolar penetration of vancomycin is associated with significant low survival rates and should no longer be considered as first line therapy [60]. Initial antibiotic therapy with a carbapenem should be considered if *Staphylococcus aureus* is a probable pathogen.

Conclusions

Severe community-acquired pneumonia is an important challenge for clinicians, due to the high rate of mortality despite the use of new antibiotics and the introduction of high technology in the ICU setting. Although risk factors of mortality are well known, pneumonia is a dynamic process that needs careful evaluation within the first hours after diagnosis has been established. In addition, given the relevance of pulmonary infections due to *Legionella sp* and PRP, we believe that antibiotic treatment must cover these microorganisms when the etiology is unknown. Antibiotic coverage for *P. aeruginosa* is necessary in selected patients at risk (bronchiectasis, neutropenia, HIV infection).

In general, a beta-lactam with PRP activity along with a new macrolide or a fluoroquinolone, administered intravenously, remains the preferred choice for initial treatment of patients with SCAP. Aminoglycosides and glicopeptides have poor alveolar penetration, exposing patients to an enormous risk of clinical failure. Fluoroquinolones represent an alternative for patients with beta-lactam allergy or pharmacologic interactions (transplant patient). Early recognition of severity and improvements in adjunctive therapy for shock and respiratory failure (noninvasive ventilation and a protective ventilatory strategy) are key elements to improve survival.

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