Community-Acquired Pneumonia (International Vision)

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Abstract

Community-acquired pneumonia (CAP) is generally regarded as pneumonia requiring a specific clinical approach in the intensive care unit (ICU). Between 10% and 36% of patients with CAP who are hospitalized need ICU treatment, and mortality ranges from 20% to 50%. The ICU admission and management should be customized in each patient.

The spectrum of causative agents of severe CAP (SCAP) is similar to that found in hospitalized patients or outpatients with CAP. *Streptococcus pneumoniae* and *Legionella* species (spp.) account for 50% of cases with etiologic diagnosis. However, *Legionella* spp. are rarely reported in South America, where *S. pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* are the most frequent findings. Interestingly, ICU admission for tuberculosis can reach 10% of total cases in some countries.

The usefulness of diagnostic testing in the management of SCAP is a subject of controversy. However, knowledge of the causative agents is useful, given the possibility of adjusting antibiotic treatment, and improves the outcome. Blood culture, Gram stain, and urinary detection of antigens should be done.

Shock and refractory hypoxemia management do not differ for the general population with septic shock. The goal of resuscitation in shock is the restoration of tissue perfusion. Normalization of cellular metabolism and noninvasive forms of ventilation or a protective ventilatory strategy using low tidal volumes are recommended.

The guidelines for initial antibiotic management should be customized to each country or to each institution and patient. We believe that cefotaxime/ceftriaxone should be the cornerstone of therapy in combination with macrolide, but antibiotic coverage for *Legionella* spp. and *Pseudomonas aeruginosa* might be necessary in intubated critically ill patients when SCAP etiology is unknown.

Introduction

Community-acquired pneumonia (CAP) is among the most common infectious diseases, although the precise figures are not available for most countries, because appropriate studies have not been performed. CAP accounts for more than 600,000 hospital admissions in the United States¹ and for more than 50,000 in the United Kingdom each year.² Studies in Spain³ and Finland suggested frequencies of 2.6 and 4.7 per 1,000 in the general population per year. The frequency of the condition is country related and age related, with the highest rates in the extreme of life. Its frequency, costs, morbidity, and mortality (20% to 50%) are the reasons CAP is such an important disease.⁴⁻⁶

The steady increase in the number of senior citizens and immunocompromised patients, the better survival rates of patients affected by chronic illness, and the necessary administration of appropriate empirical antibiotics (ATB) justify continuing research in this field. In the last decade, several medical societies published guidelines for the initial CAP management for attempts to reduce the high mortality.⁷⁻⁹ The clinical utility, acceptance and use for the physician, and impact on the outcome of such guidelines are unknown.

This chapter focuses on the subgroup of CAP patients that are admitted to the ICU (approximately 10% of patients hospitalized) and reviews the most important factors regarding etiology, prognosis, diagnostic tools, and treatment. Finally, we develop an algorithm of diagnosis and treatment (Figure 3.1).

Definition

CAP is defined as an acute lower respiratory tract infection characterized by the following: (a) an acute pulmonary infiltrate evident on the chest radiographs and compatible with pneumonia, (b) confirmatory clinical examination, and (c) acquisition of the infection outside the confines of the hospital, chronic care facility, or nursing home. Pneumonia is characterized pathologically by inflammation within and around the alveolar spaces (lung consolidation) with disruptions of the normal gas exchange and clinical symptoms of dyspnea, cough, and expectoration.^{8,9}

However, no consensus has been reached among researchers with regard to 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 and the infrastructure may differ from hospital to hospital. The American Thoracic Society (ATS) guidelines,⁷ recently validated, suggested 10 items for definition of severity (Table 3.1). However, Ewing, et al.¹⁰ found that the presence of at least one of 10 criteria had high sensitivity (98%) but low

Figure 3.1. Diagnostic and treatment algorithm for severe CAP.

Table 3.1. ATS criteria of severity in CAP

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- Respiratory rate > 30/min
 - Severe respiratory failure ($\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} < 250$)
 - 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 vasopressors > 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
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specificity (32%). The authors suggested that the definition of *severity* would need one “major” criterion (requirement of vasopressors of more than 4 hours or mechanical ventilation) or at least two “minor” criteria (systolic blood pressure of less than 90 mmHg, $\text{PaO}_2/\text{FiO}_2$ of less than 250 mmHg, involvement of more than two lobes in chest radiograph).

Using multivariate analysis, the British Thoracic Society (BTS)¹¹ concluded that only three variables were associated with an increased risk of mortality: respiratory rate of more than 30 breaths/min, blood urea of more than 7 mmol/L, and diastolic blood pressure of less than 60 mmHg. The association of at least two of these variables increased the mortality risk 21 times.

A recent study¹² reports that the pneumonia severity index (PSI)¹³ has a poor positive predictive value of 16%. These findings agree with previous reports, which find that inappropriate hospitalization rates were 5%¹⁴ and 23%.¹⁵ We believe that the decision with regard to ICU admission must be individualized (patient-based selection) rather than based on a severity index. It should be based on the stability of the patient’s clinical condition, the risk of death or complications, and the presence of other active medical problems.

Etiology and Risk Factors

The spectrum of causative agents of SCAP is similar to that found in hospitalized patients or outpatients with CAP. However, a number of issues may confound the results of etiologic studies in CAP. Health care factors (criteria for ICU admission, proportion of patients admitted to hospital) and several factors related to the population being studied (number of patients studied, the age mix, antibiotic therapy, etc.) may have an impact on etiologic results.

Table 3.2 shows that *S. pneumoniae* and *Legionella* spp. account for 50% of cases with etiologic diagnosis. Interestingly, in some countries, such as those of South America, *Legionella* spp. are rarely reported, and *S. pneumoniae*,

Table 3.2. Isolated Pathogens of Community-Acquired Pneumonia in Trial from Many Countries in Last 10 Years

Author	Relio	Moine	Leroy	Relio	Hirani	Luna	Sadias	Relio	Wattanathum
Year	1993	1994	1995	1996	1997	2000	2003	2003	2003
Episodes	(n=58)	(n=132)	(n=229)	(n=95)	(n=57)	(n=292)	(n=306)	(n=204)	(n=147)
Reference	24	25	26	27	2	60	57	29	28
Intubation	87.5	61	50	87.3	96.4	13.3	14	51.9	25.8
Etiological diagnosis	60.3	72	66	39	67	30.1	22.5	57.3	71.4
<i>Streptococcus</i>	37	45	30.8	29.4	18	14.4	10.5	20.1	22.4
<i>Legionella</i>	22.8	4.2	—	3.1	16	2.0	—	11.2	5.5
<i>spp.</i>									
Enterobac- teriaceae	11.4	14.7	18.1	6.3	—	6.7	4.2	1.9	11.6
<i>Haemophilus</i>	—	14.7	10	—	—	8.2	3.9	5.3	2.7
<i>influenzae</i>									
<i>Pseudomonas</i>	—	—	3	—	1.7	3.6	1.3	3.9	0.7
<i>aeruginosa</i>									
Staphylococci	—	5.2	22†	1	12	5.2	4.2	2.9	6.8
Atypical	—	7.3	3	3.1	5.2	13.0	—	1.4	23.1
pathogens*									
<i>Pneumocystis</i>	8.5	—	—	1	5.2	0.5	—	4.9	—
<i>carinii</i>									
<i>Mycobacterium</i>	11.4	—	—	—	1.7	3.6	—	0.9	—
<i>tuberculosis</i>									
Virus	2.8	7.3	—	1	7	10.4	1.6	0.5	—
Others	5.6	10.5	12.7	—	1.7	17.1	12.4	3.8	10.9

*Atypical pathogens. *M. pneumoniae*, *Chlamydia psitticae*, *C. pneumoniae*, *Rickettsia colonii*, *Coxiella burnetii*.

†Coagulase-negative staphylococci obtained from endotracheal aspirates that suggest contamination.

The values are presented as percentages.

Haemophilus influenzae, and *S. aureus* are the most frequent findings. In developing countries, ICU admission for tuberculosis can reach 10% of total cases.

The most important risk factors for *S. pneumoniae* infection are chronic hepatic disease, alcoholism, influenza, cigarette smoking, and chronic obstructive pulmonary disease (COPD).⁶ A recent Spanish multicenter study in elderly patients¹⁶ found *S. pneumoniae* in 49% of patients in isolation. The impact of age appears to be mainly on the frequency of pneumococcal infection, which is more common in the elderly. In patients with human immunodeficiency virus (HIV) infection, the risk of pneumococcal infection correlates with the CD4 count (below 200 significantly increases the risk of pneumococcal pneumonia).⁶

The most important risk factors for *Legionella* spp. infection are advanced age, smoking, steroid therapy, COPD, alcoholism, and other forms of immunosuppressive therapy.^{6,17-19} *Legionella* spp. are an uncommon cause in the hospital, but infection from this source in previously healthy patients has been reported, even in case of nosocomial acquisition.⁶ Legionnaires disease may occur in previously healthy subjects, and the absence of underlying disease should not be a reason for excluding the diagnosis.¹⁸ On the other hand, nosocomial Legionnaires disease may occur in epidemics, but the detection of most such outbreaks usually infers the existence of prior unsuspected sporadic nosocomial cases.^{18,19}

In South America, *Legionella* pneumonia is rarely found. Lopardo et al.²⁰ studied the incidence of acute infection due to *Legionella* spp. in a group of adult patients in Buenos Aires. Ninety-two of the enrolled patients could be evaluated. Only three patients (3.3%) fulfilled the serologic diagnostic criteria for *Legionella* spp. acute infection. Recently, eight patients were reported in Chile.²¹ Both series made the etiologic diagnosis just by urinary antigen or serologic test. No diagnoses were confirmed by microorganism cultures, and the mortality was extremely low. There is a perception that the *Legionella* organism occurs more often in Mediterranean countries and in the United States and is less frequent in northern European and South American countries.⁶⁻²²

H. influenzae is the third most common cause of CAP requiring hospitalization and accounts for between 6% and 15%²³⁻²⁸ of pneumonia that requires ICU admission. COPD, elderly, and HIV patients are mainly affected.

S. aureus and Gram-negative enteric bacteria are uncommon in disease managed outside a hospital, but infection from these sources shows a pattern of progressive increase in frequency with increasing severity.²² Pneumonia caused by *S. aureus* is usually a severe infection, requiring ventilatory support in up to 90% of cases.⁶ The infection occurs after epidemic influenza or via the bloodstream.

Among Gram-negative bacteria, *P. aeruginosa* stands out on account of its extreme virulence. Fortunately, the incidence in CAP is low, and this etiology should be considered in patients with structural lung disease and patients with neutropenia. However, in a recent study²⁹ in patients admitted to the ICU

with SCAP our group found *P. aeruginosa* in only eight patients (3.9%), but seven patients died. Interestingly, *P. aeruginosa* was fourth in the ranking of lethal pathogens in intubated patients and was not predicted by the presence of comorbidities.²⁹ This finding suggests that empiric therapy for SCAP in intubated patients should be active against this pathogen because a delay in therapy is associated with increased mortality.²⁹

Chlamydia pneumoniae is one of the least well understood organisms as it has been detected in the most recent studies.²² In South America the incidence of *C. pneumoniae* and *Mycoplasma pneumoniae* was reported at about 10%.^{30–32} A recent prospective cohort study³³ in Canada reported that only 2.2% (12/539) of patients have acute *C. pneumoniae* pneumonia and an additional 5.9% (32/539) had possible acute infection. Interestingly, in only 38% patients, *C. pneumoniae* was the sole pathogen finding. In 62% of cases, this microorganism was isolated as a co-pathogen to *S. pneumoniae* and respiratory syncytial or influenza virus. These results suggest that *C. pneumoniae* is an important cause of CAP, but the true role in SCAP is uncertain.

Finally, in a high percentage of patients (30% to 50%) the causative agent is impossible to determine. The frequency of this situation varies among studies for several reasons, depending on diagnostic methods. Recently, Menéndez et al.,³⁴ using polymerase chain reaction (PCR) techniques, confirmed that in patients with unknown etiology, *S. pneumoniae* was the most probable cause.

Diagnosis

The usefulness of diagnostic testing in the management of CAP is a subject of controversy.³⁵ Therefore, the empiricism is the usual approach in many patients with CAP. Indeed, some guidelines strongly recommend it.⁷ Several previous reports^{36,37} have evaluated the impact of diagnostic testing in the population hospitalized in medical wards. They state that knowledge of the pathogen may not affect clinical outcome, concluding that routine microbiological investigation is unhelpful and is probably unnecessary. However, knowledge of the causative agent is useful, given the possibility of adjusting antibiotic treatment. In our experience²⁹ the result of microbiologic investigation in the clinical setting of critically ill patients led to a change in therapy in approximately 40% of cases. Moreover, the identification of the microorganism after the initial incorrect empirical therapy and subsequent correction of treatment to cover the offending pathogen was followed by clinical resolution in seven of 11 patients. In addition, performing microbiologic studies led to simplification of treatment in one-third of patients, reducing antibiotic expense, helping to reduce side effects, and preventing antibiotic abuse.

At clinical practice, in SCAP, we recommend obtaining at least two blood cultures and respiratory samples for culture and Gram stain. However, it is extremely difficult (only 20%) to obtain a good sputum sample (more than 25

Table 3.3. Advantages/Disadvantages of the Sputum Gram Stain

Advantages

- Easily within risk
- Provides early information about specific pathogen
- Can be used as a guide to treatment
- Inexpensive

Disadvantages

- Difficult to obtain
- Errors of interpretation
- Skilled microbiologist required
- Insensitive

Modified from Jasovich A, Soutric J, Morera G, et al. Efficacy of amoxicillin-sulbactam, given twice a day for the treatment of community-acquire pneumonia. A clinical trial based on a pharmacodynamic model. J Chemother 2002;14:591–6.

neutrophils and fewer than 10 epithelial cells per microscopic field (<100)) for Gram stain from these patients.³⁸ In addition to the difficulty of obtaining the sample, the interpretation of the results is complicated and depends on the diagnostic criteria used, and a skilled interpreter³⁹ Table 3.3 shows the advantages and disadvantages of the sputum Gram stain in the diagnosis of CAP. The proper interpretation of Gram stain can be affected by staff training and previous use of antibiotics. Indeed, previous antibiotic use may sterilize cultures, particularly in cases due to *H. influenzae* and *S. pneumoniae*.⁶ However, the sputum induced by hypertonic saline solution has proved to be a good tool for *Pneumocystis carinii* and tuberculosis investigation, especially in AIDS.

In many countries of South America the sputum Gram stain is frequently of limited value because many patients receive antibiotics before admission (self-medication) and a skilled microbiologist is not always available.

Blood cultures (BC) are considered a standard of care for patients hospitalized for CAP. They are positive in around 10% to 30% of patients with CAP^{6,40} and are included in all major contemporary guidelines for CAP management.^{1,41} However, the clinical value of routine BC has been questioned.^{42,43} Recently, Campbell et al.⁴³ found that BC have limited usefulness in the routine management of patients with CAP. Sanyal et al.⁴² found no difference in mortality between patients in whom antibiotics were changed empirically (64%) and in those who experienced change as a result of positive microbiologic study (67%). Similar findings reported by other authors³⁷ indicated a mortality of 16% in patients with blind change in antibiotic therapy versus 25% in those who underwent microbiologically guided change. The blood culture dates did not have a significant impact in directing antibiotic changes.³⁶ In this study, 93 patients admitted with SCAP, of whom 69 (74%) had failed initial empirical antibiotic therapy, showed little benefit from microbiologic studies.

In these studies, the antibiotic therapy was changed very much later. Initial appropriate empiric antibiotic therapy is critical, particularly in critically ill patients.^{24,29,44} The late confirmation of bacteremia may occasionally be of help to verify retrospectively the diagnosis in patients with SCAP, but a late change in antibiotic therapy does not improve the outcome. The identification of a microorganism not covered by initial empiric therapy will not have a beneficial effect on survival within the first days after admission. However, our group⁴⁵ showed that an early change (less than 48 hours) in the therapy guided by culture dates from samples obtained within the first 12 hours after admission permitted rescue and clinical resolution in two-thirds of patients.

A prospective study of patients with CAP³⁹ showed that the yield of blood culture increases significantly with the severity of pneumonia and that positive cultures only impacted on the management of critically ill patients (PSI IV and V). The ICU patients with SCAP have these levels of severity. We believe that despite low sensitivity of blood culture, 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 (two samples) all argue in favor of obtaining blood cultures in patients requiring ICU admission.

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 90%, and specificity is nearly 100%.¹⁸ The main drawback is that only serogroup 1 can be detected, although serogroups account for more than 70% of *Legionella* infection. A negative urinary antigen test does not rule out legionellosis, but a positive test is highly specific. In both the ATS⁴⁶ and the Canadian guidelines⁴¹ the urine test for *Legionella* spp. is recommended in patients with CAP. This test is not influenced by previous use of antibiotic and can remain positive for a long time after pulmonary infection. Currently, techniques based on PCR and latex agglutination are available, especially in the case of the *Pneumococcus*. Procedures based on PCR techniques can be applied to noninvasive samples. Sensitivity remains high despite antibiotic treatment. In addition, the results are available within only a few hours. However, the high cost of these procedures and the lack of well-prepared laboratories preclude their worldwide use.

Other useful diagnostic tools are based on invasive tests. There is considerable controversy about the role and use of invasive testing in the diagnosis of CAP. The use of bronchoscopy for patients with CAP who had failed initial management has identified an infectious agent in fewer than 30% of patients.^{35,47} Bronchoscopy is easy to perform when a patient is intubated, but it tends to be little used because the necessary laboratory equipment and well-trained bronchoscopy staff are frequently not available. Furthermore, in nonintubated patients, respiratory failure constitutes a relative contraindication, given the possibility of speeding up urgent intubation. In the most recent guidelines for CAP management,^{8,41,46} bronchoscopic sampling is recommended for particularly severe, selected cases but not for all patients un-

der mechanical ventilation. The few studies undertaken in SCAP have reported that the reliability of bronchoscopy is high. However, in immunocompromised patients (those who have HIV infection, are under steroidal therapy, or have had a transplant) or in those with a high suspicion of atypical microorganisms, bronchoscopy with bronchoalveolar lavage (BAL) is the first step in the diagnostic approach. The availability of a skilled bronchoscopist and an experienced microbiologist is a key factor in the decision of whether to perform invasive sampling on ICU admission.

Mortality and Associated Factors

Despite advances in antibiotic treatments and technical improvements in ICU care, SCAP mortality remains unacceptably high. In different studies of SCAP that required ICU admission, crude mortality is around 20% to 54%.^{23,24,29,40} A recent metaanalysis by Fine et al.⁴⁸ confirmed these data on mortality. In that study 33,148 patients were evaluated from 127 publications. Thirteen of these studies were of patients admitted to the ICU. Mortality in hospitalized patients was 14%, and was 36.5% among those admitted to the ICU. Several factors have been associated with poor outcome.

Age has been considered for a long time as a risk factor. A study from Canada by Marrie et al.⁴⁹ in a population older than 65 concluded that the mortality rate increased with age, reaching 61% in those more than 71 years of age. In a case-control study (those more than 65 years of age) performed in 101 pneumonia patients, Riquelme et al.⁵⁰ concluded that the risk factors of CAP in this group were gastric aspiration and malnutrition. The two groups were similar with relation to age, gender, and day of admittance. The significant prognostic factors were bedridden patients (relative risk-RR, 10.7), deglutition impairment (RR, 7.3), lack of fever (RR, 10.5), respiratory rate in excess of 30/min (RR, 5.2), and bilateral and multilobar (more than three lobules) involvement in chest radiography (RR, 2.3). Recently, Fernandez-Sabe et al.⁵¹ observed that early mortality and overall mortality were significantly higher in very elderly patients (those more than 80 years of age). The factors independently associated with 30-day mortality were altered mental status on admission (Odds Ratio-OR, 3.6), shock (OR, 10.6), respiratory failure (OR, 3.5), renal failure (OR, 5.8), and Gram-negative pneumonia (OR, 20.2). Finally, age of more than 65 years (OR, 3.5) and albumin of less than 30 g/dL (OR, 4.7) were factors independently associated with the mortality for Lim et al.⁵²

However, age itself was not a factor that indicated a bad prognosis. The microbial virulence, bacterial burden, and patients' underlying diseases are very important prognostic factors. In a prospective study performed in COPD patients admitted for CAP,⁵³ 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 four ICUs⁴⁴ crude mortality in exacerbated COPD patients was

24%. This level of mortality was not related to COPD status but to multiorgan failure. However, when mortality was evaluated at 180 days, underlying disease was clearly related to mortality. Severe COPD patients had fewer possibilities of survival than less severe COPD patients. Finally, in the metaanalysis by Fine et al.,⁴⁸ neither COPD nor alcoholism were among the 11 prognostic significant factors.⁵⁴ These results agree with our findings in elderly patients²⁴ In that study, comorbidities were not related to pneumonia outcome, excepting immunosuppression.

Impact of the Use of Guidelines on Mortality

Several studies using multivariate analysis have shown that inadequate antibiotic treatment is associated with a significant increase in mortality.^{23,24,29,55} In a multicenter, retrospective study⁵⁶ of more than 14,000 patients older than 65 years with CAP, Meehan et al. reported that delaying the start of antibiotic treatment by more 8 hours and failure to perform blood cultures within the first 24 hours were associated with increased mortality at 30 days of admission. In spite of these findings, other studies that specifically addressed SCAP in the ICU reported that the correct adherence to guidelines did not increase survival.^{2,57} In these studies² of 57 SCAP patients, the management guidelines were adopted but without a reduction in mortality. The mortality was 58% versus 54% prior to ATS guidelines. In Chile, Saldías Peñafiel et al.⁵⁷ reported that the use of macrolides combined with β -lactams had no effect on clinical course or prognosis in patients with CAP. Considering the low prevalence of multiresistant pneumococci and the low incidence of atypical pathogens in many countries of South America, no clinical and/or bacteriologic basis exists for using foreign guidelines.

Therefore no simple set of guidelines is applicable to every patient. Ultimately, treatment decision depends on good clinical judgment and must take into account patient demographics, local antibiotic resistance patterns, and epidemiologic data. A great variability may be noted among different countries in the selection of first-choice antimicrobial agents. This may be because of many microbial causes of CAP and specialties involved, as well as different health-care systems, which affect the availability or cost of antibiotics. Therefore, each country should develop local evidence-based guidelines for the initial management of CAP. Recently, in South America a committee of physicians with a strong interest in CAP recommended initial antimicrobial treatment of CAP on the basis of local evidence.⁵⁸

Antibiotic Treatment

Usually, antibiotic treatment is started empirically, trying to cover the most frequent microorganisms and taking into account the risk factors for specific agents. For accurate treatment, it is critical to identify whether pulmonary

infection is due to *P. aeruginosa*, *Legionella*, or penicillin-resistant pneumococci (PRSP). Given that clinical differentiation is usually inaccurate, most guidelines recommend expanded-spectrum antibiotic therapy. A combination of two antibiotics is generally preferred.

P. aeruginosa is a possible agent in CAP only in certain settings and requires specific therapy. The 2001 update of the ATS guidelines⁴⁶ recommends that this pathogen be considered only when specific risk factors (bronchiectasis) are present. Our group²⁹ reported that patients with SCAP who underwent intubation were exposed to significant risk of infection by relatively infrequent but highly lethal pathogens, such as *Legionella* or *Pseudomonas* spp. We suggest that both pathogens be covered (in addition to the pneumococcus, of course) in the empiric therapy of all intubated patients while awaiting bacteriology results.

In the IDSA guidelines¹ for ICU patients, third-generation cephalosporin such as cefotaxime or ceftriaxone (or β -lactam/ β -lactamase inhibitors) plus macrolide or fluoroquinolones are recommended. The use of macrolides (or new quinolones) is due to the high incidence of *Legionella* infection. In a recent study, our group⁵⁹ evaluated the different antibiotic choices and their relation to outcome in patients with SCAP. The mortality was similar in patients receiving a macrolide alone (18%) and in those who received it in combination with β -lactam (27%). Interestingly, we found an excess mortality (14%) for initial treatment with an aminoglycoside alone or with another agent. In addition, no different mortality was found between monotherapy or combination therapy. However, these results should be reevaluated for South America, where the prevalence of PRSP and legionellosis is low.^{20,21,60}

In some geographic areas PRSP has become an important problem. Data for invasive isolates collected in 2001 by European Antimicrobial Resistance Surveillance System (EARSS) identifies Spain and Greece as having the highest (more than 30% of isolates) frequencies of penicillin resistance, followed by 10% to 29% in Belgium, Poland, Hungary, and Slovenia.²² The association between penicillin resistance and adverse clinical outcome has been well documented for meningitis but is not well defined for pneumonia.³⁵ Despite some reports of poor outcome among patients infected with intermediate-susceptibility strains, most current available evidence indicates that standard treatment with adequate doses of β -lactams is effective against pneumococcal pneumonia caused by strains with minimal inhibitory concentration (MIC) of less than 1 μ g/mL. A recent study⁶¹ of 100 consecutive patients with bacteremia pneumococcal pneumonia identified discordant therapy using the 2002 National Committee for Chemical Laboratory Standards (NCCLS) breakpoints as a significant variable associated with mortality (OR, 27). Using cefotaxime or ceftriaxone, the risk of discordant therapy is only 2%. Cefuroxime should not be used because it has a significant association with mortality.⁶²

In South America a study by Artemis, carried out from 1997 to 1998, analyzed 600 strains of *S. pneumoniae*. This study found that 18.5% patients were resistant to penicillin. Nearly half of these cases were highly resistant (minimal inhibitory concentration MIC >2).⁶³ Other studies confirmed these

data with 20% to 25% of PRSP.⁶⁴ In a recent international study⁶³ the incidence of PRSP in Argentina was 2.6% and 18.7% in Brazil. These results agree with other studies in Argentina, specifically designed to compare the frequency of PRSP.⁵⁸ In 121 patients with CAP only two (4.4%) *S. pneumoniae* strains with decreased susceptibility to penicillin (MIC 0.25 to 1 µg/mL) were found among 45 isolates recovered. On the basis of the current evidence, the clinical impact of the PRSP on CAP management in South America is poor.start here

Because of the worldwide increase in PRSP and the high incidence of *Legionella* spp. infection in SCAP (not in South America), newer antibiotics have been developed to cover both microorganisms. Newer fluoroquinolones (levofloxacin, grepafloxacin, moxifloxacin, and trovafloxacin) seem to offer good coverage against PRSP and *Legionella*, and excellent lung tissue levels have been reported. These antibiotics might be a good alternative for CAP patients with β -lactam hypersensitivity. Unfortunately, no clinical trials in patients with SCAP are available, and their use in critically ill patients is not supported by evidence.

Shock Management

Hemodynamic instability is defined by the need for vasoactive drugs, once the hypovolemic state has been corrected, in order to achieve a mean arterial blood pressure (MAP) sufficient to preserve peripheral perfusion. About 25% to 50% of patients with CAP have shock septic criteria when admitted to the ICU.

The specific management of patients with SCAP and shock does not differ from that of the general population with septic shock.⁶⁵ The volume repletion in patients with septic shock produces increases in cardiac output and oxygen delivery, and generally is enough to reverse hypotension.⁶⁶ However, the requirements of volume are not easily determined in critically ill patients. We believe that central venous pressure (CVP) is initially required to assess intravascular volume. If CVP increases or the patient develops respiratory failure and requires mechanical ventilation, a pulmonary artery catheter is necessary before administration of vasoactive drugs. In addition, patients should have an arterial catheter in place for continuous blood pressure monitoring and withdrawal of blood samples.

Dopamine is the first approach to patients with septic shock. It increases mean arterial pressure (MAP) primarily by increasing cardiac index. High doses of dopamine increase systemic vascular resistance and might impair splanchnic blood flow.⁶⁷ We suggest that the dopamine doses not exceed 10 mg/kg/min, and norepinephrine should be administered (alone or with dopamine) to improve MAP.

Norepinephrine is probably more effective than dopamine at reversing hypotension in septic shock patients. Norepinephrine usually causes a clinically significant increase in MAP (vasoconstrictive effects) with little change

in heart rate or cardiac output.⁶⁸ In addition, it significantly improves glomerular filtration, and this is particularly true in hyperdynamic septic shock.⁶⁶ We believe that norepinephrine should be used early in septic shock and not as a final tool.

The precise level of MAP is not entirely certain and is likely to vary among patients. Assessment of regional and global perfusion should be evaluated by mixed venous oxygen saturation,⁶⁹ blood lactate levels (>2 mEq/L)⁷⁰ or gut tonometry⁷¹ to guide optimum reanimation. We believe that the goal of resuscitation in shock is the restoration of tissue perfusion and normalization of cellular metabolism and not simply to reverse the hypotension.

Treatment of Refractory Hypoxemia

Among patients admitted to the ICU for SCAP, between 58% and 88% need mechanical ventilation.^{6,38} The goal in these patients is to improve gas interchange, keeping plateau pressure low (< 30 mmHg) in order to avoid acute lung injury.

The main drawback of intubation and invasive mechanical ventilation is that it increases the probability of superinfections. New forms of ventilation without intubation have been promoted in recent years.^{72,73} Noninvasive forms of ventilation (NIV) have been tested in several diseases and are very useful in COPD patients. In SCAP patients, Confalonieri et al.⁷⁴ reported that NIV was associated with a significant reduction in the rate of endotracheal intubation and duration of ICU stay. In addition, a significant reduction of mortality was observed in COPD patients. On the other hand, despite initial improvement in arterial oxygenation with NIV in patients non-COPD with SCAP, the intubation rate was high (66%).⁷⁵ However, the more favorable outcome and shorter ICU stays were observed when intubation was avoided.

In general, our policy is to implement NIV whenever possible 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 and the nature (severity) of the acute lung injury.

SCAP is associated with acute respiratory distress syndrome (ARDS) in about 10% of cases.³⁸ When ARDS is developed, mechanical ventilation is needed, requiring high levels of oxygen delivery as well as high levels of PEEP to ensure arterial oxygen saturation of 90%. Two goals in this context are the maintenance of low FiO_2 and tidal volume. In general, it is desirable to achieve a level PEEP that maintains FiO_2 below 0.6 whenever possible. A protective ventilatory strategy using low tidal volumes improves survival in patients with ARDS.⁷⁶ Alveolar recruitment (open lung therapy) maneuvers and placement of patients in a prone position as early rescue adjunctive therapy for severe hypoxemia have been tested.

Conclusion

SCAP is an important challenge for clinicians, because of the high rate of mortality despite the use of new antibiotics and sophisticated technology in the ICU setting. ICU admission and management show important divergences regarding clinical practices and should be tailored for each patient. The guidelines for initial management should be adjusted for each country or each institution and patient. Prognostic scoring rules are adjunctive tools but should not be applied to individual patients to guide ICU admission. Although risk factors of mortality are well known, pneumonia is a dynamic process that needs careful evaluation within the first hours of onset. Blood cultures, Gram stain, and urinary detection of antigens should be done.

Given the relevance of pulmonary infection due to PRSP (throughout the world) and *Legionella* spp. (some countries), we believe that antibiotic treatment must cover these microorganism in critically ill patients when SCAP etiology is unknown. In addition, antibiotic coverage for *Pseudomonas* might be necessary in intubated patients with SCAP even if risk factors are not present. Early recognition of severity, adequate empirical antibiotic therapy, and improvements in adjunctive therapy for multiorgan dysfunction are key elements for improving outcome.

We believe that cefotaxime/ceftriaxone should be the cornerstone of therapy in those patients with a high prevalence of PRSP in combination with macrolide, whereas new fluoroquinolones should be reserved for allergic patients or documented *S. pneumoniae* with MIC of more than 4 µg/mL, which is isolated very infrequently.

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References

1. Barlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults. Clin Infect Dis 2000;31:347–82.
2. Hirani NA, Macfarlane JT. Impact of management guidelines on the outcome of severe community acquired pneumonia. Thorax 1997;52:17–21.
3. Almirall J, Bolibar I, Vidal J, et al. Epidemiology of community-acquired pneumonia in adults: a population-based study. Eur Respir J 2000;15:757–63.
4. Jokinen C, Heiskanen L, Juvonen H, et al. Incidence of community-acquired pneumonia in the population of four municipalities in Eastern Finland. Am J Epidemiol 1993;137:977–88.
5. Lave JR, Lin CJ, Fine MJ, et al. The cost of treating patients with community-acquired pneumonia. Semin Respir Crit Care Med 1999;20:189–97.
6. Gallego M, Rello J. Severe community-acquired pneumonia. In: Rello J, Vallés J, and

- Kollef M, eds. Critical care infectious diseases textbook. Dordrecht: Kluwer Academic Publishers, 2001:37:611–23.
7. American Thoracic Society. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity and initial antimicrobial therapy. *Am Rev Respir Dis* 1993;148:1418–26.
 8. European Study on Community-Acquired Pneumonia (ESOCAP) Committee. Guidelines for management of adult community-acquired lower respiratory tract infections. *Eur Respir J* 1998;11:986–98.
 9. BTS guidelines for the management of community-acquired pneumonia in adults. *Thorax* 2001;56[Suppl 4]:S1–S64.
 10. Ewing S, Ruiz M, Mensa J, et al. Severe community-acquired pneumonia: assessment of severity criteria. *Am J Respir Crit Care Med* 1998;158:1102–8.
 11. Research Committee of British Thoracic Society and the Health Laboratory Service. Community-acquired pneumonia in adults in British hospitals in 1982–83: a survey of aetiology, mortality, prognostic factors and outcome. *Q J Med* 1987;62:195–201.
 12. Arnold FW, Ramirez JA, McDonald LC, et al. Hospitalization for community-acquired pneumonia. *Chest* 2003;124:121–4.
 13. Fine MJ, Auble TE, Yealy DM, et al. A predictive rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;336:243–50.
 14. Rosón B, Carratalá J, Dorca J, et al. Etiology, reasons for hospitalization, risk classes, and outcome of community-acquired pneumonia in patients hospitalized on the basis of conventional admission criteria. *Clin Infect Dis* 2001;33:158–65.
 15. Marras TK, Gutierrez C, Chan C. Applying a prediction rule to identify low-risk patients with community-acquired pneumonia. *Chest* 2000;118:1339–43.
 16. Zalacain R, Torres A, Celis R, et al. Community-acquired pneumonia in the elderly: Spanish multicentre study. *Eur Respir J* 2003;21:294–302.
 17. El-Ebiary M, Sarmiento X, Torres A, et al. Prognostic factors of severe *Legionella* pneumonia requiring admission to ICU. *Am J Respir Crit Care Med* 1997;156:1467–72.
 18. Roig J, Rello J. Legionnaires' disease: a rational approach to therapy. *J Antimicrob Chemother* 2003;51:1119–29.
 19. Roig J, Sabria M, Pedro-Botet ML. *Legionella* spp: community acquired and nosocomial infections. *Curr Opin Infect Dis* 2003;16:145–51.
 20. Lopardo G, Sturba E, Martínez ML, et al. Detection of acute infection due to *Legionella pneumophila* in patients with community acquired pneumonia in Buenos Aires city. *Medicine (B. Aires)* 2002;62:145–8.
 21. Cabello H, Cortes C, Ruiz M, et al. Community acquired pneumonia. Report of 8 cases of severe pneumonia by serogroup 1 *Legionella pneumophila* in Chile. *Rev Med Chil* 2002;130:309–13.
 22. Woodhead M. Community-acquired pneumonia in Europe: causative pathogens and resistance patterns. *Eur Respir J* 2002;20[Suppl 36]:20S–27S.
 23. Pachón J, Prado MD, Capote F, et al. Severe community acquired pneumonia: etiology, prognosis and treatment. *Am Rev Respir Dis* 1990;142:369–73.
 24. Rello J, Quintana E, Ausina V, et al. A three-year study of severe community acquired pneumonia with emphasis in outcome. *Chest* 1993;103:232–5.
 25. Moine P, Vercken JB, Chevret S, et al. Severe community-acquired pneumonia: etiology, epidemiology, and prognosis factors. *Chest* 1994;105:1487–95.
 26. Leroy O, Santré C, Beuscart C, et al. A five-year study of severe community-acquired

- pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. *Intensive Care Med* 1995;21:24–8.
27. Rello J, Rodríguez R, Jubert P, et al. Severe community-acquired pneumonia in the elderly: epidemiology and prognosis. *Clin Infect Dis* 1996;23:723–8.
 28. Wattanatham A, Chaoprasong C, Nunthapisud P, et al. Community-acquired pneumonia in Southeast Asia. The microbial differences between ambulatory and hospitalized patients. *Chest* 2003;123:1512–9.
 29. Rello J, Bodi M, Mariscal D, et al. Microbiological testing and outcome of patients with severe community-acquired pneumonia. *Chest* 2003;123:174–80.
 30. Jasovich A, Soutric J, Morera G, et al. Efficacy of amoxicillin-sulbactam, given twice a day for the treatment of community-acquired pneumonia. A clinical trial based on a pharmacodynamic model. *J Chemother* 2002;14:591–6.
 31. Soca A, Bazet C, Battistesa S, et al. Severe community-acquired pneumonia. *Pac Crit* 1999;12:96–107.
 32. Bantar C, Bavestrello L, Crucio D, et al. Acute community-acquired pneumonia in adults. Guidelines for initial antimicrobial therapy based on local evidence from a South American Working Group (Conesur). *J Chemother* 2002;14[Suppl 4]:S1–S22.
 33. Marrie TJ, Peeling RW, Reid T, et al. *Chlamydia* species as a cause of community-acquired pneumonia in Canada. *Eur Respir J* 2003;21:779–84.
 34. Menéndez R, Córdoba J, de la Cuadra P, et al. Value of the polymerase chain reaction assay in noninvasive respiratory samples for diagnosis of community-acquired pneumonia. *Am J Respir Crit Care Med* 1999;159:1868–3.
 35. Rello J, Paiva A, Dias CS. Current dilemmas in the management of adults with severe community-acquired pneumonia. In: Vincent JL, ed. *Yearbook of intensive care and emergency medicine*. New York: Springer-Verlag, 2003:162–74.
 36. Ewing S, Bauer T, Hasper E, et al. Value of routine microbial investigation in community-acquired pneumonia treated in a tertiary care centre. *Respiration* 1991;63:164–9.
 37. Waterer GW, Wunderink RG. The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. *Respir Med* 2001;95:78–82.
 38. Leeper KV, Torres A. Community-acquired pneumonia in the intensive care unit. *Clin Chest Med* 1995;16:155–71.
 39. Rosón B, Guidol F. Utility of Gram stain and sputum culture in the management of community-acquired pneumonia. *Clin Pulm Med* 2003;10:1–5.
 40. Ewing S, Torres A. Severe community-acquired pneumonia. *Clin Chest Med* 1999;20:575–80.
 41. Mandell LA, Marrie TJ, Grossman RF, et al. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by Canadian Infectious Diseases Society and Canadian Thoracic Society. *Clin Infect Dis* 2000;31:383–421.
 42. Sanyal S, Smith PR, Saha AC, et al. Initial microbiologic studies did not affect outcome in adults hospitalized with community-acquired pneumonia. *Am J Respir Crit Care Med* 1999;160:346–8.
 43. Campbell SG, Marrie TJ, Anstey R, et al. The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia. A prospective observational study. *Chest* 2003;123:1142–50.
 44. Vallés J, Rello J, Ochagavía A, et al. Community-acquired bloodstream infection in critically ill adult patients. Impact of shock and inappropriate antibiotic therapy on survival. *Chest* 2003;123:1615–24.

45. Rello J, Gallego M, Mariscal D, et al. The value of routine microbial investigation in ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1997;156:196–200.
46. American Thoracic Society. ATS guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity. Antimicrobial therapy and prevention. *Am J Respir Crit Care Med* 2001;163:1730–54.
47. Feinsilver SH, Fein AM, Niederman NS, et al. Utility of fiberoptic bronchoscopy in non-resolving pneumonia. *Chest* 1990;98:1322–6.
48. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community acquired pneumonia: a meta-analysis. *JAMA* 1996;276:134–41.
49. Marrie TJ. Epidemiology of community acquired pneumonia in the elderly. *Semin Respir Infect* 1990;5:260–8.
50. Riquelme R, Torres A, El-Ebiary M, et al. Community acquired pneumonia in the elderly. A multivariate analysis of risks and prognostic factors. *Am J Respir Crit Care Med* 1996;154:1450–5.
51. Fernández-Sabé N, Carratalà J, Rosón B, et al. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics and outcomes. *Medicine (Baltimore)* 2003;82:159–69.
52. Lim WS, van der Eerden MM, Laing R, et al. Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;58:377–82.
53. Torres A, Dorca J, Zalacaín R, et al. Community-acquired pneumonia in chronic obstructive pulmonary disease. A Spanish multicenter study. *Am J Respir Crit Care Med* 1996;154:1456–61.
54. Seneff MG, Wagner DP, Wagner RD, et al. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA* 1995;274:1852–7.
55. Torres A, Serra-Batlles J, Ferrer A, et al. Severe community acquired pneumonia: epidemiology and prognostic factors. *Am Rev Respir Dis* 1991;114:312–5.
56. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcome in elderly patients with pneumonia. *JAMA* 1997;278:2080–4.
57. Saldías Peñafiel F, O'Brien Solar A, Gederlini Gollerino A, et al. Community-acquired pneumonia requiring hospitalization in immunocompetent elderly patients: clinical features, prognostic factors and treatment. *Arch Bronconeumol* 2003;39:333–40.
58. Bantar C, Bavestrello L, Curcio D, et al. Acute community-acquired pneumonia in adults: guidelines for initial antimicrobial therapy based on local evidence from a South American Working Group (ConsenSur). *J Chemother* 2002;14:1–22.
59. Rello J, Catalán M, Díaz E, et al. Associations between empirical antimicrobial therapy at the hospital and mortality in patients with severe community-acquired pneumonia. *Intensive Care Med* 2002;28:1030–5.
60. Luna C, Famiglietti A, Absi R, et al. Community-acquired pneumonia: etiology, epidemiology and outcome at a teaching hospital in Argentina. *Chest* 2000;118:1344–54.
61. Lujan M, Gallego M, Fontanals D, et al. Association of discordant antibiotic therapy and mortality in adults with bacteremic pneumococcal community-acquired pneumonia. *Crit Care Med* 2004;32(3):625–31.
62. Yu VL, Chiou CCC, Feldman C, et al. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotic administered and clinical outcome. *Clin Infect Dis* 2003;37:230–37.
63. Orranti AR, Silva H, Pontani D, et al. El grupo de estudio Artemis para America Latina: el proyecto Artemis, un estudio sobre la actividad de algunos ATB de uso común para

- el tratamiento de las infecciones en diez países de Latinoamérica. *Rev Panam Infectolog* 1998;2:68–75.
64. Guzmán-Blanco M, Casellas JM, Sader HS, et al. Bacterial resistance to antimicrobial agents in Latin America. The giant is awakening. *Infect Dis Clin North Am* 2000;14:67–81.
65. Vidaur L, Rodríguez A, Rello J. ATB therapy for sepsis, severe sepsis and septic shock.:A patient-based approach inspired on “The Tarragona Strategy.” In: *Yearbook of intensive care and emergency medicine*. New York: Springer-Verlag, (in press).
66. Vincent JL. Hemodynamic support in septic shock. *Intensive Care Med* 2001;27:S80–S92.
67. Neviere R, Mathieu D, Chagnon JL, et al. The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. *Am J Respir Crit Care Med* 1996;154:1684–8.
68. Marik PE, Mohedin J. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA* 1994;272:1354–7.
69. Ronco JJ, Fenwick JC, Tweeddale MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA* 1993;270:1724–30.
70. Kellum JA, Kramer DJ, Lee K, et al. Release of lactate by lung in acute lung injury. *Chest* 1997;111:1301–5.
71. Gutierrez G, Palizas F, Doglio GR, et al. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992;339:195–9.
72. Girou E. Prevention of nosocomial infections in acute respiratory failure patients. *Eur Respir J* 2003;42[Suppl]:72–6.
73. Domenighetti G, Gayer R, Gentilini R. Noninvasive pressure support ventilation in non-COPD patients with acute cardiogenic pulmonary edema and severe community-acquired pneumonia: acute effects and outcome. *Intensive Care Med* 2002;28:1226–32.
74. Confalonieri M, Potena A, Carbone G, et al. Acute respiratory failure in patients with severe community-acquired pneumonia: a prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med* 1999;160:1585–91.
75. Jolliet P, Abajo B, Pasquina P, et al. Non-invasive pressure support ventilation in severe community-acquired pneumonia. *Intensive Care Med* 2001;27:812–21.
76. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301.