RECOMMENDATIONS

Recommendations for the Treatment of Severe Nosocomial Pneumonia

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Introduction

Delay in initiating appropriate antibiotic treatment in patients with severe nosocomial pneumonia (SNP) is associated with a more unfavorable prognosis,[1-6] longer hospital stays, and consequently higher healthcare costs. Moreover, in the context of ventilator-associated pneumonia (VAP), changing inappropriate empiric antibiotic regimens after the causative pathogen has been isolated does not significantly improve the initial unfavorable prognosis.[1,2] It would, therefore, seem clear that the choice of an appropriate empiric antibiotic regimen is one of the few factors predicting mortality in cases of SNP that can be modified. On the other hand, it should be remembered that the indiscriminate use of antibiotics and excessively long antimicrobial treatments can lead to the emergence of multiresistant flora and therefore have negative repercussions on the antibiotic policies of hospitals.

Methodology

A task force of experts in the treatment of infectious disease in critically ill patients was formed from the members of the 3 scientific associations who participated in this project. The agenda of this task force was to deal with the following issues related to the treatment of SNP: *1)* a critical review of the existing guidelines and risk categories; *2)* criteria for admission to intensive care units (ICUs) for patients with SNP; *3)* treatment of SNP according to risk category; *4)* special situations associated with the treatment of SNP; and *5)* the follow up that must be carried out during treatment.

Starting with an initial proposal based on a review of the relevant literature, a set of draft recommendations were drawn up. These were then revised and improved jointly by the members of the task force, who debated the content of each recommendation. The overall objective was to draw up guidelines for the rational use of antibiotics in routine practice, whether prescription is empiric or guided by antibiogram. The target public included all professionals who treat patients at risk of contracting nosocomial pneumonia irrespective of the level of care offered by the hospital where they work. In this document we have included information on the degree of consensus on the content of each recommendation reached by the members of the task force attending the final meeting, although in some instances members abstained from giving an opinion because they did not have personal experience of the subject matter.

The recommendations in these guidelines were classified according to the following levels of evidence:[7]

1. Recommendations based directly on scientific evidence.
2. Recommendations based on scientific evidence, supplemented by expert opinion.
3. Recommendations based on expert opinion alone.
4. Recommendations not supported by scientific evidence or expert opinion.

These guidelines are not applicable to children since that population requires specific treatment in keeping with its unique characteristics.

Treatment Protocols for Nosocomial Pneumonia Drawn Up by Scientific Associations. Definition of Risk Categories

Over the last 10 years, clinical research into nosocomial pneumonia (NP) has given rise to a considerable amount of information concerning the pathogenesis, diagnosis, treatment, and prevention of

*A list of the members of the expert committee is given at the end of this article. The Wyeth Farma laboratory in Spain facilitated task force work meetings.

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this disease. The need to provide a systematic review of all this information led to the publication of 2 guideline documents: the first of these, which was published in 1996, was the result of a meeting of experts belonging to the American Thoracic Society (ATS),[8] and the second, which came out a year later, was sponsored by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).[9]

The ATS guidelines make the point that proper management of NP requires close cooperation between lung specialists, intensivists, and infectious disease specialists, an assertion that reflects the spirit of the present document. Both of these guidelines defined the basic schema for classifying patients into groups according to the main variables used to define the etiology and consequently the appropriate treatment of NP. This section summarizes the recommendations for empiric treatment of NP laid down in the 2 earlier guidelines.[8,9]

ATS Recommendations[8]

The spectrum of potentially causative pathogens in NP can be defined by assessment of a variety of factors, including the severity of the pneumonia itself, the presence of risk factors for specific organisms, and the length of time spent in hospital prior to the onset of pneumonia. It has been confirmed that these 3 variables quite adequately determine the causative microorganism in NP.

The severity of pneumonia is defined by the presence of the following variables: ICU admission; severe respiratory failure (defined as the need for mechanical ventilation or the need for a fraction of inspired oxygen >35% to maintain PaO_2 >90%); radiographic progression, cavitation, or multilobar pneumonia; and evidence of severe sepsis with hypotension or organ dysfunction (systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg, need for vasopressors for >4 h, urine output <20 mL/h or 80 mL/4 h, acute rental failure requiring dialysis). This definition of severity is extrapolated from the ATS guidelines for community-acquired pneumonia published in 1993[10] and has not been specifically validated for NP.

The second variable considered was the presence of risk factors for specific microorganisms, which are as follows: *a)* anaerobic microorganisms: recent abdominal surgery or aspiration into the airways; *b) Staphylococcus aureus*: coma, head injury, diabetes mellitus, or renal failure; *c) Legionella* spp: high dose steroids; and *d) Pseudomonas aeruginosa*: prolonged ICU stay, steroid or broad-spectrum antibiotic treatment, and structural lung disease.

The third variable taken into account was the length of hospital stay prior to onset. Five days was the cut-off point used to classify the pneumonia as early (<5 days) or late onset (>5 days) because it has been shown that anomalous colonization of the oropharynx by hospital-acquired flora begins around 5 days after admission.

These 3 variables can be used to classify patients into 3 groups. Each group corresponds to a different group of likely causative microorganisms and, consequently, defines the empiric treatment that should be used:

– Group I: patients with mild to moderate NP, no risk factors, and onset at any time, or patients with early onset NP. The organisms most likely to cause infection in this group are as follows: *Streptococcus pneumoniae; Haemophilus influenzae;* methicillin sensitive *S aureus*; and gram negative enteric bacteria (GNEB), such as *Escherichia coli, Klebsiella pneumoniae, Proteus* spp, and *Enterobacter* spp. These pathogens are called "core organisms" because they are considered to be potentially pathogenic agents in any of the 3 groups.

– Group II: patients having mild to moderate NP with risk factors and onset at any time. In addition to the core organisms, infection in this group may also be caused by anaerobic bacteria in the case of postoperative patients, *S aureus* in patients with altered consciousness, and *Legionella* spp or *P aeruginosa* in patients receiving corticosteroid therapy.

– Group III: patients with early onset SNP and risk factors plus patients with late onset SNP. In this group the possible etiology should include, in addition to the core organisms, multiresistant organisms, such as *P aeruginosa, Acinetobacter* spp, and methicillin resistant *S aureus* (MRSA).

The ATS guidelines also deal with the following issues: the tissue penetration of the antimicrobial agents and their bactericidal mechanism (bactericidal or bacteriostatic); the postantibiotic effect of some antimicrobial agents; the administration of aminoglycosides in a single dose; the indications for single-drug and combination therapy; the duration of antibiotic treatment; evaluation of the response to empiric treatment (pattern of resolution, possible reasons for a lack of response, and response assessment). Because it would take a very long document to deal with all of the above issues we refer the reader to the ATS guidelines for this information.[8]

Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) Recommendations[9]

The SEPAR recommendations were quite similar to those of the ATS guidelines published a year earlier. There were no differences with respect to risk groups. The only differences were in the antibiotic treatments recommended for use. We will not, therefore, give details of these recommendations in this section.

Conclusions

1. The guidelines described above represented the first attempt to systematize the empiric treatment of NP. Although the criteria used to assess patient risk have not changed very much, new scientific evidence has emerged since the recommendations were published, making an update necessary.

2. Recent studies have shown that the duration of mechanical ventilation and the type and duration of prior antibiotic treatment are the factors most significantly associated with the presence of microorganisms potentially resistant to antibiotics.[11]

Recommendations

No guidelines dealing specifically with the treatment of VAP have been published, a situation reflected recently in the recommendations of the European Task Force set up by a group of European societies.[12] The starting point for any recommendations for the treatment of VAP should be the categorization of patients to determine empiric treatment. Level II evidence. Agreement among experts 17/17 (100%).

The most important factor in the etiology of VAP is prior hospitalization. Severity is not a factor that needs to be considered in the categorization of patients with VAP since the need for intubation and mechanical ventilation is in itself an indication of severity. It has been clearly shown that after 5 days of hospitalization changes involving the appearance of hospital-acquired microorganisms may occur in a patient's oropharyngeal flora.[13] Other factors that contribute to changes in colonizing flora should also be taken into account. These include antimicrobial therapy during the preceding 15 days[11] and factors directly related to the host.[8] Finally, information concerning the peculiarities of the flora in each treatment site is essential.[14] Level II evidence. Agreement among experts 17/17 (100%).

Table 1 shows the proposed classification based on the considerations detailed above. When potentially multiresistant microorganisms are endemic in a specific treatment site or hospital, this should be evaluated as a risk factor for the site. Level II evidence. Expert agreement 16/17 (94%).

TABLE 1
Classification of Severe Nosocomial Pneumonia*

Group I. Patients without risk factors who have been hospitalized for less than 5 days
Potential microorganisms
1. Methicillin-sensitive *Staphylococcus aureus*
2. Anaerobic microorganisms
3. Haemophilus influenzae
4. Streptococcus pneumoniae
5. Mixed flora (anaerobic microorganisms plus any of the other pathogens)
Patients in medical or traumatic coma are more likely to be infected by *S aureus,* and patients who have COPD or present aspiration of anaerobic microorganisms, by *H influenzae*

Group II. Patients hospitalized for 5 days or more or with distinct risk factors†
Potential microorganisms:
1. Group I microorganisms, plus the following:
Gram negative enteric bacteria
Enterobacter spp
Escherichia coli
Klebsiella pneumoniae
Proteus spp
Serratia marcescens
2. Potentially multiresistant microorganisms
Pseudomonas aeruginosa
Acinetobacter spp
Citrobacter spp
Stenotrophomonas maltophilia
Methicillin-resistant *S aureus*

†Specific risk factors: COPD with an FEV_1 of <35%, *Pseudomonas*; prior prolonged corticosteroid therapy, *Legionella* spp, potentially multiresistant microorganisms, and *Aspergillus* spp; antimicrobial therapy during the preceding 15 days, potentially multiresistant microorganisms; aspiration (also consider anaerobic microorganisms).

*COPD indicates chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second.

Indications for ICU Admission of Patients With Nosocomial Pneumonia

General Considerations

Most patients with SNP present a varied spectrum of etiological agents. Hemodynamic instability and hypoxemia are the 2 principal causes of death. Early identification of patients at high risk based on studies that have identified predictors of a bad prognosis[8,15-18] facilitates early initiation of specific treatment and support measures that can reduce mortality.[19] Conversely, any delay in the initiation of such measures is associated with a worse prognosis, especially once the patient is suffering from acute respiratory distress syndrome (ARDS) or multiple organ failure.

Transfer to the ICU should be considered in the case of patients who can benefit from special medical or nursing care. ICU admission should not be delayed until the patient requires intubation because the early use of noninvasive positive pressure ventilation can obviate the need for intubation in patients who do, notwithstanding, require intensive monitoring.

The initial evaluation should be made on the basis of respiratory rate and arterial gases after oxygen has been administered via face mask at appropriate concentrations. Chest radiography will provide the necessary information for the assessment of radiographic extension and progression.

Specific Indications for ICU Admission

The presence of any of the following conditions, which were recently evaluated in Spain,[20] justifies classifying a case as severe pneumonia and establishes the need for ICU admission in this setting[8,10]:

1. Severe respiratory failure defined in any of the following ways: *a)* respiratory rate more than 30 breaths/min; *b)* inability to maintain an arterial oxygen saturation over 90% while receiving oxygen via face mask at a concentration greater than 35% (except in patients with chronic hypoxemia); or *c)* requirement for ventilatory support for any reason.

*2. S*evere sepsis with hypotension or multiple organ dysfunction, which is evidenced by any of the following: *a)* presence of septic shock (sepsis with hypotension despite delivery of adequate volume seen in conjunction with hypoperfusion, which may include, but is not limited to, lactic acidosis, oliguria, or an acute alteration in mental state); *b)* requirement for vasopressors for more than 4 hours (patients taking inotropic or vasopressor drugs may not have hypotension when the signs of peripheral hypoperfusion are detected); and *c)* acute renal failure requiring dialysis or diuresis lower than 0.5 mL/kg/h, once other possible causes have been ruled out.

The presence of serious radiographic abnormalities, which are defined as multilobar pneumonia and progression of the pulmonary infiltrates to over 50% in under 48 hours, has been included by some authors as an indication for ICU admission.[20] Such serious abnormalities are indicative of a bad prognosis, and ICU admission is necessary when they are found in conjunction with any of the criteria listed above.[21]

Conclusions

Owing to the fact that SNP is a complex entity associated with high mortality, patients suffering from this disease should be admitted to the ICU for monitoring and treatment. SNP is defined both by the signs directly related to the involvement of the lung parenchyma and by the repercussions of sepsis. Early detection and treatment of the disease leads to a reduction in mortality. However, most cases of SNP present in intensive care units and are associated with the use of mechanical ventilation.

Recommendations

Early ICU admission is recommended for patients with SNP. Any delay in ICU admission increases mortality. Level II evidence. Agreement among experts 17/17 (100%).

In order to be classified as SNP, the case must meet one of the following criteria: respiratory rate over 30; arterial oxygen saturation less than 90% with a fraction of inspired oxygen over 35%; radiographic progression in 48 hours or multilobar pneumonia; requirement for mechanical ventilation (invasive or noninvasive); the presence of severe sepsis, septic shock; or dysfunction of an organ other than the lung. Level I evidence. Agreement among experts 17/17 (100%).

Treatment of Severe Nosocomial VAP

Early VAP Without Risk Factors (Group I)

Various studies have shown that most cases of pneumonia occurring between 48 hours and 5 days after admission are caused by primary endogenous flora, such as *S pneumoniae, H influenzae,* and MRSA, or enterobacteria, such as *E coli, K pneumoniae,* and *Enterobacter* spp. Probably the group of patients most predisposed to infection by primary endogenous flora are those with acute neurological lesions (craniocerebral injury and stroke),[22,23] and a particular relation has been observed between head injury and infection/colonization by *S aureus.*[24] The presence of MRSA in early-onset pneumonia is exceptional, and this possibility need only be considered in certain cases of recently hospitalized patients or patients transferred from chronic care centers.

Early-onset VAP has a mortality of around 24%.[25] VAP elevates health care costs because it prolongs the duration of mechanical ventilation and ICU stays.[26] None of the studies in the literature have been specifically designed to evaluate the efficacy of different antibiotics in the treatment of early pneumonia. The treatment regimens proposed are based on the opinions of experts and are taken from the therapeutic guidelines issued by various scientific societies.[27] The treatment recommended for this group of patients (defined in all cases as low-risk Group I) is monotherapy with amoxicillin-clavulanic acid, cefuroxime, or a third-generation cephalosporin not active against *P aeruginosa*. Combination therapy does not appear to be necessary for this group of patients.[28] When selecting the optimum antibiotic regimen, the physician must take into account the increasing emergence in Spain of organisms resistant to various drugs, especially strains of *S pneumoniae, H influenzae,* and *E coli*. In a recent Spanish study it was reported that 25% of the strains of *H influenzae* tested were beta-lactamase producers, and in some regions this percentage rose to 47.9%. Resistance to clarithromycin was observed in up to 22% of strains.[29] The increase in the resistance of *S pneumoniae* to penicillin, and by extension to other beta-lactam agents, is well known. However, this resistance is not usually important when such antibiotics are prescribed in routine clinical practice.

The fluoroquinolones are currently being used much more in the treatment of severe pneumonia[30] because of their in vitro activity, pharmacokinetic properties, and penetration into lung tissue. However, their indiscriminate use has promoted an increase in resistance to these drugs. In one study, levofloxacin 750 mg/12 h demonstrated the same efficacy as imipenem in the treatment of NP.[31] However, given the variability among cases (not only ventilated patients, not differentiated by risk group, need for the addition of new antibiotics against multiresistant organisms), more studies are required to properly evaluate this finding. Levofloxacin therapy is recommended in patients with adverse reactions to beta-lactams. A combination of aztreonam and glycopeptides also provides appropriate empiric coverage for the causative microorganisms, and is the alternative recommendation for this group of patients.

The recommended empiric treatment for early-onset pneumonia is shown in Table 2.

Conclusions. Early pneumonia in the absence of distinct risk factors is caused mainly by primary endogenous flora and is not usually associated with multiresistant organisms. Onset occurs within 5 days of hospital admission, and the most important determinant of the type of flora is the prior use of antibiotics. In view of the gradual increase in resistance to cephalosporins and macrolides observed in strains of *S pneumoniae* and *H influenzae*, caution should be exercised in the use of these antibiotics in the empiric treatment of early pneumonia. Third generation quinolones are another treatment option.

Recommendations. Early-onset pneumonia may be treated with single-drug therapy using amoxicillin-clavulanic acid or cephalosporins. Third generation cephalosporins are preferable unless precise information is available concerning the sensitivity of the causative pathogens to second generation cephalosporins. Level I evidence. Agreement among experts 17/17 (100%).

At the moment, third generation fluoroquinolones should be considered an alternative treatment until more studies evaluating their efficacy are available. However, given their demonstrated usefulness in the treatment of other types of infections, they may be considered as an alternative treatment. The combination of glycopeptides and aztreonam is recommended as an alternative treatment in the case of patients with adverse reactions to beta-lactam antibiotics. Level III evidence. Agreement among experts 16/17 (94%).

Early-Onset VAP With Risk Factors or Late-Onset VAP (Group II)

Recommended antibiotic regimen. The regimen most frequently recommended is combination treatment with a beta-lactam and an aminoglycoside.[32] The use of empiric single-drug therapy does, in principle, merit consideration given the broad antimicrobial spectrum provided by the modern quinolones and beta-lactams, which provide coverage for most GNEB and *P aeruginosa*. These antibiotics have moderate-to-good penetration into lung tissue, good safety profiles, and a number of studies have demonstrated their efficacy.[33] However, it has been observed that resistant strains frequently emerge during treatment with these drugs, especially strains of *P aeruginosa*, a pathogen often associated with treatment failure.[28] It is, therefore, generally considered that single-drug treatment should not be used in VAP patients having risk factors for infection with *P aeruginosa*.

Combination therapy extends the spectrum of activity. This is of particular importance because the etiology of up to 55% of VAPs is polymicrobial, and combination therapy minimizes the possibility of inappropriate empiric treatment. It can also serve to reduce the development of resistance during treatment[34] and produces better results because of the synergistic effect of the combination. This result has been demonstrated by certain authors who report reduced mortality in serious bacteremic infections caused by *P aeruginosa* or *Klebsiella* spp.[35,36] On the other hand, combination therapy may be more costly and carries a greater risk of toxicity, particularly in the case of regimens including aminoglycosides.[37]

TABLE 2
Recommended Empiric Treatment for Group I Cases of Nosocomial Pneumonia

Empiric Treatment	Alternative Treatment
Single-drug therapy Amoxicillin-clavulanic acid* Non-antipseudomonal second or third generation cephalosporins	Glycopeptide + aztreonam Third generation fluoroquinolone (levofloxacin, moxifloxacin)

*Preferred treatment in neurocritical patients.

It seems reasonable, therefore, that during the initial days of treatment before microbiological results are received, empiric treatment for patients with SNP and risk factors—and especially for patients with multiple organ failure and severe sepsis—should include a beta-lactam agent active against *P aeruginosa* (a cephalosporin, a ureidopenicillin with or without beta-lactamase inhibitors, monobactam, or carbapenem) in combination with an aminoglycoside at optimal dosage.

Combinations of 2 beta-lactam antibiotics offer few advantages and are associated with secondary problems, such as the induction of chromosomal beta-lactamases (which might inactivate both drugs)[38] and hematological side effects.

The combination of a beta-lactam and a quinolone is an attractive option, but its efficacy has not yet been compared to other treatments and the literature contains some references to possible cross resistance between ciprofloxacin and imipenem.[39]

The aminoglycosides achieve maximum efficacy when administered in high doses and in a single daily dose.[40] In order to obtain the required clinical response, a peak concentration 8- to 10-fold higher than the minimum inhibitory concentration (MIC) is required. The use of a single daily dose is more effective and reduces side effects, in particular nephrotoxicity and ototoxicity.[41]

The beta-lactams, on the other hand, seem to achieve maximum bactericidal capacity when administered continuously.[42,43] Topical administration of antibiotics such as colistin, aminoglycoside, and ceftazidime has been used both as a prophylactic measure and as a treatment, particularly in patients with cystic fibrosis.[44] The efficacy of these antimicrobial agents in the treatment of VAP has not been properly evaluated.[45,46]

As a general rule, scientific associations recommend ensuring coverage of the so-called "core microorganisms" of early pneumonias and of the specific pathogens associated with particular risk factors. Such pathogens are generally multiresistant.

In treatment sites where there is a high prevalence of MRSA, a glycopeptide should be included, especially if

the patient has received prior treatment with beta-lactam antibiotics. Recently published data on the efficacy of linezolid in the empiric treatment of VAP showed a survival rate of 80% for patients in the MRSA subset receiving linezolid as compared to 62.5% for MRSA patients treated with vancomycin.[47] However, this study was a retrospective analysis of data from 2 trials neither of which showed this efficacy when analyzed separately. Moreover, the same efficacy was not observed in the *S aureus* group as a whole, and the drug had to be administered to all the patients in order to cover 14% of the infections (with the additional cost this represents). It would, therefore, appear advisable to await further studies confirming these good results.

Duration of antibiotic treatment. The duration of treatment in VAP is a controversial issue, and to date a duration of between 14 and 25 days has been recommended, particularly if the pathogens isolated prove to be multiresistant. Recently, Chastre et al[48] observed the same mortality in patients treated for 8 days as in those treated for 15 days. In both groups, 30% of the pathogens were potentially conflictive (*P aeruginosa, Acinetobacter* spp, *Stenotrophomonas* spp, and MRSA), and 11% of the infections were polymicrobial. However, a significantly higher rate of superinfections and recurrent infections was observed in the group treated for 8 days when the infection was caused by nonfermenting GNEB. This was not observed when the causative microorganism was MRSA.

Therefore, if the clinical response is good and the causative agent belongs to the primary endogenous flora, an 8-day regimen is sufficient. Although Chastre et al[48] have reported that infections caused by MRSA appear to respond in the same way, in view of the high morbidity and mortality reported, we recommend waiting for the results of specific studies undertaken to confirm this finding. Consequently, a longer regimen—at least 14 days—is the current recommendation when multiresistant microorganisms, and in particular nonfermenting GNEB, are involved. In no case should treatment be discontinued before the clinical picture has improved and the patient has been apyrexial for at least 48 hours.

Conclusions. Antibiotic treatment should be started as early as possible.

Empiric treatment should be a combination therapy including antibiotics not previously administered

Antimicrobial therapy should be adjusted or changed according to the results of microbiology.

Treatment protocols should be adapted to the local situation.

If antimicrobial therapy is changed, the new antibiotics must belong to a different group.

Since etiology and resistance patterns may vary according to geographical area, hospital, type of unit, and timing of onset, the guidelines for treating VAP drawn up by the various scientific societies should be adapted to take into account local patterns of etiology and sensitivity.

TABLE 3
Recommended Empiric Treatment for Group II Nosocomial Pneumonia*

Cefepime or piperacillin-tazobactam (particularly in cases involving digestive surgery or aspiration) or carbapenem†
+
Aminoglycosides (tobramycin or amikacin depending on the sensitivity pattern of the hospital)
Consider glycopeptides or linezolid if MRSA is present. Consider replacing the aminoglycosides with ciprofloxacin in cases of renal failure. Use carbapenems initially if *Acinetobacter* spp is multiresistant

*MRSA indicates methicillin-resistant Staphylococcus aureus.
†In vivo and in vitro studies support the hypothesis that these agents may induce resistance.

Recommendations. Treatment should be started as early as possible. Level I evidence. Agreement among experts 17/17 (100%).

S aureus and *P aeruginosa* must always be covered because of their prevalence. Level I evidence. Agreement among experts 17/17 (100%).

Empiric treatment should be a combination therapy chosen with a view to achieving a broad spectrum, reduction of resistance, and a synergistic effect. Level II evidence. Agreement among experts 17/17 (100%).

This combination therapy should include an aminoglycoside plus a beta-lactam antibiotic with activity against *P aeruginosa* and MRSA. The recommended treatment is shown in Table 3. Level II evidence. Agreement among experts 17/17 (100%).

Aminoglycosides should be used at high doses and administered in a single daily dose. Level II evidence. Agreement among experts 17/17 (100%).

In the case of patients who have received prior antibiotic treatment, it is important to prescribe agents from a different antibiotic family. Level III evidence. Agreement among experts 17/17 (100%).

Insufficient evidence has been adduced to confirm the efficacy of combination therapy using a beta-lactam agent plus a quinolone, so that it is preferable that this combination be used as an alternative antibiotic therapy. Level III evidence. Agreement among experts 16/17 (94%).

The quinolones are the alternative to beta-lactam therapy in patients allergic to penicillin. Level III evidence. Agreement among experts 17/17 (100%).

The endemic status of MRSA and multiresistant GNEB should be taken into account; when present, these resistant microorganisms should be covered. Level II evidence. Agreement among experts 17/17 (100%).

Special Situations

VAP Caused by Acinetobacter baumannii

Pneumonia caused by *A baumannii* is found mainly in patients on mechanical ventilation. According to data from the ENVIN study, the frequency of VAP in Spain

has remained quite stable over the last 5 years with a rate of 16.6 episodes/1000 days of mechanical ventilation in 2002, and the maximum frequencies recorded for *A baumannii* were 18% in 1994 and 13% in 1996.[49] These episodes represented around 10% of the late-onset pneumonias in this population.

In recent years, these microorganisms have developed resistance to all the known antibiotic families, and especially to the modern beta-lactams, aminoglycosides, fluoroquinolones, and, more recently, carbapenems. The antibiogram pattern can, however, vary depending on the strains and hospitals in question. Resistance to carbapenems, a recent phenomenon, is particularly worrying, since imipenem was the standard treatment for severe infections, including VAP, caused by *A baumannii*.[50] According to data from the ENVIN study, the percentage of resistance to carbapenems among pneumonias caused by *A baumannii* was 31.2% in 1998, 57.5% in 1999, and 28% in 2000.[49] In a recent multicenter study carried out by the Nosocomial Infection Study Group of the Spanish Society of Infectious Diseases and Clinical Microbiology (GEIH-SEIMC) in patients hospitalized in the ICUs and general wards of over 40 Spanish hospitals, around 40% of the strains of *A baumannii* isolated were found to be resistant to imipenem. In many of these cases, colistin is the only antibiotic that sustains in vitro activity, and it has been suggested that this antibiotic should be used as a single-drug treatment in patients with this type of pneumonia. Over the last 3 decades, systemic colistin therapy has been used only very rarely owing to the drug's nephrotoxicity and because it was considered to be less potent than the beta-lactams, aminoglycosides, and fluoroquinolones. Although the clinical information available to date concerning its use in the treatment of VAP caused by *A baumannii* is scant, some trials demonstrate the efficacy and low toxicity of intravenous colistin.[51]

In light of the difficulty of treating these infections and the mortality associated with them, it is reasonable to consider the possible contribution of topical treatment with aerosolized colistin. Although no comparative information is available on this treatment, the high concentrations of antibiotic that can be achieved using aerosols in the bronchi and the peculiarities associated with systemic colistin therapy make the topical administration of the drug preferable in cases of infection caused by strains resistant to carbapenems. When calculating the dose, the physician should take into account the fact that a vial of colistin contains 1 000 000 U or 80 mg of colimycin sulphomethate (equivalent to 33.3 mg of base colistin); the aerosols are administered at doses of 500 000-1 000 000 U (16.6-33.3 mg of base colistin)/6 h diluted in 5 mL of physiological serum.

A recent study compared the efficacy of colistin to that of the beta-lactams, the aminoglycosides, and rifampicin in a model of pneumonia caused by *A baumannii* in mice.[52] The results of the comparison demonstrated that colistin was the least effective antibiotic against both infection caused by strains sensitive to the antibiotics studied and even against strains with reduced sensitivity to beta-lactam agents, aminoglycosides, and rifampicin. This would suggest that these antibiotics could be more active than colistin even though they demonstrate lower in vitro activity. The efficacy of rifampicin in this model was particularly notable, despite the fact that the strains studied showed moderate resistance (MIC 8-16 µg/mL). Tobramycin was the most effective aminoglycoside, whether administered alone or in combination.

Conclusions. Pneumonia caused by *A baumannii* is especially predominant in ICUs. The clinical repercussions of this entity appear to be clearly less serious than those of other GNEB, since in endemic situations the isolation of this pathogen may only be a marker of the epidemiological situation. However, there are indications in the data that this infection may be associated with high mortality so that caution should be exercised not to underestimate its importance. Empiric treatment of patients with suspected pneumonia caused by *A baumannii* should depend on the degree of suspicion and the epidemiology of the ICU in question.

Recommendations. Depending on the case, empiric use of a combination of imipenem plus aminoglycosides or colistin would seem to be the most appropriate treatment. The advisability of starting the administration of aerosolized colistin empirically should be considered. The physician should take into account the degree of resistance of the predominant strain in the ICU. Level III evidence. Agreement among the experts 17/17 (100%).

Treatment of strains sensitive to beta-lactams or fluoroquinolones can take the form of single-drug therapy. If the strain is sensitive to any of the beta-lactams which are usually more active (ticarcillin, piperacillin, ceftazidime, cefepime, and imipenem), these antibiotics could be considered to be the best option. Level III evidence. Agreement among experts 17/17 (100%).

In the case of strains with reduced sensitivity to beta-lactam antibiotics (intermediate sensitivity or moderate resistance) and those resistant to fluoroquinolones, the combination of beta-lactams and aminoglycosides is probably the best alternative; in such cases it may be advisable to use aerosolized colistin in addition to the oral treatment (Table 4). Level III evidence. Agreement

TABLE 4
Treatment of Pneumonia Caused by *Acinetobacter baumannii*

Sensitive to or Moderately Resistant to Beta-lactam Antibiotics	Resistant to Sulbactam and Imipenem
Ticarcillin Ceftazidime Cefepime ± aminoglycosides Sulbactam* Imipenem	Colistin ± Rifampicin ± topical colistin

*Dose of 4-8 g/day.

among experts 17/17 (100%).

For the treatment of pneumonia caused by strains with high resistance to fluoroquinolones, aminoglycosides, and beta-lactam agents (including imipenem and sulbactam), the administration of colistin systemically and by aerosol should be considered. It is, however, advisable in such cases to combine this therapy with rifampicin if the strains are sensitive to or show only moderate resistance to this antibiotic (MIC 8-16 µg/mL). The possibility of using rifampicin in other combinations, or of administering other types of antibiotics, such as co-trimoxazole, tetracyclines or macrolides, should be considered in light of the antibiogram for the treatment site. Level III evidence. Agreement among experts 17/17 (100%).

TABLE 5
Antibiotic Dosage Regimen for Ventilator-Associated Pneumonia Caused by *Pseudomonas aeruginosa

Antipseudomonal Beta-lactams	
Piperacillin/tazobactam	4/0.5 g IV every 6-8 h
Ceftazidime	2 g IV every 6-8 h
Cefepime	2 g IV every 8-12 h
Imipenem	1 g IV every 6-8 h
Meropenem	1-2 g IV every 8 h
Aminoglycosides	
Amikacin	15 mg/kg/day IV once daily
Tobramycin	5-7 mg/kg/day IV once daily
Gentamicin	5-7 mg/kg/day IV once daily
Fluoroquinolones	
Ciprofloxacin	400 mg IV every 8 h

*IV indicates intravenous.

VAP Caused by P aeruginosa

SNP caused by *P aeruginosa* accounts for 15% to 20% of nosocomial pneumonias in the United States of America,[53] and between 20% and 45% of the cases of VAP.[54,55] According to the ENVIN study, this pathogen is responsible for 15.9% of all the episodes of VAP in Spanish ICUs.[49] VAP caused by *P aeruginosa* (VAP-P) is a particularly serious entity associated with high mortality (27% to 70%) because of the virulence of the organism and the immune status of the patients affected by this disease.[56,57] The course of the disease is often slow, with frequent relapses, persistent colonization, and recurrent infections owing to the presence of pulmonary lesions.[7] *P aeruginosa* has a notable capacity to develop resistance, even in the course of an appropriate antibiotic regimen.[28] Resistance emerges more frequently when patients are treated with single-drug therapy, whether with beta-lactams, aminoglycosides, or fluoroquinolones.

Another issue in the treatment of VAP-P is the doubtful efficacy of aminoglycosides in infected lung tissue. For this reason aminoglycosides should always be used in combination with other types of antibiotics, and their administration by inhalation has been considered.[12,58] However, aminoglycosides do still play an important role in the treatment of these infections because they have greater intrinsic activity against *Pseudomonas* spp than the beta-lactam antibiotics and a potent concentration-dependent bactericidal action that makes once-daily dosing possible. They also have a marked postantibiotic effect. Tobramycin and amikacin are the most active of the aminoglycosides against *P aeruginosa*.[58]

Of the cephalosporins, ceftazidime, and cefepime have the greatest time-dependent bactericidal activity against *P aeruginosa*. In light of this fact and given the difficulty of treating this class of infections, the usefulness of ceftazidime administered as a continuous infusion has been investigated,[59] although more studies will be needed to confirm the results obtained. Meropenem has greater intrinsic activity against *P aeruginosa* than imipenem. It also has a better toxicity profile so that administration at higher doses is possible.[60] A combination of piperacillin and tazobactam in the treatment of VAP-P is just as effective as carbapenem antibiotics and as the cephalosporins mentioned above.[57,61] The combination of beta-lactams and aminoglycosides often has a synergistic effect, even against strains resistant to one of the 2 agents; some trials have reported this kind of synergy more frequently when piperacillin is combined with tazobactam than when ceftazidime is used.[62] Aztreonam, a monobactam, has received considerable attention as a result of a meta-analysis published by Boucher,[63] a review that highlighted this agent's excellent activity and safety profiles in VAP caused by GNEB.

Of the quinolones, ciprofloxacin has the greatest activity against *P aeruginosa*, although the dose used to treat VAP-P (400 mg/8 h) is higher than that used against other infections. Moreover, ciprofloxacin must always be administered in combination with other antibiotics.[28]

In summary, we recommend the use of antibiotics with a synergistic effect,[64] preferably a broad-spectrum antipseudomonal antibiotic (cefepime, ceftazidime, piperacillin-tazobactam, meropenem, or imipenem) in combination with an aminoglycoside, or with ciprofloxacin.[17] Using a combination of 2 beta-lactam agents is not recommended because this could promote the induction of beta-lactamase and give rise to secondary effects.[38] The choice of combination is conditioned by the antibiogram and the ecological characteristics of each treatment site.

Table 5 shows the antibiotic dosage regimen recommended for the treatment VAP caused by *P aeruginosa*.

Direct instillation of antibiotics via the endotracheal or tracheostomy tube has been used, particularly with aminoglycosides, in an attempt to increase antibiotic concentrations in bronchial secretions and lung tissue while possibly avoiding systemic toxicity.[58] The use of this inhaled route has made it possible to recover the use of antibiotics which had been abandoned because of their inherent toxicity when used parenterally despite their efficacy against multiresistant *P aeruginosa*.

Hamer[65] obtained satisfactory results using aerosolized colistin in 2 patients with VAP-P and in a third patient on mechanical ventilation who had tracheobronchitis caused by multiresistant *P aeruginosa*. Moreover, the good results obtained using a nebulized solution of tobramycin to treat chronic bronchial infection caused by *P aeruginosa* in cystic fibrosis suggest that this treatment could also be effective in VAP-P.[66]

Conclusions. The treatment of pneumonia caused by *P aeruginosa* remains controversial owing to the considerable capacity of this organism to acquire resistance, and the high mortality associated with this type of infection. Various different antibiotic combinations have been shown to be effective in vitro; however, treatment failure is around 20% in almost all case series. Other treatment options, such as continuously infused beta-lactams and aerosolized aminoglycosides, which were trialed with a view to taking advantage of the pharmacodynamic advantages of these routes, have not to date been associated with significant improvements in prognosis.

Recommendations. VAP-P should always be treated with a combination therapy composed of a beta-lactam and an aminoglycoside or else, when this is not possible and particularly in the presence of kidney failure, a third generation quinolone. Level I evidence. Agreement among experts 17/17 (100%).

Among the beta-lactam antibiotics, ceftazidime, cefepime, and piperacillin/tazobactam are the preferred recommendations. The carbapenems should be reserved for special situations or cases of high resistance, and ciprofloxacin for patients who experience side effects with beta-lactams. Level III evidence. Agreement among experts 17/17 (100%).

The duration recommended for treatment with beta-lactam antibiotics is 15 days. Level II evidence. Agreement among experts 17/17 (100%).

If clinical response is adequate it is probable that the aminoglycoside will only be necessary during the first 5 to 7 days. Level III evidence. Agreement among experts 17/17 (100%).

VAP Caused by MRSA

Glycopeptides have been the standard treatment for most MRSA infections in Spain. Consequently, this group of antibiotics is often included in the empiric therapies prescribed in treatment sites where a high percentage of patients have MRSA infections. The resulting high consumption of these agents has increased the risk of such treatment promoting the development of resistance among gram positive cocci.

When analyzing MRSA antibiogram patterns we are well aware that resistance to methicillin implies resistance to all beta-lactams. Until a few years ago, most MRSA infections in Spain were caused by a very predominant clone called the "Iberian clone," which is only sensitive to glycopeptides, co-trimoxazole, chloramphenicol, and fosfomycin. However, a change has recently been observed in the epidemiology of MRSA in both Spain and other European countries with the emergence and growing predominance of other more sensitive clones; the strains isolated in Spain are sensitive to clindamycin in 40% of cases, and to rifampicin in around 80% of cases, as well as to the other antibiotics mentioned above. For this reason, the assumption that any severe MRSA infection requires the administration of glycopeptides may need to be reconsidered in light of current data and the type of infection.

Furthermore, the efficacy of glycopeptides in the treatment of MRSA VAP has been questioned. They are less lethal against *S aureus* than the beta-lactam antibiotics. Therefore maximum concentrations well above the MIC are required to ensure efficacy, and it is difficult to achieve such high concentrations given the potential toxicity and narrow therapeutic range of this drug. Moreover, the need for maximum concentrations could be of particular importance in the treatment of pneumonia because of the poor diffusion within the lung of these antibiotics.[67] The recommended dosage regimen is 1 g/12 h for vancomycin and 400 mg/12 h for teicoplanin. However, the possibility has been considered of using continuous infusion or inhalation to increase these doses. One study reported that the pharmacokinetic and antibiotic activity of vancomycin administered via continuous infusion (500 mg loading dose, followed by 2 g/24 h) was equivalent to that obtained with conventional dosing (1 g/12 h) when adequate peak and trough concentrations were maintained.[68] The information available concerning the inhalation of aerosolized glycopeptides is scant,[69] and the therapy is not risk free.[70]

Experience of treating VAP with other antibiotics, such as fosfomycin and co-trimoxazole, is also very limited.[71,72] In a randomized, placebo-controlled study of severely burned patients, the incidence of MRSA VAP was significantly lower in patients who received a prophylactic administration of trimethoprim-sulfamethoxazole as compared to the placebo group (4.8% vs 36.8%; *P*=.017).[73] In recent years, 2 new molecules, quinupristin/dalfopristin (QD) and linezolid, have been incorporated as possible treatments of MRSA infections including those caused by glycopeptide-resistant strains. Both products are expensive with an average cost of treatment of E 2700 and E 1260 respectively.[74] The bactericidal effect of QD against clindamycin-resistant strains of *S aureus* is not well documented,[75] and to date the Food and Drug Administration of the United States of America has only approved this drug as a treatment for bacteremia caused by vancomycin-resistant *Enterococcus faecalis*. Both of these drugs have demonstrated clinical efficacy similar to that of vancomycin in various comparative clinical trials[76-79]; the experience with linezolid in the treatment of MRSA VAP is, however, still deemed insufficient. A recent study by Wunderink et al,[47] which

did not deal with targeted treatments has generated new expectations for the treatment of MRSA VAP. An important added advantage of these drugs is that dosage adjustment is not required in the case of renal failure.

Given the therapeutic difficulties associated with all of the single-drug therapies mentioned above, and the seriousness of MRSA VAP, the possible benefit of using a combination of antibiotics with a synergistic effect has been considered. Evidence of synergism between vancomycin and various beta-lactam antibiotics, such as oxacillin[80,81] and imipenem,[82,83] has been demonstrated in strains of *S aureus* with a certain degree of resistance to glycopeptides. Synergy between QD and vancomycin, cefepime, ceftazidime, and imipenem has also been described.[75] The problem of synergy is that it is an in vitro phenomenon difficult to extrapolate to clinical situations, and that the clinical benefit of using a combination therapy has not been demonstrated. On the balance, in cases of severe MRSA VAP the combination of vancomycin with rifampicin, clindamycin, or even QD or linezolid may be considered.

Recommendations. Glycopeptides have been the standard treatment for MRSA VAP to date. Level III evidence. Agreement among experts 17/17 (100%).

However, in light of the current appraisal of this treatment, other antibiotic agents should also be considered, such as rifampicin, clindamycin, or fosfomycin, depending on the antibiogram of the causative strain. Level II evidence. Agreement among experts 17/17 (100%).

The activity of vancomycin is equivalent to that of teicoplanin if the dose of the latter is increased, although the toxic effects of the 2 treatments are then equal. The preference for using vancomycin is supported by the fact that most of the trials undertaken have dealt with this antibiotic, the use of which can be monitored by measuring serum levels. Level II evidence. Agreement among experts 17/17 (100%).

The recommendation to increase the dose of vancomycin is not supported by any level of evidence, and the administration of this antibiotic via continuous infusion could reduce toxicity while achieving similar efficacy. Level IV evidence. Agreement among experts 17/17 (100%).

Glycopeptides should not be administered via aerosols. Level II evidence. Agreement among experts 17/17 (100%).

Serum concentrations should be monitored systematically during treatment of VAP with vancomycin in order to ensure the required efficacy and to minimize the possibility of renal toxicity. The profile of the ICU patient with multiple risk factors should be taken into account. Level II evidence. Agreement among experts 17/17 (100%).

Notwithstanding the lack of comparative evidence, it would appear reasonable to use glycopeptides in combination with rifampicin, clindamycin, fosfomycin, and beta-lactams (in the case of glycopeptide-resistant *S aureus*), or even with QD or linezolid (in severe cases or when the clinical course is unfavorable). Level III evidence. Agreement among experts 17/17 (100%).

The new antibiotics with activity against MRSA (QD and linezolid) appear to be as effective (QD) or more effective (linezolid) than vancomycin. At this time, treatment with linezolid could be considered, but the available experience is still scant. Its use as a single-drug therapy should therefore be restricted to glycopeptide-resistant strains or patients with abnormal kidney function. Level II evidence. Agreement among experts 17/17 (100%).

Antibiotics, such as clindamycin and linezolid may have better pharmacokinetic properties and lung penetration than the glycopeptides. Level III evidence. Agreement among experts 17/17 (100%).

VAP Without Microbiological Diagnosis

In 10% to 20% of cases the techniques used to diagnose VAP fail to isolate any pathogen.[84] In Spain, there was no etiological diagnosis in up to 10.6% of pneumonia cases. This figure varies depending on the timing of onset; thus, while in the first episode of VAP the culture was negative in 13.5% of cases, a negative result occurred in only 2.3% of cases in the second episode, and in none in the third.[49]

When no causative pathogen is identified, the patient's condition may be due to the presence of a noninfectious process (atelectasis, heart failure, ARDS)[85] and this may give rise to the inappropriate use of antibiotics. In other cases, the negative result may occur because the patient has received prior antibiotic treatment or may have been receiving such treatment when respiratory samples were taken. The yield of samples taken in these situations can be reduced by over 40%.[86] Very occasionally, the etiology is not bacterial, and other types of diagnostic tests are required.

Singh et al[87] proposed a model for differentiating between pneumonia and noninfectious processes. Their model is based on the Clinical Pulmonary Infection Score (CPIS) developed by Pugin et al,[88] which has been modified (CPISm). Antibiotic treatment was suspended for patients who had a CPIS of 6 or less after 3 days of treatment with ciprofloxacin. This strategy was not associated with any differences in mortality or other clinical or radiographic parameters, but the utilization of antibiotics was lower, fewer multiresistant strains emerged (above all *P aeruginosa*, MRSA, and enterococcus), and the cost of treatment was lower.

In a recent prospective study which evaluated the correlation between CPISm scoring and the course of VAP, Luna et al[89] observed that the course of the illness was satisfactory in patients whose CPISm score went down in contrast to those whose CPISm scores remained higher than 6.

Recommendations. In cases of suspected VAP without microbiological diagnosis, the patient must be

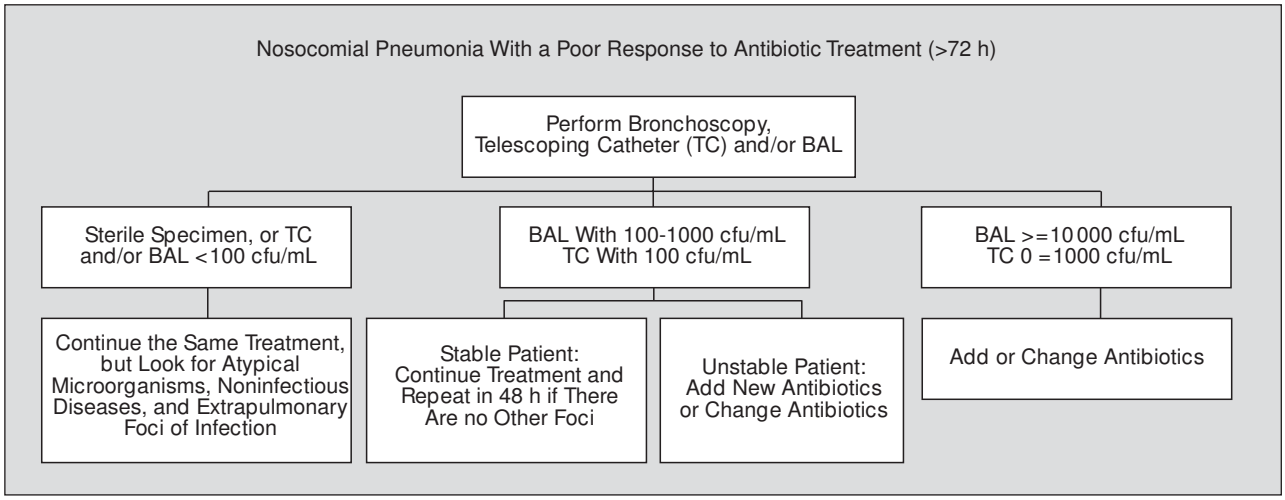

Figure 1. Nonresponding pneumonia characterized by persistence of local and systemic signs of pulmonary infection. BAL indicates bronchoalveolar lavage; cfu, colony forming units.

assessed clinically at onset and again on the third day using CPIS or CPISm scores. If the score is 6 or less, withdrawal of antibiotic therapy is recommended. Level II evidence. Agreement among experts 16/17 (94%).

If the CPIS is greater than 6, more diagnostic tests should be performed using invasive methods, and therapy should be scaled up to cover the microorganisms not previously included. Level III evidence. Agreement among experts 17/17 (100%).

VAP With a Poor Clinical Response

The resolution of VAP, which is based on clinical and microbiological criteria, is not clearly defined. From the standpoint of clinical response, resolution or improvement of VAP corresponds to improvement in or gradual disappearance of the signs and symptoms that determined the diagnosis (fever, purulent secretions) together with the results of complementary tests (number of leukocytes, ratio of PaO_2 to the fraction of inspired oxygen, and radiographic findings).[90] The most important factor in this definition is the period of time that elapses before response to treatment is deemed inadequate. If we use the criteria applied to nosocomial pneumonia in general, the point at which clinical response is normally assessed is 72 hours after start of treatment,[91] although no studies specific to VAP have been carried out in this respect. Three terms are used to define poor clinical response in VAP. The first of these is *progressive VAP*, which is defined as rapid deterioration (≤72 hours) in signs and symptoms despite antibiotic treatment. The second is *nonresponding VAP,* which refers to cases of pneumonia in which the signs and symptoms do not improve in spite of ≥72 hours of antibiotic treatment. And, the third is *slowly resolving VAP*, defined as an improvement in the signs and symptoms but with a radiographic resolution of under 50% in one week.[92] Causes of poor response include factors related to the host and the infecting microorganisms, in addition to noninfectious pathologies. In the case of progressive pneumonia, the most frequent causes of lack of response to treatment are noninfectious pathology, the presence of microorganisms with primary resistance to the empiric antibiotic treatment, highly virulent microorganisms, and a severe systemic response (severe sepsis or septic shock). The most common causes of persistent or slowly resolving pneumonia are noninfectious disease, persistence of the infection (whether caused by the primary resistance of infecting microorganisms not covered by empiric therapy, emerging resistance, inadequate antibiotic dose, or anatomical complications such as empyema or abscess), superinfection by a different organism, or concomitant extrapulmonary infection.[93,94]

Recommendations. In progressive pneumonia (deterioration in the first 72 hours), pending definitive results of initial diagnostic studies, the following possible causes should be ruled out: a noninfectious pulmonary pathology, or an extrapulmonary focus of infection (computed tomography, extrapulmonary cultures, isotopes). Initial empiric treatment should, in addition, be modified by changing the antibiotics or increasing coverage. Level III evidence. Agreement among experts 17/17 (100%).

New lung samples should be obtained via fiberoptic bronchoscopy and tested for unusual pathogens, such as *Legionella, Mycobacterium tuberculosis, Aspergillus,* and *Nocardia*. Figure 1 shows the action that should be taken once an etiological diagnosis has been obtained. Level III evidence. Agreement among experts 17/17 (100%).

Recurrent or Relapsing VAP

Pneumonia is defined as recurrent when a new episode of VAP occurs more than 72 hours after suspension of a course of antibiotics that was correct in terms of spectrum, dose, and duration, and the causative

pathogen isolated is the same organism that caused the previous episode.[95]

Approximately between 18% and 22% of VAP cases may take this course[95-98]; the responsible pathogen is usually *P aeruginosa*, *E coli*, MRSA, or methicillin-sensitive *S aureus*. Using genetic replication techniques, Rello et al[96] demonstrated that 93% of *P aeruginosa* strains isolated in 9 episodes of recurrence corresponded to the same initial microorganisms.

The most important predisposing factors identified by multivariate analysis were ARDS and chronic obstructive pulmonary disease.[96,97] Other notable factors were lack of bronchial drainage, immunosuppression, and the presence of reservoirs of infection (orotracheal intubation, empyema, and abscessed pneumonia).[57,98] Another microbiological finding was that over 50% of the isolates presented resistance to the antibiotics administered during the initial episode.

Recommendations. Recurrent VAP should be highly suspected in patients with prior episodes of VAP caused by *P aeruginosa*, *S aureus,* or *E coli*. Level II evidence. Agreement among experts 17/17 (100%).

Since factors related to the host and microbiological factors are not modifiable, the presence of reservoirs must be actively ruled out. Computed chest tomography is recommended for this purpose. Level III evidence. Agreement among experts 17/17 (100%).

Antibiotic treatment should always be started using antibiotics not previously administered. Level III evidence. Agreement among experts 17/17 (100%).

Monitoring the Treatment of Nosocomial Pneumonia

Antibiotic prescription in patients with VAP should not simply follow a set routine. Such treatment should be followed up by careful monitoring of the clinical response, which is an indicator of efficacy. Physicians should also monitor the appearance of side effects and the selection of new, multiresistant pathogens during or at the end of the course of treatment.[99]

Assessment of Clinical Response

The first assessment of clinical response to treatment must be made 72 hours after the initiation of empiric treatment. The appearance of new signs of infection or of a worsening of the initial signs should lead the physician to suspect that the antibiotics prescribed initially are not appropriate for treating the pathogens causing the pneumonia. In such cases, new lung

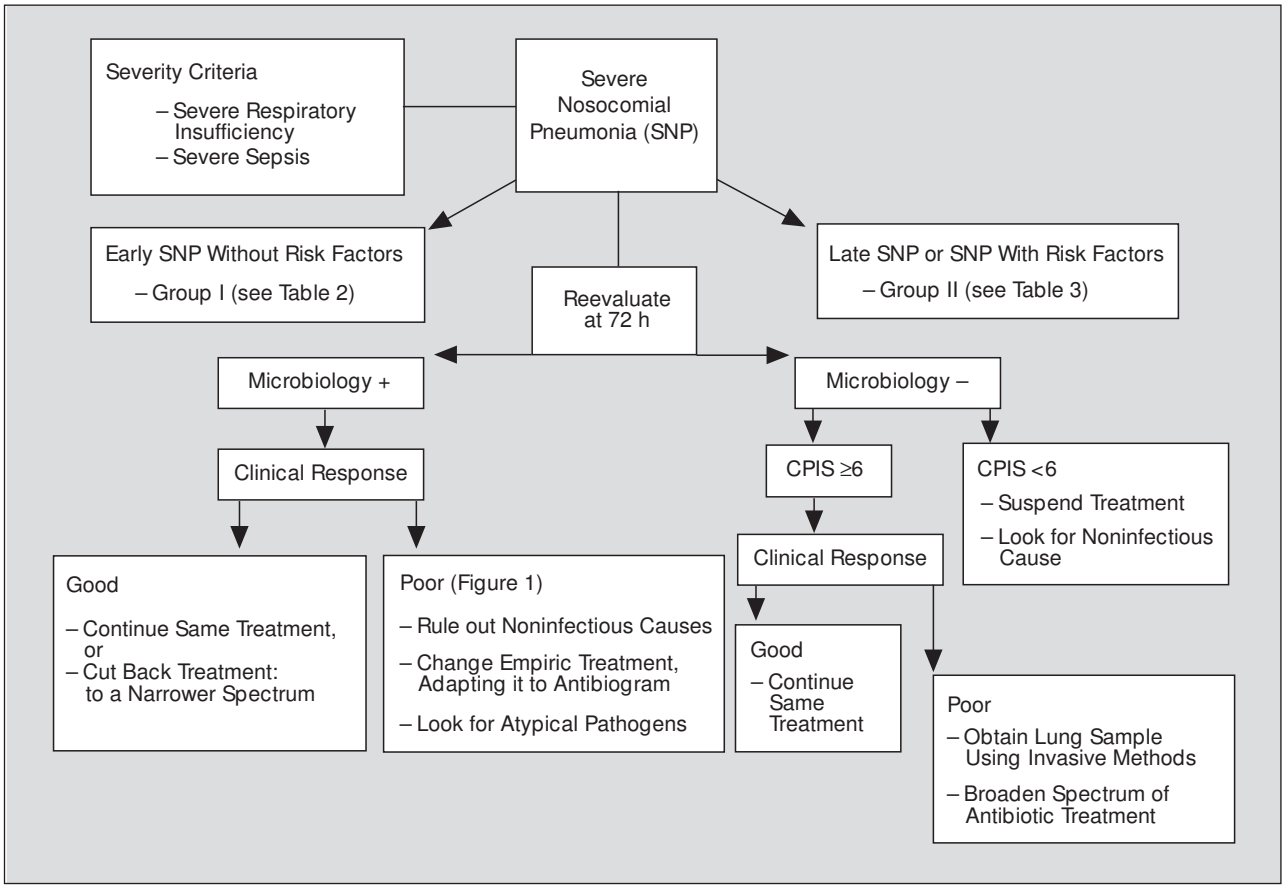

Figure 2. Algorithm for the treatment of severe nosocomial pneumonia.

samples must be obtained (using invasive methods if possible) in addition to new blood samples. The initial antibiotic prescription should be changed, increasing the level of therapeutic intervention with stronger antibiotics, a broader spectrum, and with coverage for less common pathogens. Conversely, when an improvement in the initial signs is observed, treatment should be continued until the causative pathogens are identified and their sensitivity measured. It is then possible to readjust the treatment regimen using the first line antibiotics for each of the organisms isolated.

When a patient's condition deteriorates in spite of antibiotic treatment that is appropriate in terms of sensitivity, the physician should reconsider the pharmacokinetic properties of the antibiotics prescribed in terms of penetration into infected tissues, the dose, and the dosage intervals used with a view to ensuring adequate concentrations of the drug in the focus of infection.

Measurement of Serum Concentrations

Critically ill patients often present hemodynamic abnormalities, renal and hepatic failure, generalized edema, and other complications that affect the metabolism, distribution, and elimination of antibiotics. This gives rise to considerable interindividual variation in the serum concentrations obtained with the same dose. Antibiotic dose must therefore be optimized, particularly in the case of antibiotics, such as aminoglycosides and vancomycin, which have a narrow therapeutic range (the difference between toxic and therapeutic concentrations). Serum concentrations should be measured on the second day of antibiotic treatment when it may be supposed that an equilibrium has been achieved between serum and other compartments in the distribution. Using pharmacokinetic programs specially designed to monitor antibiotics, dosage regimens can be adjusted so as to obtain maximum efficacy with minimum side effects.[100]

Microbiological Monitoring to Detect the Emergence of Multiresistant Strains or of New Pathogens Resistant to the Antibiotics Prescribed

The use of antibiotics to treat patients with VAP promotes the emergence of multiresistant pathogens which can cause the prescribed treatment to fail in a specific patient and also have important epidemiological repercussions. Selection of the flora that make up the ecosystem of each treatment site will determine the future antibiotic policies of that ICU.[101-103]

New samples should be obtained whenever an unfavorable clinical response occurs. The performance of microbiological studies at the end of treatment in patients who continue on mechanical ventilation is not recommended as a routine practice outside the context of epidemiological studies.

Recommendations. Assess the clinical response to treatment after 72 h (±24 h). When the course of the illness is unfavorable, new samples should be taken (preferably using invasive methods), new empiric antibiotic treatment should be prescribed with broader coverage for usual pathogens plus coverage for other, less common, pathogens. If the course of the illness is satisfactory and when the pathogen and its sensitivity are known, treatment should be adjusted accordingly. Level II evidence. Agreement among experts 17/17 (100%).

Serum concentrations of aminoglycosides and glycopeptides should be measured whenever possible. Evaluate whether these measurements need to be repeated in light of the patient's condition and the results of previous tests. Level I evidence. Agreement among experts 17/17 (100%).

Respiratory samples should be analyzed when clinical response is poor. Level II evidence. Agreement among experts 17/17 (100%).

Algorithm for the Treatment of SNP (Figure 2)

– Start empiric treatment guided by timing of onset and presence of risk factors, in particular prior antibiotic treatment. In the case of Group I SNP, initiate single-drug therapy with beta-lactams. In the case of Group II SNP, a combination of an antipseudomonal beta-lactam and an aminoglycoside is recommended. The empiric use of glycopeptides depends on the endemic situation in each treatment site.

– Reevaluate clinical response after 72 hours, and whenever a microbiological result is obtained.

– If clinical response is good and a pathogen has been identified, adjust antibiotic treatment to cover the more specific spectrum, including single drug therapy when multiresistant bacteria are not involved.

– If clinical response is poor, possible causes of persistent SNP should be ruled out, and treatment should be reevaluated in light of the microorganisms isolated and therapy adapted in accordance with the antibiogram. In the case of multiresistant bacteria, the use of synergistic combinations is recommended.

– When clinical response is poor and the causative agent has not been identified, new samples for culture should be obtained using fiberoptic bronchoscopy. These should also be tested for unusual pathogens and the spectrum and type of antibiotic treatment modified accordingly.

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