REVIEW ARTICLE

Drugs 2000 Dec; 60 (6): 1289-1302
0012-6667/00/0012-1289/$25.00/0

Diagnosis of Pneumonia and Monitoring of Infection Eradication

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Abstract

Pneumonia can be classified as community-acquired (CAP) or hospital-acquired (nosocomial). Both are frequent infections that demand a great amount of medical resources.

The diagnosis of CAP is based on clinical signs and the presence of a pulmonary infiltrate visible on chest radiograph. For practical purposes, CAP has been classified as typical, with an acute onset in which the most representative microorganism is *Streptococcus pneumoniae*, and atypical, with a subacute onset (*Mycoplasma pneumoniae*). Nevertheless, so far no studies have clearly demonstrated the utility of this classification in predicting the aetiology. Guidelines on CAP recommend associating the aetiology of CAP with comorbidity, age and severity.

The microbiological diagnosis relies mainly on Gram stain and sputum culture, but this technique has disadvantages such as frequent contamination of the sample with oropharyngeal commensal flora, frequent sterile cultures associated with previous antibiotic treatment, and the fact that approximately 40% of patients are not able to expectorate. Other diagnostic techniques such as blood cultures, serological tests and fibreoptic bronchoscopy must be reserved for patients who are hospitalised, especially if they need admission to an intensive care unit.

Compared with CAP, nosocomial pneumonia has major diagnostic problems due to the presence of other diseases able to mimic pneumonia and frequent bacterial colonisation of the lower respiratory tract. Most of the diagnostic techniques produce a high percentage of false-negative and false-positive results. This is especially true for ventilator-associated pneumonia. There is controversy over using a comprehensive aetiological work-up based on bronchoscopic techniques or only on quantitative culture of endotracheal aspiration. By contrast, there is consensus about the importance of the adequacy of empirical antibiotic treatment, since mortality rates are higher in patients who are inadequately treated.

Once treatment of pneumonia has begun, it must be maintained for 48 to 72 hours because this is the minimum time to evaluate a clinical response. Antibacterial agents have to be adjusted according to microbiological findings. In nonresponding patients, pneumonia-related complications and the presence of multiresistant micro-organisms or non-covered pathogens must be ruled out.

Community-acquired pneumonia (CAP), recognised two centuries ago, is a frequent and potentially lethal illness with global mortality rates close to 14%, which can reach 36% in patients who require admission to an intensive care unit (ICU).[1] Recent studies carried out in the US estimate that approximately 4 million cases of CAP occur annually, with an attack rate of 12 per 1000 adults per year.[2] 20% of these cases required hospitalisation,[3] which means a global cost of $US23 billion per year.[2] CAP is currently the sixth leading cause of death in the US.[2]

Important changes have occurred in the antibiotic era. Before this, almost all cases of CAP were due to *Streptococcus pneumoniae*. Currently, in approximately half of hospitalised patients with CAP, the responsible pathogen is not defined.[4] Although *S. pneumoniae* continues to be the most frequent pathogen isolated,[4] other pathogens, including *Legionella pneumophila*, *L. micadei* and *Chlamydia pneumoniae*, have been found to cause CAP.[5]

Most of the changes observed in the aetiology of CAP are explained by changes in the populations at risk of developing the disease. For example, prolongation of life expectancy has increased the population of elderly patients, who have a higher risk of acquiring CAP.[5] Similarly, immunocompromised patients, such as transplant recipients, those with HIV infection and oncology patients, are susceptible to infection by current pyogenic bacteria and may also have CAP caused by less frequent pathogens, such as Gram-negative bacilli and opportunistic micro-organisms.[6,7]

On the other hand, hospital-acquired or nosocomial pneumonia reaches an average incidence of 5 to 10 cases per 1000 hospitalised patients.[8] This incidence is increased in ICU patients 10- to 20-fold.[9] Nosocomial pneumonia has the highest mortality rate of all nosocomial infections, which ranges from 7 to 70%, depending on the groups studied.[8,10] Ventilator-associated pneumonia is a particular type of nosocomial pneumonia that has very high mortality.[11]

In this article we discuss different aspects related to the diagnosis of CAP and nosocomial pneumonia, and the monitoring of infection eradication.

1. Diagnosis of Community-Acquired Pneumonia

CAP refers to parenchymal lung infections causing infiltrates visible on chest radiographs, in which the causative micro-organism is most likely to have been acquired outside the hospital. Clinical suspicion of CAP includes the presence of new infiltrates in addition to clinical signs of pneumonia (fever, cough, purulent secretions).[12,13] Patients hospitalised during the preceding month have to be considered as having nosocomial pneumonia.[12,14,15]

For reasons that are not clear, aetiological studies usually exclude immunocompromised patients, although they are at particular risk of acquiring CAP.[6,7,16] Residents in nursing homes are also excluded in most of the series, although we believe they should be classified as having CAP.[5]

Classically, 2 types of clinical syndrome have been defined:

- Typical syndrome: defined as an illness with an acute onset of short duration characterised by high fever, chills, productive cough and pleuritic pain. Semiologically it is easy to detect by the presence of bronchial breath sounds or localised crackles. The chest radiograph shows a homogeneous opacity. This is a common clinical picture for *S. pneumoniae* infection, although other 'classical' bacteria may have a similar presentation.
- Atypical syndrome: persistent dry cough that can last for many days. The physical findings may vary, but in general tend to minimise the radiological images (clinical radiological dissociation). Chest radiograph findings are variable, with a tendency to have a mixed pattern (alveolar plus interstitial); overall atypical clinical presentation is more frequent in young people.[17]

This classification, which tries to link the clinical picture with the aetiology, is not completely reliable.[4] For example, pneumonia caused by *L. pneumophila* may be indistinguishable from that caused by *S. pneumoniae*, except for the presence of diarrhoea and elevated blood levels of creatine phosphokinase (CPK).[18,19] In 395 hospitalised patients with CAP in the Hospital Clinic in Barcelona, the sensitivity and specificity of the atypical syndrome was very low for detecting atypical pneumonia (causative organisms *Mycoplasma pneumoniae*, *C. pneumoniae*, *Coxiella burnetti*, etc.). Instead, the factors associated with an atypical aetiology were age >60 years, lack of comorbidity, and smoking habits.[20] By contrast, Riquelme and co-workers[21] found that, in 101 hospitalised patients with CAP who were aged >65 years, the presence of pleuritic chest pain was associated with a typical bacterial aetiology. However, in our opinion, distinguishing between typical and atypical syndromes may be useful only in young patients without comorbidity, as suggested by Gleason and coworkers.[22] In elderly people, respiratory and nonrespiratory symptoms are less frequent than in the younger population. It is important that this be remembered by clinicians faced with CAP.[23] This reinforces the idea that the clinical diagnosis of CAP can be difficult and the aetiological orientation based only on clinical presentation is really misleading.

1.1 Chest Radiograph

A chest radiograph is the gold standard for diagnosis of CAP and must be interpreted with the clinical findings, because an opacity in the chest may be due to other causes, including pulmonary oedema, diffuse pulmonary disease, drug adverse reactions and others.[24] Interpretation of a chest radiograph may be difficult in elderly patients, because they may not be able to hold their breath during the examination, and in severely impaired patients because the chest radiograph must be obtained in the supine position. The presence of other diseases, such as chronic obstructive pulmonary disease (COPD) or heart failure, may interfere with the radiological diagnosis. On the other hand, the insufficient exposure to x-rays results in an accentuation of the pulmonary vascular bed with the misimpression of the presence of pulmonary interstitial infiltrates.[24,25]

The chest radiograph can also help to locate infiltrates in patients with a negative physical examination. In young patients in whom the chest phys-

ical examination is normal, up to 25% of chest radiographs show alveolar infiltrates.[5] Conversely, some patients with clinical findings compatible with the diagnosis of pneumonia may initially not present radiological infiltrates that become evident hours or days later.[5] Likewise, it is known that up to 30% of patients with AIDS and *Pneumocystis carinii* pneumonia have a normal chest radiograph at the time of diagnosis.[2]

Some findings of chest radiographs are suggestive of certain micro-organisms. For example, patients with *Staphylococcus aureus* infection may show multiple pneumatoceles and those with mycobacterial infections may show cavitations in upper lobes.[26] By contrast, various types of radiological infiltrates can be seen with common micro-organisms causing CAP. For example, an incomplete consolidation is frequent in patients with pulmonary emphysema.[5]

Computed tomography of the chest is especially useful to investigate the presence of interstitial infiltrates, masses, cavitations and abscesses, and to detect empyema.[27] This technique is useful in cases of pneumonia that do not respond to initial antibacterial therapy and to evaluate the complications mentioned above.[4] Ultrasonic investigations are helpful to diagnose pleural effusions, to differentiate parapneumonic effusion from empyema and to guide the drainage of both.[5]

The chest radiograph not only gives diagnostic orientation but also provides prognostic information. Involvement of more than 2 lobes and radiological progression, defined as an increase in more than 50% of radiological infiltrates during the 48 hours after initial diagnosis, are severity criteria.[1,3,4,27]

1.2 Aetiological Diagnosis

There is controversy about the utility of obtaining an aetiological diagnosis in CAP.[4,15,28] No studies have demonstrated the cost-effectiveness of a complete aetiological work-up. However, we think it is reasonable to make an effort to identify the causative pathogen in order to restrict the spectrum of antibacterial agent used. This should be the first measure to control the emergence of resistant pathogens, reduce costs and avoid adverse effects of antibacterials. In addition, aetiological information is very important to design and to validate the accuracy of guidelines for empirical treatment.

Table I. Microbiological methods for diagnosis of pneumonia

Noninvasive techniques
Gram stain and sputum culture
Blood culture
Serology:
ELISA
Microimmunofluorescence
Complement fixation
Antigen detection:
Counterimmune electrophoresis
ELISA
Direct immunofluorescence
Polymerase chain reaction
Invasive techniques
Quantitative (via fibreoptic bronchoscopy):
Protected specimen brush
Bronchoalveolar lavage
Nonquantitative:
Pulmonary puncture
Pulmonary biopsy

ELISA = enzyme-linked immunosorbent assay.

Aetiological diagnostic techniques can be classified into noninvasive and invasive (table I). Immunological techniques refer to the detection of microbial antigens in blood or antibodies against bacteria and viruses. Polymerase chain reaction (PCR) and *in situ* hybridisation are procedures based on molecular biology that will probably become more important in the future. Some of these techniques can be applied in samples obtained by invasive or noninvasive methods, alike.

1.2.1 Noninvasive Methods

Gram Stain and Sputum Culture

Although sputum culture has been criticised for its low sensitivity and specificity, it is still the cornerstone for the diagnosis of CAP in nonventilated patients. The main disadvantage of sputum culture is the frequent contamination that may occur when passing the oropharynx. Murray and Washington[29] demonstrated that contamination by oropharyngeal

flora was more likely when 10 or more epithelial cells per field were present. A sample of good quality that represents the lower respiratory tract should therefore contain fewer than 10 epithelial cells and more than 25 leucocytes per field.[29] Another frequent problem is that some patients are not able to expectorate; this problem may affect up to 40% of patients with CAP.[20] Finally, it is very important to process the samples as soon as possible in order to maintain maximum sensitivity.[30]

Antibacterial treatment administered before sampling of sputum also affects its yield. It is well known that a single dose of ampicillin is sufficient to prevent bacterial growth when the pathogen is as sensitive as, for example, *S. pneumoniae* or *Haemophilus influenzae*.[30] In addition, it is crucial to select only the purulent areas of the sputum and to cultivate only samples of good quality.[29] It is, however, important to point out that in immunocompromised patients all sputum samples must be processed, since these patients may have primary respiratory pathogens as a cause of CAP. With all the recommendations given above, the yield Gram stain can reach 70% of sensitivity and specificity. The yield of the culture (growth of potentially pathogenic micro-organisms) ranges between 50 and 80%, depending on the type of micro-organism isolated and the prior use of antibacterials.[30]

Blood Culture

Patients with bacteraemic pneumonia have a higher mortality independent of the presence of other risk factors.[31] The frequency of bacteraemia in CAP ranges between 5 and 25%[30,32] and the specificity is high.[15] The recommendations are to obtain at least 2 blood samples for culture in patients hospitalised with CAP.[14]

Serological Methods

Serological methods try to detect immunological evidence of infection by the presence of antibodies or antigens. Table II shows the most important techniques and their diagnostic yield.[30,33] Methods that try to detect antigens of micro-organisms are not importantly modified by prior antibacterial treatment. In pneumococcal pneumonia it is possible to detect the capsular antigen (Ag coA or Ag C) by using counterimmune electrophoresis, a method that is 60% sensitive.[30] The detection of the C wall polysaccharide of *S. pneumoniae* with a urinary antigen test,[34] using an immunochromatographic assay, has been recently approved by the US Food and Drug Administration and is being commercially developed in several countries. Test results are interpreted by the presence or absence of visually detectable pink-to-purple lines. A positive result can be read in 15 minutes or less, depending on the concentration of antigen present in urine. Sensitivities ranging between 86 and 90% and specificities ranging between 71 and 94%, depending on the population studied, have been reported but not published. Currently, a study on severe CAP using invasive methods as a reference test for *S. pneumoniae* detection is being evaluated and this probably will clarify the real value of this promising technique.

The culture of *M. pneumoniae* is a time-consuming procedure (7 to 10 days), and it is not used in clin-

Table II. Serological diagnostic techniques to detect immunological evidence of infection in patients with pneumonia

Pathogen	Method	Observations
Streptococcus pneumoniae	ELISA Counterimmune electrophoresis in sputum and urine	Good specificity Low sensitivity
Mycoplasma pneumoniae	Cryoagglutinin in serum	Nonspecific
	Complement fixation in serum	75-80% sensitivity 80-90% specificity
	ELISA in serum	92% sensitivity 95% sensitivity
Chlamydia pneumoniae	Direct immunofluorescence in respiratory samples	20% sensitivity 85% sensibility
	Complement fixation in serum	Cross-reaction with *C. psittaci*
	MIF in serum	70-80% sensitivity 90-100% specificity
Legionella pneumophila	ELISA in urine	80-90% sensitivity (type 1) 99% specificity
	Direct immunofluorescence in respiratory samples	25-75% sensitivity 95-99% specificity
	IFI in serum	75% sensitivity 95-99% specificity

ELISA = enzyme-linked immunosorbent assay. **IFI** = indirect immunofluorescence; **MIF** = micro-immunofluorescence.

ical practice. Detecting specific immunoglobulin (Ig)M or a 4-fold increase in IgG titres during a period of 4 weeks makes the diagnosis. Enzyme-linked immunosorbent assay (ELISA) improves the level of *Mycoplasma* detection and will possibly be of interest in the future.[30] Culture of *C. pneumoniae* is also complicated, since it requires two special cellular lines that must be renewed every 48 hours; the yield is close to 60%. For this reason in clinical practice we use immunological tests, such as the detection of specific IgM or IgG antibodies by micro-immunofluorescence. The diagnosis is established with titres of IgM ≥1 : 16 or IgG ≥1 : 512 in acute phase or a 4-fold increase in IgG titres during a 4-week period.[35] *L. pneumophila* is a very difficult micro-organism to culture, which explains why, despite the use of special cultures (BCYEα), the sensitivity is not higher than 40%. The ELISA technique for urinary antigen detection is valid only for serotype 1 of *L. pneumophila*, which is responsible for 80% of infections.[12] For this organism, we currently use the detection of specific IgM antibodies in the acute period of the infection and a 4-fold increase in IgG titres. It is important to know that elderly patients may have late seroconversion (up to 3 months after infection).[30] Detection of IgM and IgG seroconversion is also used for *C. psittaci* and *C. burnetti* respiratory infections.

Polymerase Chain Reaction

This revolutionary technique, which has potential applications in many microbiological areas, consists of the identification of DNA sequences of variable sizes located in both extremes of DNA bands through pieces of complementary DNA (primer). Once the pieces have been attached to each extreme, the polymerase enzyme is added and it duplicates each sequence. Every time this operation is repeated, the DNA sequence is amplified until the preparation undergoes electrophoresis and the amplified DNA bands are identified.

The sensitivity and specificity of this technique is reasonable for every tested micro-organism. However, the routine application of PCR has been hindered by several unresolved problems: complexity and the time-consuming nature of the procedure, the need for personnel trained in molecular biology techniques, and the need to define the optimum samples and methods for each micro-organism.[30,33]

In clinical practice PCR detection is useful for micro-organisms that are not common causes of CAP, such as *Mycobacterium tuberculosis* and *P. carinii*. However, recent information suggests that the detection of *S. pneumoniae* by PCR could be diagnostically useful. Menéndez et al.[36] studied the serum PCR assay for *S. pneumoniae*, *M. pneumoniae* and *C. pneumoniae*. The diagnosis of pneumonia caused by *S. pneumoniae* was 5 times greater using PCR in serum than with blood culture. However, this test was neither sensitive nor specific for *C. pneumoniae* and *M. pneumoniae*. Lorente et al.[37] recently examined the diagnostic value of blood PCR detection in pneumococcal CAP and found 55% sensitivity and 100% specificity. The results from these studies are very promising and open a new perspective in the rapid and early diagnosis of *S. pneumoniae* pneumonia.

1.2.2 Invasive Techniques

As mentioned above, the main disadvantage of respiratory samples obtained by noninvasive methods is contamination by the oropharyngeal flora that decreases the specificity of the methods and may induce overtreatment. During recent years there has been development of techniques that avoid contamination from upper respiratory airways. These so-called invasive methods have gained large popularity in Europe and are used for the diagnosis of nosocomial pneumonia and ventilator-associated pneumonia, in particular. Their potential utility in the aetiological study of CAP, however, has not yet been clarified.

Protected Specimen Brush

The protected specimen brush (PSB) method, developed at the end of the 1970s, consists basically of a brush hidden in a double system of telescopic catheters. The method requires the use of a bronchoscope. The PSB samples approximately 0.001ml of lower respiratory secretions, which are diluted in 1ml of saline. Concentrations of 10^3 colony-forming units (cfu)/ml or more in quantitative cul-

ture correspond, therefore, to a concentration of 10^5 cfu/ml in respiratory secretions. The first study conducted with this method was in patients with CAP without previous antibacterial treatment. In that study 95% of samples had isolation of pathogenic micro-organisms in significant counts.[38] Örtqvist and co-workers[39] applied this method in 10% of patients hospitalised with CAP because of early antibacterial treatment failure and poor clinical evolution of patients with severe CAP. They found a sensitivity of 30%, a negative predictive value of 81% and an overall accuracy of 79%. It is important to point out that the highest yield was obtained in patients with severe CAP without prior antibacterial treatment.[39] In clinical practice the prior use of antibacterial agents is found in about 25% of cases of CAP.[3]

This technique is not usually available 24 hours a day and when available its utility in the management of CAP is doubtful. It is reported that in severe CAP the use of invasive diagnostic techniques modified the empirical antibacterial treatment in only 6% of cases.[40] We think that routine use of PSB in CAP cannot be recommended, and PSB sampling should be restricted to patients with severe CAP who are intubated or do not respond to the initial empirical antibacterial treatment.[28,39]

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) consists of wedging of the bronchoscope in subsegmentary bronchi and instillation of saline solution, which is aspirated through the channel of the bronchoscope. No consensus exists about the total amount of instilled saline but it seems that at least 100ml is necessary to obtain a representative sample.[41] The recovered volume varies between 5 and 70% of the instilled volume and at least 5ml is needed for accurate processing. The threshold of quantitative cultures to distinguish colonisation from infection is 10^4 cfu/ml.[42] Few studies have evaluated the utility of BAL in CAP. Only Jimenez and co-workers[43] have studied this technique in intubated patients without previous antibacterial treatment, finding an adequate correlation with quantitative cultures of PSB ($r = 0.71$). The role of BAL is well defined in the aetiological diagnosis of immunocompromised patients with pneumonia, especially when radiological infiltrates are diffuse.[6] For example, in patients with AIDS and *P. carinii* pneumonia, the diagnostic yield is about 90%.[41,44] In our opinion, there is little benefit in using BAL in the initial diagnostic strategy in CAP. The use of BAL in CAP should be restricted to immunosuppressed patients or to those who fail to respond to the initial empirical antibacterial treatment.

Transthoracic Puncture with Ultrathin Needle

Direct sampling of the lung through percutaneous puncture aspiration of the thorax is an old technique used in paediatric patients several decades ago. Complications associated with this procedure have limited its use. The availability of ultrathin needles (22 to 25 gauge) has renewed interest in this technique. Percutaneous needle aspiration can be performed at the bedside without radiographic guidance. 4ml of saline is instilled and 1ml is recovered for culture.[42] Sensitivity of the technique ranges between 34 and 94%, increasing when immunological tests are applied in addition to Gram stain and cultures. Specificity ranges from 90 to 100%.[28] Contraindications include haemorrhagic diathesis, bullous emphysema, severe pulmonary hypertension, severe hypoxaemia, uncontrolled cough, lack of co-operation, and mechanical ventilation. The incidence of pneumothorax ranges between 5 and 20%.[28,45] Transthoracic lung puncture for the diagnosis of CAP has been widely used in Spain. Again, there is no rationale for using this method in the initial diagnostic approach and it should be restricted to nonresponding patients.

All invasive methods can be theoretically applied to patients with CAP; however, they are inappropriate in outpatients with CAP, since the overall mortality in this group is below 1%.[46] In hospitalised patients with CAP, the effort to obtain a microbiological diagnosis needs to be increased with the severity of the condition or if the patient is not responding to initial antibacterial treatment. Table III shows the diagnostic studies suggested by different guidelines according to the severity of CAP.

Table III. Diagnostic management of community-acquired pneumonia (CAP)

	Chest radiograph	Sputum culture	Blood culture	Serology	Invasive techniques
Outpatients					
Aged <60y without comorbidity	R	TBC	NR	NR	NR
Aged ≥60y or with comorbidity	R	TBC	NR	NR	NR
Hospitalised					
Nonsevere CAP	R	R	R	R	NR
Severe CAP	R	R	R	R	TBC

NR = not recommended; **R** = recommended; **TBC** = to be considered.

2. Diagnosis of Nosocomial Pneumonia

The clinical diagnosis of nosocomial pneumonia is more complex than that of CAP, especially when dealing with ventilator-associated pneumonia. Clinically it is defined by the presence of new or progressive pulmonary infiltrates on radiograph associated with clinical signs that demonstrate that the infiltrates have an infectious origin. These signs include fever, purulent sputum, and leucocytosis or leucopenia.[8] If these criteria occur in a hospitalised nonventilated patient without comorbidities it is likely that the current episode is nosocomial pneumonia. Nevertheless, in mechanically ventilated patients there are other conditions that may mimic pneumonia. For example, Torres and co-workers,[47] using immediate postmortem pulmonary biopsies as the standard, found that clinical diagnostic parameters had a poor diagnostic yield. This means that the diagnosis of nosocomial pneumonia based only on clinical criteria in ventilated patients includes a high rate of false-negative and -positive results. False-positive results may promote overuse of antibacterial agents, which in turn can lead to the development of multiresistant micro-organisms.[48,49] False-negative results may underestimate pneumonia, a dangerous clinical situation, since it has been demonstrated that inadequate antibacterial treatment is a key factor contributing to the increase of mortality in ventilator-associated pneumonia.[50,51] The relatively poor performance of clinical criteria can be improved by microbiological diagnosis of nosocomial pneumonia, particularly in mechanically ventilated patients. In nosocomial pneumonia diagnostic methods can be classified as noninvasive or invasive, in accordance with the classification in CAP.

2.1 Noninvasive Methods

2.1.1 Sputum Culture

The utility of sputum culture in patients with nosocomial pneumonia is limited and the results must be interpreted with caution. Data regarding the diagnostic value of Gram stain and sputum culture in nosocomial pneumonia are scarce.[52] Markers of pneumonia such as detection of elastin fibre or antibody coating bacteria are not very specific. Again there is no doubt about the utility of sputum for searching for primary pathogens.[8]

2.1.2 Blood Culture

In nosocomial pneumonia, the rate of positive blood cultures ranges between 8 and 20%.[8,30,53] However, in critically ill patients bacteraemia does not imply a pulmonary origin, and in fact approximately 30% of critically ill patients with positive blood culture may have an additional source of infection.[53,54]

2.1.3 Quantitative Cultures of Endotracheal Aspirates

Several studies have demonstrated that qualitative cultures obtained by endotracheal aspirates through a nasotracheal or orotracheal tube or tracheostoma are nonspecific.[55] These cultures are rarely negative in mechanically ventilated patients who have fever and radiological infiltrates, which may lead to an excess in the diagnosis of ventilator-associated pneumonia.[56,57] The use of quantitative cultures of endotracheal aspirates may avoid part of these false-positive results. Using a thresh-

old between 10^5 and 10^6 cfu/ml, the sensitivity for detecting ventilator-associated pneumonia ranges from 50 to 70% and the specificity from 70 to 85%.[58-60] A good correlation has been demonstrated with quantitative cultures of invasive diagnostic methods such as PSB or BAL.[60-62] Endotracheal aspirates have the advantage that they can be obtained without the need for skilled personnel or specialised equipment. Detractors of this technique argue that the results lead to an excess diagnosis of pneumonia, but the rate of false-positives is similar to that obtained by invasive techniques when used in combination with quantitative bacterial cultures.[11]

2.2 Invasive Methods

2.2.1 Protected Specimen Brush

The utility of PSB in the diagnosis of nosocomial pneumonia has been studied in animal and human models, which have demonstrated a sensitivity ranging from 64 to 100% and a specificity from 69 to 100%.[55,59] These results have been confirmed in studies with immediate postmortem pulmonary biopsies as the standard. The yield of PSB quantitative cultures is decreased by prior antibacterial treatment. Nevertheless, when the antibacterials given are not directed towards the current episode of pneumonia, the diagnostic value of the technique is acceptable.[63] Montravers and coworkers[64] demonstrated that antibacterial agents rapidly sterilise bronchial secretions within 3 days, confirming the importance of obtaining samples before starting or changing treatments.

False-negative results may occur during the early phases of pneumonia. In addition, histopathological studies have shown that the presence of bronchiolitis (or so-called early infection) may explain false-negative results of quantitative cultures without radiographic consolidation.[42] The false-positive rate of PSB is approximately 30%. False-positive results are related to contamination of the brush when passed through the bronchoscope channel. The presence of more than 1% of squamous epithelial cells is indicative of upper airway contamination. Potentially pathogenic micro-organisms frequently colonise patients with bronchiectasias and COPD, and the PSB obtained may yield false-positive cultures.[42,55,65]

2.2.2 Bronchoalveolar Lavage

BAL is another technique used to diagnose nosocomial pneumonia, particularly in ventilated patients. We found that a cut-off value of 10^4 cfu/ml generated an average sensitivity of BAL in 23 studies of 73 ± 18%, and a specificity of 82 ± 19%.[66] The reasons for this variability are similar to those mentioned for PSB. The negative predictive value is higher than with PSB, because BAL explores a much broader lung area than PSB. As with PSB, the presence of ≥1% of squamous epithelial cells is indicative of contamination from upper airways.[42,55] Protected BAL is a technique that can be used to reduce upper airway contamination. The catheter has a balloon in its tip, which is wedged in subsegmentary bronchi to avoid retrograde aspiration. The volume instilled ranges between 50 and 120ml. The sensitivity and specificity described in 1 study were 97 and 92%, respectively.[55]

2.3 Invasive versus Noninvasive

Cultures of PSB and BAL are not available until 48 to 72 hours after sampling. For this reason, techniques that give a rapid diagnostic orientation are desirable. A very useful and rapid method is the staining of cytocentrifuged BAL specimens with May-Grünwald-Giemsa or Diff-Quik stains for the detection of inflammatory cells (macrophages and neutrophils) with intracellular organisms (ICO). The detection of more than 2% of ICO in cells from BAL fluid of mechanically ventilated patients is indicative of pneumonia. The sensitivity of ICO detection ranges between 37 and 100% and the specificity between 89 and 100%.[42,55] This method is useful to guide initial antibacterial treatment in nosocomial pneumonia acquired during mechanical ventilation. Systematic use of noninvasive or invasive techniques for the diagnosis of ventilator-associated pneumonia is a matter of controversy.[67] Proponents of invasive techniques (bronchoscopy with PSB with or without BAL) have recommended use of these techniques for the management of pa-

tients with clinical suspicion of pneumonia acquired during mechanical ventilation. The arguments in favour of the invasive strategy are:

- The poor specificity of the clinical diagnosis may lead to excessive antibacterial use, which is associated with the development of ventilator-associated pneumonia and the appearance of multiresistant micro-organisms.[11,68]
- Ventilator-associated pneumonia has an attributable mortality of 30%; consequently it is very important to confirm this diagnosis.[11,48,69]
- Some investigations have shown that PSB and BAL positive cultures have a good association with histopathological evidence of ventilator-associated pneumonia.[65]

Chastre and co-workers[11] proposed a protocol in which empirical antibiotic treatment was given to patients with >5% of cells with ICO. This treatment must be adjusted according to the microbiological cultures. Maintenance of antibacterials is recommended if the results of the quantitative cultures of the PSB are above the cut-off points. We believe that this strategy is dangerous, since some patients may not receive adequate treatment.

Other authors have recommended the use of quantitative cultures of endotracheal aspirates and administration of a standard antibacterial treatment according to the American Thoracic Society guidelines.[8,42] The arguments in favour of this strategy are:

- In many ICUs 24-hour coverage of bronchoscopic techniques is not provided.
- The variability of diagnostic techniques leads to a higher rate of false-negative results, which may in turn increase the number of patients who are not treated for pneumonia. Because ventilator-associated pneumonia has attributable mortality, this subgroup of patients could have a higher mortality rate.[11,42,47,55,59,65]
- Endotracheal aspirates show good agreement with quantitative cultures of invasive techniques.[59,60]
- Inadequate initial empirical antibacterial treatment is an important risk factor for mortality, even if it is adjusted to the microbiological findings.[51,70,71]

Table IV. Mortality rates in 2 groups of patients with ventilator-associated pneumonia managed with noninvasive or invasive diagnostic methods

	Noninvasive	Invasive	p-Value
Crude mortality	18/39 (46%)	14/37 (38%)	0.46
Attributable mortality	10/18 (56%)	10/14 (71%)	0.31
Microbiologically confirmed	10/23 (44%)	10/23 (44%)	1.0

Recently, 2 randomised studies tried to clarify another controversy in terms of cost-effectiveness and outcome. Both studies, with a total of 126 patients, concluded that there are no significant differences in morbidity and mortality between invasive and noninvasive diagnostic strategies, especially if the antibacterial treatment is standardised. In addition, no differences were found in the antibacterial agents used, although there was a major antibacterial cost with the use of PSB and BAL[61,72] (table IV). In view of these findings, we recommend the systematic use of endotracheal aspirates to adjust the empirical antibacterial treatment in patients with ventilator-associated pneumonia. The role of invasive techniques in patients who do not respond to the initial antibacterial treatment remains to be clarified. Most probably, these nonresponding patients could benefit from a complete work-up diagnostic strategy including invasive techniques.

3. Monitoring of Infection Eradication

Clinical suspicion of CAP and nosocomial pneumonia justifies early initiation of antibacterial treatment, because any delay may potentially harm the patient.[28,46] Because the causative micro-organism is not identified at the time of initiation of antibacterial therapy, treatment is usually empirical. We recommend using standard empirical antibacterial treatment according to the recommendations of published guidelines and local epidemiological studies.[4,14,15,73] In addition, antibacterial treatment must be adjusted according to the microbiological results. Overall, if there is a favourable clinical response, sequential oral and intravenous therapy is recommended. A favourable clinical response is

difficult to define in practical terms. Indeed, there is no universally accepted definition. Some authors suggest that the pattern of the fever curve, the absolute neutrophil count and a chest radiograph analysed on the third day are sufficient criteria to confirm the presence or absence of an adequate clinical response.[42,74] Others add the daily follow-up of serum C-reactive protein as a marker of unfavourable evolution.[75] In practical terms it seems that one of the best indicators of a favourable outcome is the resolution of fever 48 to 72 hours after antibacterial therapy has been started.[73]

In young adults with pneumococcal pneumonia the resolution of fever takes an average of 2.5 days. This period can be longer in elderly patients if there is bacteraemia. In case of infection with *M. pneumoniae*, fever may last 2 to 3 days. Likewise, pneumonia caused by *Legionella* may last an average of 5 days if it is treated correctly.[15] Leucocytosis lasts an average of 4 days and crackles disappear on day 7 in 20 to 40% of patients.[4] Bacterial cultures are negative 24 to 48 hours after initiation of antibacterial therapy unless anatomical abnormalities such as bronchiectasias are present.[15] Chest radiographs in patients without comorbidity who are aged <50 years become normal after 4 weeks of treatment. In contrast, this period can be considerably longer in elderly patients, with severe pneumonia or comorbidity. A chest radiograph shows complete resolution in 12 weeks in only 55% of cases of pneumonia caused by *Legionella*.[76,77]

It is recommended that initial antibacterial treatment should not be changed during the first 3 days unless a marked deterioration is observed. Montravers et al.[64] pointed out the importance of microbiological re-evaluation of patients with nosocomial pneumonia 3 to 4 days after the start of treatment, using PSB cultures, to optimise antibacterial therapy especially in patients not responding to initial treatment. They demonstrated that this strategy can detect an incorrect choice in the initial antibacterial treatment, identify patients with early superinfection and predict the clinical outcome for the first 15 days after the onset of therapy.[64]

Table V. Factors indicating a poor prognosis in community-acquired pneumonia

Requirement for mechanical ventilation
Requirement for positive end-expiratory pressure
Inspiratory oxygen fraction >0.6
Septic shock
Presence of acute respiratory distress syndrome
Presence of renal failure
Radiographic spread of pneumonia despite appropriate therapy

If the clinical course is unfavourable or bad prognostic criteria appear (table V), the following conditions must be considered:[4,78]

- The causative organism may be resistant to the antibacterial agent or agents used in the empirical treatment: this is the case with penicillin-resistant *S. pneumoniae*, which has a high prevalence in regions such as North America and the Mediterranean.[79-81] Strains resistant to penicillin may be resistant to erythromycin and cephalosporins as well.[78] This cause of non-response is more frequent in ICUs, where there is an elevated rate of multiresistant micro-organisms.
- The causative organism is not covered by the antibacterial treatment: e.g. pathogens such as *Pseudomonas aeruginosa* and *S. aureus*, which are not covered by the empirical antibacterial treatment,[14,15] are not infrequent in severe CAP.[3,4,20] The same can occur in patients with AIDS and *P. carinii* pneumonia.[7]
- Organisms that do not respond to antibacterials may cause the infection (e.g. viruses and fungi). These must be suspected on epidemiological background and the clinical history of immunosuppression.[78] We found 10% of positive serology for influenza viruses A and B in patients hospitalised with CAP.[20]
- Superinfection by nosocomial pathogens.
- Pneumonia can progress to necrosis or empyema: the former can evolve to a necrotising pneumonia or pulmonary abscess; in the latter, only pleural drainage can resolve the infection.
- Structural pulmonary disorders may obstruct the resolution of pneumonia: bronchiectasias or

endoluminal tumours may impede drainage of secretions.

- Incorrect diagnosis of pneumonia: in this case, alternative diagnoses must be considered, such as pulmonary emboli, congestive heart failure, pulmonary carcinoma, and diffuse pulmonary disease [such as bronchiolitis obliterans organising pneumonia (BOOP), Wegener's granulomatosis and eosinophilic pneumonia).[4,78]

All possibilities must be considered in patients who do not respond to empirical antibacterial treatment both in CAP and in nosocomial pneumonia. In these patients we recommend performance of invasive methods (bronchoscopy with PSB or BAL) and thoracic CT scan (fig. 1).

In both CAP and nosocomial pneumonia adequate empirical antibacterial treatment is the most important strategy. Rapid techniques that offer information within a few hours may help in guiding initial treatment. Antibacterial treatment must be adjusted according the results of initial cultures. Patients who do not respond to initial treatment must be re-evaluated in microbiological terms, including in this case the use of invasive techniques.

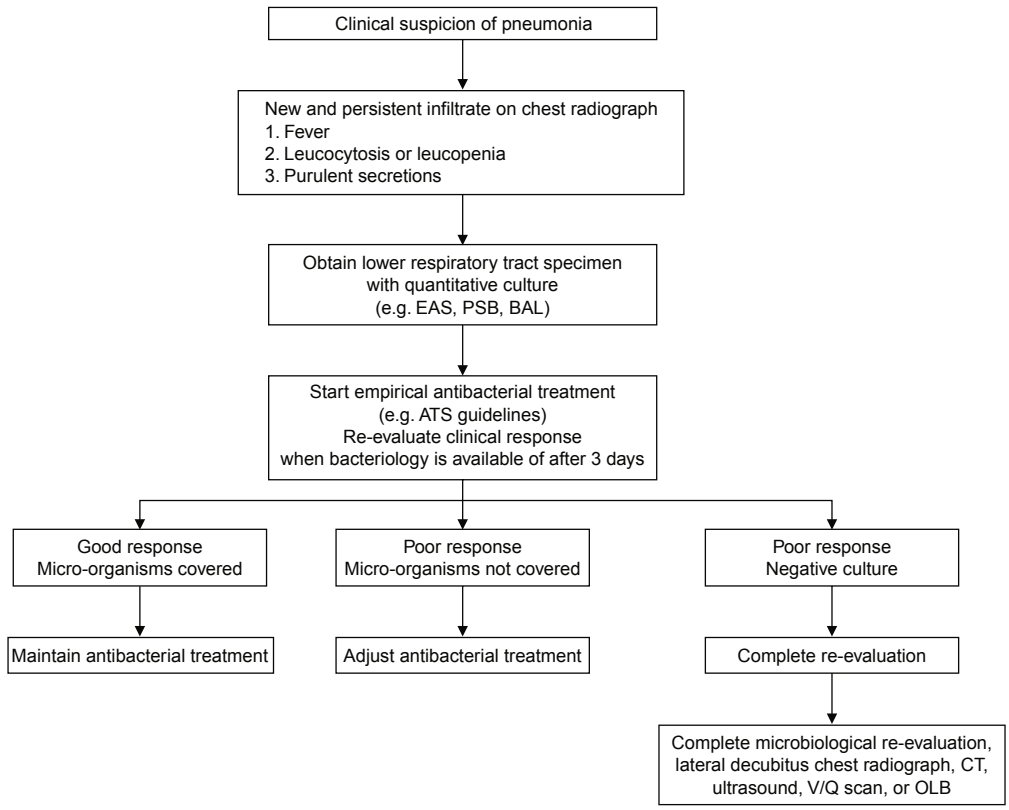

Fig. 1. Clinical algorithm for diagnosis and follow-up of nosocomial pneumonia. Clinical suspicion of pneumonia can be assumed in the presence of new and persistent pulmonary infiltrates plus 2 of the 3 criteria (1 to 3). Antibiotic treatment should be started immediately according to standardised guidelines (e.g. American Thoracic Society; ATS[8]). The clinical response should be re-evaluated after 3 days of antibiotic treatment, and therapy should be adjusted according to microbiological results. In nonresponding patients a complete work-up is recommended. This includes invasive sampling and further diagnostics to rule out noninfectious causes of pulmonary infiltrates. The value of open lung biopsy (OLB) has not been investigated and the application should be limited to severe cases. **BAL** = bronchoalveolar lavage; **CT** = computed tomography; **EAS** = endotracheal aspirates; **OLB** = open lung biopsy; **PSB** = protected specimen brush; **V/Q scan** = ventilation/perfusion scan.

Acknowledgements

Supported by the Commisionat per a Universitats i Recerca de la Generalitat de Catalunya 1997 SGR 00086, IDIBAPS Hospital Clinic Barcelona, and FISS 98/0138. Dr Bauer was supported in 1999 by an educational grant of IDIBAPS, Barcelona, Spain.

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