Drug Treatment of Pneumonia in the Hospital
What are the Choices?

M. Aoun and *J. Klastersky*
Service de Médecine, Institut Jules Bordet, Brussels, Belgium

Contents

Summary

Mortality and morbidity of nosocomial pneumonia remain high. Successful treatment of pulmonary infections depends on several factors including type of infection, offending pathogen, status of host defences, and adequate choice of antibiotic therapy. The physician's decision should aim at achieving antibiotic concentrations beyond the MIC at the site of infection.

Gram-negative bacilli, notably *Pseudomonos aeruginosa, Klebsiella pneumoniae* and *Escherichia coli,* remain the most frequent agents in nosocomial pneumonia.

Staphylococcus aureus and *Streptococcus pneumoniae* predominate among the Gram-positive cocci. *Pneumocystis carinii* predominates in immunocompromised patients.

Protected sample bronchoscopy associated with quantitative cultures of samples, and quantification of intracellular microorganisms in cells recovered by broncho-alveolar lavage are two promising procedures which might replace previous, more aggressive methods. Penetration of antibiotics into lung tissue depends on physicochemical properties of the drug and the degree of inflammation of lung tissue.

Quinolones, macrolides, tetracyclines and trimethoprim penetrate well into bronchial secretions. Penetration is moderate to low for aminoglycosides and β-lactams.

Fluoroquinolones and new β-lactam agents, including third-generation cephalosporins imipenem, aztreonam and ticarcillin-clavulanate, showed comparative clinical efficacy in treatment of nosocomial pneumonia, with an efficacy rate close to 80%. Aminoglycosides should not be used alone.

Combination therapy reduces but does not eliminate the risk of selection of Gram-negative resistant mutants. It should not be used routinely except for *P. aeruginosa, Enterobacter cloacae* and *Serratia marcescens* infections.

Successful treatment of pulmonary infections depends on several factors, including the type of infection, the offending pathogen, the status of host defences, the underlying disease, and the adequate choice of antibiotic therapy (Pennington 1981). This latter factor only can be modulated directly by the physician's decision, which results from an integration of epidemiological, radiological, clinical and microbiological diagnostic clues. Despite many investigations, specific aetiological identification of the pathogen may be difficult, adding to the challenge of managing pneumonia (Donowitz & Mandell 1983).

The antibiotics chosen should have an intrinsic antimicrobial activity against the presumptive or documented infectious agent, and sufficient penetration into the lung interstitial fluids, as well as into alveolar and bronchial secretions, in order to achieve therapeutic concentrations at the site of infection well beyond the MIC of the pathogen (Wong et al. 1975). The number of microbial agents that cause pneumonia is large, and a single antibiotic or regimen for all these possibilities does not exist. Nevertheless, the responsibility of the physician is to approach the specific diagnosis as closely as possible. The medical history must define clearly the epidemiological features related to hospital contacts, and it is useful to know which microorganisms are causing frequent nosocomial infections at a given hospital (Rubin & Greene 1988). Of great practical importance is the differentiation between community-acquired and hospital-acquired pneumonia because the pathogens, and consequently the treatments, are very different (Donowitz & Mandell 1983).

Some associations are helpful in approaching the specific diagnosis; for instance, *Herpes labialis* is frequently associated with pneumococcal pneumonia and bullous myringitis with mycoplasmal pneumonia (Donowitz & Mandell 1990). The underlying disease is another helpful factor: patients with chronic obstructive pulmonary disease frequently develop pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae* (Groeneveld et al. 1990; Marrie et al. 1989). Cystic fibrosis predisposes to recurrent infection with resistant pathogens, especially *Pseudomonas aeruginosa* and *Pseudomonas cepacia* (Marks 1971). Alveolar proteinosis is frequently associated with nocardial pneumonia (Simon 1988).

In addition, in the diagnostic approach, the physician must also clearly define the immunological status of the patient developing pneumonia. Immunodeficiency, whether induced by a treatment or related to an underlying disease, puts a patient at high risk not only for common pulmonary pathogens but also for opportunistic organisms (Rubin & Greene 1988).

Patients with AIDS, lymphoma, leukaemia, or who have undergone organ transplantation who develop pneumonia must be evaluated for *Pneumocystis carinii,* mycobacteria and cytomegalovirus (Singer et al. 1979). Granulocytopenic patients are at major risk of developing Gram-negative bacillary pneumonia, and prolonged and profound granulocytopenia must also alert the physician to the possibility of aspergillosis (Cordonnier et al. 1986).

1. Aetiology

Table I lists the main pathogens responsible for nosocomial pneumonia. As mentioned previously, the spectrum of potential pathogens is not only very wide but is continually changing.

Gram-negative bacilli remain the predominant organisms, accounting for 60% of all cases of nosocomial pneumonia (Donowitz & Mandell 1983), with *P. aeruginosa, Klebsiella pneumoniae,* and *Escherichia coli* being the most frequently isolated.

Staphylococcus aureus (10% to 28%) and *S. pneumoniae* (2% to 10%) are the most commonly reported of the Gram-positive cocci. Bartlett et al. (1986) in a recent review, using only strict criteria for microbiological studies such as transtracheal aspirates, empyema fluids, or positive blood cultures, found that *S. pneumoniae* was the most frequently isolated microorganism, alone or mixed with Gram-negative bacilli. Although, most pneu-

Table I. Aetiology of nosocomial infection

Gram-negative rods
Klebsiella pneumoniae
Pseudomonas aeruginosa
Escherichia coli
Enterobacter spp.
Serratia marcescens
Proteus spp.
Citrobacter spp.
Haemophilus influenzae
Legionella pneumophila
Branhamella catarrhalis

Gram-positive cocci
Staphylococcus aureus
Streptococcus pneumoniae

Anaerobes (aspiration pneumonia)
Peptococcus spp., Peptostreptococcus spp., Fusobacterium spp.
Bacteroides melaninogenicus
Bacteroides fragilis

Viral
Respiratory syncitial virus
Influenza
Adenovirus

Others
Chlamydia
Mycoplasma pneumoniae

Opportunistic pathogens

Aspergillus spp.	Mycobacteria
Candida spp.	Strongyloides stercoralis
Mucor spp.	Pneumocystis carinii
Histoplasma capsulatum	Herpes simplex, VZV, CMV

Abbreviations: VZV = varicella zoster virus; CMV = cytomegalovirus.

mococci are sensitive to penicillin, resistant pneumococci might be more common in hospital-acquired infections (Pallares et al. 1987).

Some species, like *Acinetobacter calcoaceticus* subspecies *anitratus,* are being more frequently reported as a cause of pneumonia in intensive care units. Harstein et al. (1988) reported an outbreak of such infections in ventilated patients. Fagon et al. (1989) found that *Acinetobacter* sp. was the third most frequent microorganism recovered from

patients with pneumonia in intensive care units, after *P. aeruginosa* and *S. aureus*. Enterococci in patients receiving total parental nutrition, and β-haemolytic streptococci (group B) in elderly patients are also two emerging pathogens (Berk & Verghese 1989; Berk et al. 1983; Verghese et al. 1982). Other species like moraxella (*Branhamella catarrhalis*) have only recently been recognised as respiratory pathogens (Hager et al. 1987; Slevin et al. 1984).

In the absence of a specific diagnostic test, the role of *Legionella pneumophila* in nosocomial pneumonia is probably underestimated. Kugler et al. (1989) reported a frequency of 13% among bone marrow transplant patients and in some hospitals, it has been found to be a frequent cause of nosocomial pneumonia, associated with cooling-tower reservoirs or hospital potable water (Woo et al. 1986).

More than 80% of AIDS patients will acquire *P. carinii* pneumonia, and a substantial proportion of pneumonias in lymphoma patients, organ transplant recipients and those receiving immunosuppressive therapy is also caused by this organism.

In most studies dealing with nosocomial pneumonia, common respiratory viruses are not detected; however, there are important exceptions. Cytomegalovirus causes a variety of syndromes after organ or bone marrow transplantation, the most obvious being pneumonia; 15% patients undergoing allogeneic bone marrow transplantation will eventually develop it (Meyers 1986). In AIDS patients, pulmonary disease due to cytomegalovirus as the only pathogen is uncommon; infection usually occurs in conjunction with *P. carinii* (Glatt et al. 1988).

Aspergillus pneumonia occurs almost exclusively in patients with granulocytopenia; the risk increases with the duration of granulocytopenia (Gerson et al. 1984).

Adenovirus pneumonia was reported in 5% of bone marrow transplant recipients; usually, it is bilateral and interstitial, with pleural effusions in about 20% of cases (Meyers 1986). Herpes simplex and varicella zoster virus are two potential pathogens for respiratory tract in the immunocompromised patients (Ramsey et al. 1982); varicella zoster virus pneumonia is usually part of a

disseminated visceral infection (Miliauskas & Webber 1984).

The incidence of tuberculosis has increased during the last years with the development of HIV infection (Choisson & Slutkin 1989). Many cases of tuberculosis are recognised only after several days or weeks of hospitalisation: this provides the opportunity for the disease to be transmitted, especially to immunosuppressed patients.

2. Diagnosis

Although characteristic symptoms and signs of pneumonia are well known, it should be stressed that granulocytopenic patients with pneumonia may lack cough or sputum production and that about one third will not present with râles or consolidation signs (Sickles et al. 1975). Radiological imaging may require more sophisticated means than standard chest x-ray. Table II summarises some of the clinical and radiological features helpful for presumptive diagnosis in opportunistic pneumonias.

The usual problem that the physician faces is to establish the specific aetiology. Sputum examination is not reliable because of frequent contamination by oropharyngeal secretions; blood or pleural fluid cultures are positive in less than 10% of cases. Transtracheal aspiration may resolve the issue of oropharyngeal contamination, but is not without some risk. Direct transthoracic needle aspiration is very specific, but its sensitivity is low due to the small size of the sample obtained and the difficulty in reaching precisely the infected area. However, this technique is the method of choice in diagnosing pulmonary abscesses, peripheral lung cancers, nodular lesions and fungal infections (Grinan et al. 1990).

During the last 10 years, two other new techniques have been developed. Protected sample bronchoscopy has been evaluated recently using quantitative cultures of samples (Chastre et al. 1989a). This method appears to be highly reliable in establishing the differentiation between colonisation and true infection in ventilated patients. Broncho-alveolar lavage now has an established

value in the diagnosis of bacterial pneumonia. Furthermore, the quantification of intracellular microorganisms in cells recovered by this method, developed by Chastre et al. (1989b), seems to be a new promising procedure and might replace other more aggressive methods.

3. Treatment

Antibiotics penetrate into lung tissue across the blood broncho-alveolar barrier. Passive diffusion seems to be the mechanism of transport for most antibiotics, in relation to the concentration gradient across this barrier and depending on the physicochemical properties of the drug, such as molecular size, lipid solubility, and protein binding (Pennington 1981; Wong et al. 1975). Inflammation of lung tissue may enhance the permeability of antibiotics, and conversely, fibrosis reduces it significantly.

Antibiotic concentration in bronchial secretions is determined by penetration rate, metabolism in the lung and clearance from bronchial secretions. With few exceptions, higher serum concentrations will result in higher bronchial concentrations (Pennington 1981). Table III shows concentration values of different antibiotics in serum and bronchial secretions. In general, quinolones, macrolides, tetracyclines and trimethoprim penetrate well into bronchial secretions; penetration is moderate for aminoglycosides and low for β-lactams.

The correlation between the bronchial concentrations of an antibiotic and the resulting bactericidal activity within bronchial secretions and clinical outcome, has been well established (Klastersky et al. 1981).

3.1 Aminoglycosides

Despite *in vitro* susceptibility of causative organisms, poor results have been obtained in bronchopulmonary Gram-negative infections when aminoglycosides were used alone. Bronchial serum ratio is about 30%, and the low concentrations found in bronchial secretions with conventional doses, in comparison to MIC values of most En-

Table II. Clinical characteristics of opportunistic pneumonias

Cause	Skin or mucocutaneous lesions	Dyspnoea	Onset	Hypoxia	Chest pain	Neutropenia	CNS involvement	Chest x-ray infiltration
Pneumocystis carinii		+	Subacute	+				Interstitial
Mycobacterium tuberculosis			Chronic					Cavity (apex)
Nocardia asteroides	+		Chronic			+	+	Nodular/cavitary consolidation
Legionella spp.		+	Acute	+			+	Consolidiation
Aspergillus spp.	+		Subacute		+	+ (> 20 days)[a]	+	Consolidation (upper lobes)
Candida spp.	+		Chronic			+		Consolidation (nodular)
CMV	+	+	Subacute	+			+	Interstitial
HSV	+	+	Subacute	+				Consolidation or interstitial

a Risk maximal after a duration of neutropenia > 20 days.
Abbreviations and symbols: CNS = central nervous system; CMV = cytomegalovirus; HSV = herpes simplex virus; + = present.

Table III. Pharmacokinetic characteristics of selected antibiotics used in the treatment of nosocomial pneumonia

Antibiotic	Dosage	Serum conc. (mg/L)	Sputum conc. (mg/L)	Bronchial secretions (mg/L)	Lung tissue level (mg/kg)	Ratio (%)	Reference
Amoxicillin/ clavulanate	2g/200mg IV	100/10.8			28.5/1.8	40/23[a]	Cox et al. (1989)
Ticarcillin	5g IV	469	4-4.1		30-45	6-9[a]	
Cefotaxime	2g IV	40	0.5		5-14	12.5-35[a]	Lode et al. (1980)
Ceftazidime	2g IV × 3	44		10.2		23[b]	Erttmann et al. (1990)
Imipenem	1g IV	10.46		2.1		20[b]	Muller-Serieys et al. (1987)
Aztreonam	2g IV	242.6		4.8-18.7		1.9-7.7[b]	Boccazzi et al. (1989)
Ciprofloxacin	0.75mg/kg × 3 IV	1.18		0.40		33.8[b]	Berré et al. (1988)
	1.5mg/kg × 3 IV	2.61		0.84		32.1[b]	
Amikacin	7.5mg/kg IV	23.7		5.23		22[b]	Dull et al. (1979)
Erythromycin	1g × 2 PO	1.37		0.59		43[b]	
Clarithromycin	500mg × 2 PO	2.51			17.47	696[a]	Frasechini et al. (1991)
Roxythromycin	150mg × 2 PO	5.6			2.12	38[a]	Frasechini et al. (1991)
Clindamycin	300mg PO	2.6		1.6		61.5	Bergogne-Berezin (1981)
Fluconazole	150mg PO	3.54	3.71			1.04[c]	Ebden et al. (1989)
Ampho B	1.2 mg/kg	1.36		0.1		7.35[b]	Pennington et al. (1975)

a   Lung tissue to serum ratio.
b   Bronchial secretions to serum ratio.
c   Sputum concentration to serum ratio.
Abbreviations: IV = intravenous; PO = oral; Ampho B = amphotericin B.

terobacteriaceae and *P. aeruginosa,* could be the explanation. In addition, the acidic intrabronchial conditions (Boden et al. 1983) and the binding of aminoglycosides to nucleoproteins in purulent exudates are associated with a decrease in bioactivity of aminoglycosides (Thys et al. 1980).

The importance of serum aminoglycoside concentrations was demonstrated by Moore et al. (1984). By a multivariate regression analysis, he demonstrated that an adequate peak concentration – 7 μg/L or greater for gentamicin and tobramycin and 28 μg/L for amikacin – was associated with a favourable outcome of pneumonia, without increased toxicity. However, the therapeutic toxic ratio of aminoglycosides is low, and high blood concentrations cannot be sustained for a long time. This prompted investigators to deliver aminoglycosides endotracheally in intubated and tracheostomised

patients. Klastersky et al. (1979) demonstrated a statistically significant lower death rate in a group of patients receiving sisomicin endotracheally, in addition to carbenicillin plus sisomicin systemically, in comparison to a group receiving systemic therapy alone. More recently, Brown et al. (1990) in a prospective double-blind, placebo-controlled study, showed that pathogens were eradicated more readily from sputum in patients with Gram-negative bacterial pneumonia receiving endotracheal tobramycin, in addition to systemic tobramycin plus either cefazolin or piperacillin.

In our opinion, aminoglycosides should not be used alone for systemic therapy but should be combined with a β-lactam. Serum concentrations of aminoglycosides must be monitored carefully for toxicity and efficacy. Our preference is for amikacin since many of the nosocomial Gram-negative strains are resistant to gentamicin and tobramycin. An intravenous loading dose of 15 mg/kg with subsequent doses adjusted to renal function, seems to be adequate. Bolus injection is to be preferred to continuous infusion and the value of single daily dosing deserves more studies.

3.2 Fluoroquinolones

Ciprofloxacin, pefloxacin and ofloxacin are the most commonly used quinolones for pneumonias. *H. influenzae, B. catarrhalis* and Enterobacteriaceae are highly susceptible to these antibiotics (Campoli-Richards et al. 1988; Gonzalez & Henwood 1989; Monk & Campoli-Richards 1987). *P. aeruginosa, S. aureus, Mycoplasma pneumoniae,* and *L. pneumophila* are moderately susceptible. *S. pneumoniae* is the least susceptible, with ciprofloxacin having slightly more activity against it than the other 2 drugs (Thys et al. 1989; Wolfson & Hooper 1989).

Quinolones achieve concentrations in bronchial secretions approaching those in serum, and may even exceed serum concentrations in lung tissue. Quinolones in animal models of experimental pneumonia caused by *P. aeruginosa* or *K. pneumoniae* demonstrated high efficacy in preventing death and decreasing bacterial counts in the lungs of surviving animals, these effects were comparable to the β-lactam or aminoglycoside regimens, alone or in combination (Peterson 1986). In experimental *L. pneumophila* pneumonia in guinea-pigs, quinolones showed a higher therapeutic efficacy than erythromycin, but were less active than rifampicin (Saito et al. 1985).

Clinical studies confirmed these experimental data. Martin et al. (1988) treated 46 mechanically ventilated patients with intravenous pefloxacin, 800mg or 1200mg twice- or three-times-daily. A favourable response was observed in 72% of patients; 5 of 7 *P. aeruginosa* and 11 of 13 *S. aureus* isolates were eradicated. The overall eradication rate was 85%; superinfection occurred in 10 patients (22%), with *Candida albicans* in 5.

Ciprofloxacin was used by Peloquin et al. (1989) for nosocomial pneumonias in 50 patients. A favourable clinical response was observed in 63% of patients; pseudomonal infection responded poorly and resistance developed in 70%.

Quinolones also play a major role in the treatment of pulmonary exacerbations of cystic fibrosis due to *P. aeruginosa;* this is based on 6 major studies reviewed by Bayer (1989). Oral ciprofloxacin was as effective as a β-lactam plus aminoglycoside combination, with a clinical improvement in 85% of patients. Decreased bacterial counts occurred frequently, but *P. aeruginosa* could not be eradicated. Increased MIC values were observed but did not alter the clinical effect. Other organisms which showed an increased MIC during quinolone therapy included *S. aureus* and *Serratia marcescens.* Combination therapy is indicated for these organisms, and further laboratory and clinical investigation should indicate which drugs can be combined synergistically with quinolones.

3.3 New β-Lactam Antibiotics

The new β-lactams are characterised by a high intrinsic activity against Enterobacteriaceae. Only a few third-generation cephalosporins, such as ceftazidime, cefsulodin, cefoperazone, and cefepime, are active against *P. aeruginosa* (Kemmerich & Lode 1988; Vuye & Pijck 1985).

In general, against staphylococci and strepto-cocci, their activity is lower than that of first- and second-generation cephalosporins. Penetration into lung tissue and bronchial secretions is approximately 20% of the serum concentrations for all new β-lactams (Marks 1971; Thadepalli 1984).

Ceftazidime has been evaluated in a rat model of experimental pneumonia caused by *K. pneumoniae*. Eradication of bacteria from the lungs was observed and ceftazidime was found more effective than cefazolin (Bakker-Vandenberg et al. 1982). In a similar model, ticarcillin plus clavulanate demonstrated a good therapeutic efficacy (Boon & Pierce 1983). Latamoxef (moxalactam), cefoperazone, cefsulodin, ceftazidime and ticarcillin were compared with tobramycin in a guinea-pig model of *P. aeruginosa* lung infection. Survival rates were lower and bacterial counts in the lungs higher with the β-lactam groups.

Ceftazidime has an enhanced antimicrobial activity against most of the Gram-negative respiratory pathogens, including *P. aeruginosa*. Although it is less active than first- and second-generation cephalosporins against *S. pneumoniae* and methicillin-susceptible *S. aureus,* it retains sufficient activity (Phillips et al. 1981).

Ceftazidime is the third-generation cephalosporin which has been most extensively used for nosocomial infections. La Force (1989) reviewed 4 of the major clinical trials reported with ceftazidime in nosocomial pneumonia; three were comparative studies: Mangi compared ceftazidime with cefoperazone, Young with a combination of ticarcillin plus tobramycin, and Mandell with a combination of cefazolin plus tobramycin. No significant difference was shown between treatments.

Cefoperazone has a similar antimicrobial activity to ceftazidime. Several reports have assessed the effectiveness of cefoperazone in Gram-negative pneumonia. Mangi et al. (1988) in a randomised trial compared cefoperazone monotherapy with either combination of clindamycin plus gentamicin or cefazolin plus gentamicin. Four of 6 patients with *P. aeruginosa* pneumonia received gentamicin or tobramycin in addition to cefoperazone. Cefoper-

azone was as effective as the combination therapy, and cure rates were 87% and 72%, respectively.

Imipenem has the broadest spectrum of antimicrobial activity among the β-lactams. It is active against Gram-positive and Gram-negative, aerobic and anaerobic bacteria, including *P. aeruginosa,* Enterococci, and *Bacteroides fragilis.* No cross-resistance has been observed between imipenem and other β-lactam antibiotics. In an open trial, Salato et al. (1985) administered imipenem monotherapy to 43 patients with bacterial pneumonia, 29 of whom had hospital-acquired pneumonia. A favourable outcome was reported in 89% of patients; 6 of 10 *P. aeruginosa* isolates developed resistance during therapy, and in 2 of them it was a cause of failure.

Miletovic and Braveny (1987) studied the development of resistance during monotherapy with imipenem, and collected data from 5 studies, comprising 277 patients. They found development of resistance in 13 (4.7%) *P. aeruginosa* infections; treatment failure because of development of resistance occurred in 7 patients, and it is noteworthy that *P. aeruginosa* was the only bacteria to show this phenomenon.

Aztreonam is a monobactam antibiotic with enhanced activity against Gram-negative aerobic microorganisms, including Enterobacteriaceae and *P. aeruginosa.* It lacks activity against Gram-positive and anaerobes. Clinical experience with aztreonam in lower respiratory tract infections was summarised by Swabb et al. (1985) 181 patients with Gram-negative pneumonia were treated with aztreonam 1g or 2g intravenously, 3 times daily. 166 (91%) demonstrated a favourable clinical response, with pathogen eradication in 78%. *P. aeruginosa* was the causative pathogen in 57 patients; 51 of them were cured or improved (89%), with pathogen eradication in 33 (58%).

Nolen et al. (1985) randomly compared aztreonam and tobramycin in 49 hospitalised patients with respiratory infections caused by Gram-negative bacilli. 35 received 1g or 2g intravenous aztreonam, 3 times daily, and 26 patients were cured (74%) and 7 improved (20%). In the tobramycin group, which included 14 patients, 5 were cured

(36%) and 2 improved (14%). These data show that aztreonam is effective as a monotherapy for the treatment of Gram-negative pneumonia. However, because of its lack of activity against Gram-positive bacteria, aztreonam must be combined with agents active against Gram-positive bacteria for empiric treatment of nosocomial pneumonia. Vancomycin or clindamycin are frequently employed for this purpose.

Clavulanic acid, a β-lactamase inhibitor, when used in conjunction with ticarcillin, has enhanced its *in vitro* activity against many β-lactamase producers such as *Staphylococci, E. coli, Klebsiella* spp., *Proteus mirabilis, H. influenzae,* and *Bacteroides* spp. Activity against *P. aeruginosa, E. cloacae* and *S. marcescens* is not influenced by the presence of clavulanate. Clavulanate penetrates well into lung tissue and can be recovered from bronchial secretions in significant concentrations.

Schwigon et al. (1986) studied the efficacy of ticarcillin/clavulanate in the treatment of nosocomial bronchopulmonary infections in intensive care units. 81 patients received either 3.2g or 5.2g intravenously 3 times daily. The clinical cure rate was 96% with pathogen eradication rate in 94%. This compares favourably with the results of third-generation cephalosporins and other new β-lactams.

3.4 Monotherapy or Combined Therapy

As mentioned above, the new β-lactam antibiotics and the fluoroquinolones, as monotherapy for hospital acquired pneumonia, demonstrate an efficacy rate close to 80% in open and controlled studies, with a high pathogen eradication rate. La Force (1989) analysed 4 studies comparing monotherapy and conventional combined therapy and concluded that there was no significant difference between the two types of approach. However, these studies compared a third-generation cephalosporin (cefoperazone or ceftazidime) to an older, less active β-lactam, like cefazolin or ticarcillin, associated with an aminoglycoside. It would have been more useful to compare a third-generation cephalosporin to its association with an aminoglycoside.

Of major concern is the selection of resistant mutants during monotherapy. Miletovic and Braveny (1987) reviewed this problem extensively. Broad spectrum penicillins, second- and third-generation cephalosporins, ciprofloxacin and aminoglycosides, showed a resistance emergence rate of about 10%. Imipenem was characterised by a lower resistance rate (4.7%) and only in *P. aeruginosa* infections. Combination therapy can substantially reduce this risk, but does not eliminate it completely (Follath et al. 1987).

In conclusion, we believe that combination therapy should not be used routinely except for pathogens which have a high risk of development of resistance, such as *P. aeruginosa, E. cloacae* and *S. marcescens.*

Table IV summarises some of the guidelines for the treatment of nosocomial pneumonia.

4. Conclusions

Despite significant improvement in the methods of diagnosis, identification of the specific pathogens of nosocomial pneumonias remains a challenge. In addition, quantitative cultures of specimens obtained by PSB or BAL accepted as the gold standard are not commonly available. In many instances, treatment is still established on an empirical basis. Before selecting an antibiotic, 4 elementary questions must be addressed:

1. Is the pneumonia community-acquired or nosocomial? Pneumonia developing within 10 days of prior hospitalisation cannot be considered of community-acquired origin.

2. Is the patient immunocompromised? The type of underlying disease and treatment received are very imporntant. Opportunistic agents such as *P. carinii,* aspergillus and cytomegalovirus must be added to the common respiratory pathogens in immunosuppressed patients.

3. What is the type and localisation of the radiological pulmonary infiltrate? Radiological findings are not pathogen pathognomonic. However, some features may be helpful. Consolidation with cavitation suggests staphylococcal, pseudomonal, *Klebsiella,* or anaerobic aetiology. Diffuse bilateral

Table IV. Guidelines for the drug treatment of nosocomial pneumonia

Organism	Antibiotic	Dose and route	Comments
Gram-negative bacillus	Ceftazidime or	2g q8h IV	Combination with aminoglycoside required for *P. aeruginosa*, *Enterobacter cloacae* and *Serratia marcescens*
	Cefoperazone or	2g q8h IV	
	Aztreonam or	2g q8h IV	
	Ciprofloxacin	750mg bid IV	
Pneumococcal	Benzylpenicillin	8.10^6 units daily IV	Resistant strains must be treated with ceftriaxone
Staphylococcus			
Methicillin-sensitive	Oxacillin	12 g/day IV	
Methicillin-resistant	Vancomycin plus	1g bid IV	
	Rifampicin	300mg bid IV	
Aspiration pneumonia	Imipenem or	1g tid IV	
	Ticarcillin/clavulanic acid	5.2g tid IV	
Mycoplasma or Legionella	Erythromycin	1g tid IV	Quinolones are also effective

P. carinii	Cotrimoxazole
	  (trimethoprim-
	   sulfamethoxazole)
	or
		15-20mg TMP IV and 75-100mg SMX/kg/day	For 2 weeks

	Pentamidine	4 mg/kg/day IV	For 2 weeks
Aspergillosis	Amphotericin B	1 mg/kg/day IV	Total dose required: 1.5-2g
Candidiasis	Amphotericin B or	1 mg/kg/day IV	
	Fluconazole	400 mg/day IV	
Tuberculosis	Isoniazid	5 mg/kg/day PO	For 6 or 9 months
	Rifampicin	10 mg/kg/day PO	
	Pyrazinamide	25 mg/kg/day PO	
CMV	Ganciclovir	7.5-15 mg/kg/day IV	
HSV or VZV	Aciclovir	25-30 mg/kg/day IV	

Abbreviations: q8h = every 8 hours; bid = twice daily; tid = 3 times daily; CMV = cytomegalovirus; HSV = herpes simplex virus; VZV = varicella zoster virus.

infiltrates are common in viral, legionella or *P. carinii* pneumonia.

4. What is the local epidemiology? It is important to enquire about the hospital contacts of the patient, and the principal microorganisms causing pneumonia at a given hospital and their susceptibility patterns.

For empiric treatment of nosocomial pneumonia, third-generation cephalosporins, carbapenems, ticarcillin-clavulanate and fluoroquinolones may be of comparable efficacy, and less toxic than the traditional regimen combining a β-lactam and an aminoglycoside. However, for *P. aeruginosa, E. cloacae* and *S. marcescens,* combination therapy is still recommended. When aspiration pneumonia is strongly considered, imipenem and ticarcillin-clavulanate should be preferred because of their aerobic and anaerobic coverage.

References

Bakker-Vandenberg IAJM, Vandenberg JC, Michel MF. Therapeutic activities of cefazolin, cefotoxine, and ceftazidime against experimentally induced Klebsiella pneumoniae pneumonia in rat. Antimicrobial Agents and Chemotherapy 22: 1042-1050, 1982

Bartlett JG, O'Keefe P, Tolly FP, Louie TJ, Gobach SL. Bacteriology of hospital-acquired pneumonia. Archives of Internal Medicine 146: 868-871, 1986

Bayer AS. Clinical utility of new quinolones in treatment of osteomyelitis and lower respiratory tract infections. European Journal of Clinical Microbiology and Infectious Diseases 8: 1102-1110, 1989

Bergogne-Berezin E. Penetration of antibiotics into the respiratory tree. Journal of Antimicrobial Chemotherapy 8: 171-174, 1981

Berk SL, Verghese A. Emerging pathogens in nosocomial pneumonia. European Journal of Clinical Microbiology and Infectious Diseases 8: 11-14, 1989

Berk SL, Verghese A, Holtsclaw SA, Smith K. Enterococcal pneumonia: occurrence in patients receiving broad-spectrum antibiotic regimens and enteral feeding. American Journal of Medicine 74: 153-154, 1983

Berré J, Thys JP, Husson M, Diamon G, Klastersky J. Penetration of ciprofloxacin in bronchial secretions after intravenous administration. Journal of Antimicrobial Chemotherapy 22: 499-504, 1988

Boccazzi A, Langer M, Mandelli M, Ranzi AM, Urso R. The pharmacokinetics of aztreonam and penetration into the bronchial secretions of critically ill patients. Journal of Antimicrobial Chemotherapy 23: 401-407, 1989

Boden CR, Lampton LM, Miller DP, Tarka EF, Everett ED. Endobronchial pH: relevance to aminoglycoside activity in Gram-negative bacillary pneumonia. American Review of Respiratory Diseases 127: 39-41, 1983

Boon RJ, Pierce CV. Distribution of amoxycillin/clavulanic acid and ticarcillin/clavulanic acid into infected pleural fluid-exudate of mice and effect of therapy. In Spits et al. (Eds) Proceedings of the 13th International Congress of Chemotherapy, pp. 4.1/6.9, H. Erdman, Wien, 1983

Brown RB, Kruse JA, Counts GW, Russel JA, Christou NV, et al. Double-blind study of endotracheal tobramycin in the treatment of Gram-negative bacterial pneumonia. Antimicrobial Agents and Chemotherapy 34: 269-272, 1990

Campoli-Richards DM, Monk JP, Price A, Benfield P, Todd PA, et al. Ciprofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 35: 373-447, 1988

Chastre J, Fagon JY, Soler P, Domart Y, Pierre J, et al. Quantification of BAL cells containing intracellular bacteria rapidly identifies ventilated patients with nosocomial pneumonia. Chest 95 (Suppl.): 190-192, 1989b

Chastre J, Fagon J-Y, Domart Y, Gibert C. Diagnosis of nosocomial pneumonia in intensive care unit patients. European Journal of Clinical Microbiology and Infectious Diseases 8: 35-39, 1989a

Choisson RE, Slutkin G. Tuberculosis and human immunodeficiency virus infection. Journal of Infectious Diseases 159: 96-100, 1989

Cordonnier C, Bernaudin JF, Bierling P, Huet Y, Vernant JP. Pulmonary complications occurring after allogeneic bone marrow transplantation. Cancer 58: 1047-1054, 1986

Cox AL, Meewis JMJM, Horton R. Penetration into lung tissue after intravenous· administration of amoxycillin/clavulanate. Journal of Antimicrobial Chemotherapy 24 (Suppl. E): 87-91, 1989

Donowitz GR, Mandell GL. Acute pneumonia. In Mandell et al. (Eds) Principles and practice of infectious disease, 3rd edition, pp. 540-560, Churchill Livingstone, 1990

Donowitz GR, Mandell GL. Empiric therapy for pneumonia. Reviews of Infectious Diseases 5 (Suppl.): S40-S54, 1983

Dull WL, Alexander MR, Kasik JE. Bronchial secretion levels of amikacin. Antimicrobial Agents and Chemotherapy 16: 767-771, 1979

Ebden P, Nell P, Farrow PR. Sputum levels of fluconazole in humans. Antimicrobial Agents and Chemotherapy 33: 963-964, 1989

Erttmann M, Ullman U, Koch EM. Results of a clinical and pharmacokinetic study of ceftazidime in patients with postoperative pneumonia on assisted ventilation. Journal of Hospital Infection 15 (Suppl. AP): 55-59, 1990

Fagon JY, Chastre J, Domart Y, Trouillet JL, Pierre J, et al. Nosocomial pneumonia in patients receiving continuous mechanical ventilation: prospective analysis of 52 episodes with use of protected specimen bush and quantitative culture techniques. American Review of Respiratory Diseases 139: 877-884, 1989

Follath F, Costo E, Thommen A, Frei R, Burdeske A, et al. Clinical consequences of development of resistance to third generation cephalosporins. European Journal of Clinical Microbiology 6: 446-450, 1987

Frasechini F, Scuglione F, Pintucci G, Maccarinnelli G, Dugnani S, et al. The diffusion of clarithromycin and roxithromycine into nasal mucosa, tonsil and lung in humans. Journal of Antimicrobial Chemotherapy 27 (Suppl. A): 61-65, 1991

Gerson SL, Tolbot GH, Hurwitz S, Strom BL, Lusk E, et al. Prolonged granulocytonia: The major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Annals of Internal Medicine 100: 345-351, 1984

Glatt AE, Chirgwin K, Landesman SH. Treatment of infections associated with human immunodeficiency virus. New England Journal of Medicine 318: 1439-1448, 1988

Gonzalez JP, Henwood JM. Pefloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 37: 628-668, 1989

Grinan NP, Lucena FM, Romero JV, Michavila IA, Dominguez SU, et al. Yields of percutaneous needle lung aspiration in lung abscess. Chest 97: 69-74, 1990

Groeneveld K, van Alphen L, Eijk Paul P. Visschers G, Jansen HM, et al. Endogenous and exogenous reinfections by Haemophilus influenzae in patients with chronic obstructive pulmonary disease: the effect of antibiotic treatment or persistence. Journal of Infectious Diseases 161: 512-517, 1990

Hager H, Verghese A, Alvarez S, Berk SL. Branhamella catarrhalis respiratory infections. Review of Infectious Diseases 9: 1140-1149, 1987

Harstein AI, Rashad AL, Liebler JM, Actis LA, Freeman J, et al. Multiple intensive care unit outbreak of Acinetobacter coleoacetiens, subspecies anitratus: respiratory infection and colonization associated with contaminated, reviable ventilator circuits and resuscitation bags. American Journal of Medicine 85: 624-631, 1988

Kemmerich B, Lode H. Rational use of new antibiotics in respiratory infections. In Pennington JE (Ed.) Respiratory infections: diagnosis and management, 2nd ed., pp. 648-657, Raven Press, New York, 1988

Klastersky J, Carpentier-Meunier F, Kahan-Coppens L, Thys JP. Endotracheally administered antibiotics for Gram-negative bronchopneumonia. Chest 75: 586-591, 1979

Klastersky J, Thys JP, Mombelli G. Comparative studies of intermittent and continuous administration of aminoglycosides in the treatment of bronchopulmonary infections due to Gram-negative bacteria. Review of Infectious Diseases 3: 74-83, 1981

Kugler JW, Armitage JO, Helms CM, Klassen LW, Goeken NE, et al. Nosocomial Legionnaires' Disease: Occurrence in recip-

ients of bone marrow transplants. American Journal of Medicine 74: 281-288, 1989

La Force FM. Systemic antimicrobial therapy of nosocomial pneumonia. Monotherapy versus combination therapy. European Journal of Clinical Microbiology and Infectious Diseases 8: 61-68, 1989

Lode H, Kemmerich B, Gzuhlke G, Dzwillo G, Koeppe P, et al. Cefotaxime in bronchopulmonary infections: a clinical and pharmacological study. Journal of Antimicrobial Chemotherapy 6: 193-198, 1980

Mangi RJ, Greco T, Ryan J, Thornton G, Andriole VT. Cefoperazone versus combination antibiotic therapy of hospital-acquired pneumonia. American Journal of Medicine 84: 68-74, 1988

Marks MI, Prentice R, Swerson R, Cotton EK, Eichkoff TC. Carbenicillin and gentamicin: pharmacologic studies in patients with cystic fibrosis and pseudomonas pulmonary infections. Journal of Pediatrics 79: 822-828, 1971

Marrie TJ, Durant H, Yates L. Community-acquired pneumonia requiring hospitalisation: 5-year prospective study. Review of Infectious Diseases 11: 586-599, 1989

Martin C, Gouin F, Fourrier F, Junginger W, Prieur BL. Pefloxacin in the treatment of nosocomial lower respiratory tract infections in intensive care patients. Journal of Antimicrobial Chemotherapy 21: 795-799, 1988

Meyers JD. Infection in bone marrow transplant recipients. American Journal of Medicine 81 (Suppl. 1A): 27-38, 1986

Miletovic D, Braveny I. Development of resistance during antibiotic therapy. European Journal of Clinical Microbiology 6: 234-244, 1987

Miliauskas JR, Webber BL. Disseminated varicella at autopsy in children with cancer. Cancer 53: 1518-1525, 1984

Monk JP, Campoli-Richards DM. Ofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 33: 346-391, 1987

Moore RD, Smith C, Lietman PS. Association of aminoglycoside plasma levels with therapeutic outcome in Gram-negative pneumonia. American Journal of Medicine 77: 657-662, 1984

Morks MI. The pathogenesis and treatment of pulmonary infections in patients with cystic fibrosis. Journal of Pediatrics 98: 173-179, 1981

Muller-Serieys C, Bergogne-Berezin E, Rowan C, Dombret MC. Imipenem penetration into bronchial secretions. Journal of Antimicrobial Chemotherapy 20: 618-619, 1987

Nolen TM, Phillips HL, Hall HJ. Comparison of aztreonam and tobramycin in the treatment of LRTI caused by Gram-negative bacilli. Review of Infectious Diseases 7 (Suppl. 4): 666-668, 1985

Pallares R. Gudiol F, Linares J, et al. Risk factors and response to antibiotic therapy in adults with bacteremic pneumonia caused by penicillin-resistant pneumococci. New England Journal of Medicine 317: 18-22, 1987

Peloquin Chuck A, Cumbo TJ, Sands MF, Schentog JJ. Intravenous ciprofloxacin for nosocomial LRTI. Review of Infectious Diseases 11 (Suppl. 5): 1225-1226, 1989

Pennington JE, Block ER, Reynolds HY. 5-Fluorocytosine and amphotericin B in bronchial secretions. Antimicrobial Agents and Chemotherapy 6: 324-326, 1975

Pennington JE. Penetration of antibiotics into respiratory secretions. Reviews of Infectious Diseases 3: 67-73, 1981

Peterson LR. Animal models: the in-vitro evaluation of ciprofloxacin. Journal of Antimicrobial Chemotherapy 18 (Suppl. D): 55-64, 1986

Phillips I, Warren C, Shannon K, King A, Hanslo D. In-vitro antibacterial activity and susceptibility of β-lactamases compared with that of cefotaxime, moxalactam and other β-lactam antibiotics. Journal of Antimicrobial Chemotherapy (Suppl. B): 23-31, 1981

Pulverer G, Peters G, Kunstman G. In vitro activity of ticarcillin with and without clavulanic acid against isolate of gram-positive and gram-negative bacteria. Journal of Antimicrobial Chemotherapy 17 (Suppl.): 1-5, 1986

Ramsey PG, Fife KH, Hackman RC, Meyers JD, Corey L. Herpes simplex virus pneumonia. Annals of Internal Medicine 97: 813-820, 1982

Rubin RH, Greene R. Etiology and management of the compromised patient with fever and pulmonary infiltrates. In Rubin RH, Young LS (Eds) Clinical approach to infection in the compromised host, pp. 131-163, Plenum, New York and London, 1988

Saito A, Sowatari K, Fukuda Y, Nogasawa M, Koga H, et al. Susceptibility of Legionella pneumophila to pefloxacin in vitro and in experimental Legionella pneumophila in guinea pigs. Antimicrobial Agents and Chemotherapy 28: 15-20, 1985

Salato RA, Gebhart RL, Palmer PL, Wade BH, Scheld WM, et al. Pneumonia treated imipenem/cilastin. American Journal of Medicine 78 (Suppl. 6A): 204-209, 1985

Schwigon CD, Mulla FW, Schulze B, Maslak A. Timentin in the treatment of nosocomial bronchopulmonary infections in intensive care units. Journal of Antimicrobial Chemotherapy 17 (Suppl. C): 115-122, 1986

Sickles EA, Greene WH, Wiernik PH. Clinical presentation of infection in granulocytopenic patients. Archives of Internal Medicine 135: 715-719, 1975

Simon HB. Mycobacterial and nocardial infections in the compromised host. In Rubin RM, Young LS (Eds) Clinical approach to infection in the compromised host, pp. 221-251, Plenum, New York and London, 1988

Singer C, Armstrong D, Rosen PP, Walzer PD, Yu V. Diffuse pulmonary infiltrates in immunosuppressed patients. American Journal of Medicine 66: 110-120, 1979

Slevin NJ, Aitken J, Thornley PE. Clinical and microbiological features of Branhamella catarrhalis bronchopulmonary infections. Lancet 1: 782-789, 1984

Swabb EA, Jenkins SA, Muir JG. Summary of worldwide clinical trials of aztreonam, with LRTI. Review of Infectious Diseases 7 (Suppl. 4): 772-777, 1985

Thadepalli M. Lower respiratory tract. In Ristuccia AM & Curha BA (Eds) Antimicrobial therapy, pp. 489, 454, Raven Press, New York, 1984

Thys JP, Husson M, Mombelli G, Klastersky J. Inactivation of netilmicin and amikacin by leukocytes. Abstract 353. In Proceedings of the Second Congress of Chemotherapy, Nice, 1980

Thys JP, Jacobs F, Motte S. Quinolones in the treatment of lower respiratory tract infections. Reviews of Infectious Diseases 11: S1212-S1219, 1989

Verghese A, Berk SL, Boelen L, Smith K. Group B streptococcal pneumonia in the elderly. Archives of Internal Medicine 142: 1642-1645, 1982

Vuye A, Pijck J. In-vitro antibacterial activity of BMY-28142, a new extended-spectrum cephalosporin. Antimicrobial Agents and Chemotherapy 27: 574-577, 1985

Wolfson JS, Hooper DC. Fluoroquinolones antimicrobial agents. Clinical Microbiology Reviews 2: 378-424, 1989

Wong GA, Peirce TH, Goldstein E, Hoeprich PD. Penetration of antimicrobial agents into bronchial secretions. American Journal of Medicine 59: 219-223, 1975

Woo AH, Yu VL, Goetz A. Potential in hospital modes of transmission of Legionella pneumophilia. American Journal of Medicine 80: 567-573, 1986