

## Clinical Aspects of Upper and Lower Respiratory Tract Infections

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### Summary

Respiratory tract infections are among the most common illnesses leading to medical consultation, and are associated with significant morbidity and mortality. Community-acquired pneumonia is a common illness and, while *Streptococcus pneumoniae* continues to be the most frequent causative agent, atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* species are now identified as additional common aetiological agents. Since clinical and roentgenographic features poorly predict the aetiological agent in most cases of community-acquired pneumonia, empirical therapy is generally recommended. Nosocomial pneumonia is the second most common hospital-acquired infection and is associated with significant mortality. Aerobic Gram-negative bacilli and *Staphylococcus aureus* are the predominant causative pathogens. New techniques to improve the diagnosis of nosocomial pneumonia have been introduced, but their role has not been entirely clarified. Therapy directed toward the most likely pathogens (aerobic Gram-negative species and *S. aureus*) on an empirical basis is recommended until more specific information is obtained. Acute exacerbations of chronic bronchitis should be treated with antimicrobial therapy directed toward *S. pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*. Because of the emergence of  $\beta$ -lactamase-producing strains of *H. influenzae* and *M. catarrhalis*, the choice of an antimicrobial agent has to be carefully considered. Group A  $\beta$ -haemolytic streptococci are the most common cause of bacterial pharyngitis and penicillin remains the drug of choice. Patients suffering from otitis media and sinusitis are infected with the same organisms as those patients with acute exacerbations of chronic bronchitis and antibacterial choices are therefore similar.

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Upper and lower respiratory tract infections are among the most common illnesses requiring medical attention. In the United States the morbidity associated with upper respiratory tract infections in the mid-1980s resulted in 75 million physician visits per year, almost 150 million days lost from work, and more than \$10 billion in costs for medical care (Dixon 1985). In the National Health Interview Survey of 1981, it was estimated that 3.3 million cases of pneumonia occurred in ambulatory children and adults, for a rate of 1.5 episodes per 100 persons per year (National Center for

Health Statistics 1982). In 1981 there were more than half a million admissions to hospital with community-acquired pneumonia in the United States (Garibaldi 1985). The problem was considerably magnified in the elderly (> 65 years), among whom the admission rate to hospital was 11.5 per 1000 population compared with 1.0 per 1000 population in the 15 to 44 age group. During the same period in the United Kingdom, respiratory tract infections accounted for > 15% of all consultations with general practitioners. 75% of these patients received antibacterial therapy, resulting in

25 million antibacterial prescriptions per year (Woodhead et al. 1987). The pneumonia mortality rate remains low in the outpatient setting (< 5%), but approaches 25% among those requiring hospitalisation (Pachon et al. 1990; Research Committee of the British Thoracic Society and the Public Health Laboratory Service 1987).

Lower respiratory tract infections are generally bacterial in aetiology, while most upper respiratory tract infections are caused by viruses but may be associated with secondary bacterial infection (Gomez-Barreto 1991). *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common causative organisms in bacterial respiratory tract infections (Fang et al. 1990; Gwaltney et al. 1992; Levy et al. 1988; Marrie et al. 1989), except for acute tonsillitis/pharyngitis and laryngitis/laryngotracheitis, in which  $\beta$ -haemolytic streptococci and *Mycoplasma pneumoniae*, respectively, are the predominant bacterial pathogens (Gomez-Barreto 1991).

Treatment of viral infections is generally symptomatic, with no empirical anti-infective therapy being required (Lang & Singh 1990). This article focuses on those infections requiring antibacterial therapy, namely bacterial pneumonia, bronchitis, tonsillitis, pharyngitis, otitis media and sinusitis.

## 1. Pneumonia

### 1.1 Clinical Features

Early institution of specific antimicrobial therapy has been shown to reduce the morbidity and mortality associated with pneumonia and to limit the associated toxicity of such therapy, by limiting exposure to antibacterials. While early diagnosis is optimal in the management of pneumonia, the aetiology is not determined in as many as 33 to 50% of all patients even if extensive diagnostic testing is performed (Fang et al. 1990).

Traditionally, physicians have used the syndromic approach to make an aetiological diagnosis of pneumonia (Pennington 1983). Patients are divided into those with a classic bacterial pneumonia syndrome and those with an atypical presentation. In the former type, best exemplified by pneumo-

coccal pneumonia, patients present with high fever of acute onset, cough productive of purulent sputum, and pleuritic chest pain with abnormal findings on physical examination of the chest. The roentgenographic abnormality found most commonly is lobar consolidation. In contrast, patients with the atypical pneumonia syndrome, frequently caused by *M. pneumoniae*, tend to have an illness with a more insidious onset, low grade temperature, and a nonproductive cough; often, physical examination of the chest is normal. The roentgenographic features of atypical pneumonia are those of bronchopneumonia, or a diffuse interstitial pattern. Unfortunately, the usefulness of this approach is limited, since the clinical features of many infections overlap, with clinical symptoms being as much a reflection of the host as they are of the pathogen involved. *H. influenzae*, *Staphylococcus aureus* and Gram-negative enteric bacteria have been implicated in clinical syndromes indistinguishable from that of *S. pneumoniae* (Wallace et al. 1978). Agents such as *Chlamydia pneumoniae* and viruses have been noted to cause atypical pneumonia syndromes (Grayston et al. 1986). The attribution of specific clinical features has been used particularly in patients infected with *Legionella* species. A gastrointestinal prodromal illness in association with hyponatraemia has been reported with this infection (Kirby et al. 1980; Yu et al. 1982). However, in a prospective study, Fang and coworkers could not identify this constellation of findings in patients infected with *Legionella* species any more frequently than in patients infected with other respiratory pathogens (Fang et al. 1990). In general, the clinical features of pneumonia cannot be sufficiently well defined in prospective studies to allow an accurate aetiological diagnosis of pneumonia to be made (Fang et al. 1990; Farr et al. 1989; Woodhead et al. 1987).

The signs and symptoms of pneumonia are easily recognised, but are not unique to pneumonia. In a recent British Thoracic Society study of 453 patients, the commonest symptoms were cough (88%), dyspnoea (71%), sputum production (69%), chest pain (64%), haemoptysis (17%), and mental confusion (14%) [Research Committee of the Brit-

ish Thoracic Society and the Public Health Laboratory Service 1987]. Fang and coworkers could not use the frequency of these findings to distinguish between the various microbial aetiologies and suggested that the syndromic approach to the aetiological diagnosis of pneumonia should be abandoned (Fang et al. 1990).

### 1.2 Epidemiology of Community-Acquired Pneumonia

While an early diagnosis is optimal in the management of community-acquired pneumonia, the aetiology of pneumonia is frequently not ascertained. No test that can identify all potential pathogens is presently available, and each diagnostic test is associated with limitations. Because of these limitations, most patients will be treated on an empirical basis. In order to facilitate the choice of antimicrobial agent, an understanding of the epidemiology of pneumonia is important. Many studies examining the frequency of various microbes have been published in the past few years. Unfortunately, many of these studies have important drawbacks: e.g. a limited duration of observation (less than 1 year), which would bias the results in favour of certain pathogens associated with epidemics (e.g. influenza, respiratory syncytial virus); reliance on a limited number of diagnostic tests; or the fact that many studies were completed before the recognition of *Legionella* species or *C. pneumoniae* as important respiratory pathogens. If one examines prospective studies of 1 or more years' duration that have been reported in the last 10 years from either Western Europe or North America, which enrolled at least 100 patients, a recognisable pattern emerges.

Fang and colleagues analysed 359 patients in Pittsburgh with community-acquired pneumonia prospectively over 1 year in a multicentre study (table I) [Fang et al. 1990]. Sputum cultures, Gram stain, blood cultures, direct fluorescent antibody stain, and serological studies for *Legionella* and antibody against *C. pneumoniae* and *M. pneumoniae* were obtained. Despite these rigorous investigations, an aetiological diagnosis was not obtained

**Table I.** Aetiology in 359 cases of community-acquired pneumonia in Pittsburgh (data from Fang et al. 1990)

	Total	%
<i>Streptococcus pneumoniae</i>	55	15.3
<i>Haemophilus influenzae</i>	39	10.9
<i>Legionella</i> spp.	24	6.7
<i>Chlamydia pneumoniae</i>	22	6.1
Aerobic Gram-negative species	21	5.9
<i>Staphylococcus aureus</i>	12	3.3
<i>Streptococcus</i> spp.	10	2.8
<i>Pneumocystis carinii</i>	7	2.0
<i>Mycoplasma pneumoniae</i>	7	2.0
Miscellaneous	10	2.8
Virus	1	0.3
Postobstructive	19	5.3
Aspiration	12	3.3
Unknown	118	32.9
<b>Total</b>	<b>359</b>	<b>100</b>

in 33% of patients. The commonest bacterial pathogen isolated was *S. pneumoniae* (15%), followed by *H. influenzae* (11%), *Legionella* species (7%) and *C. pneumoniae* (6%). Atypical pathogens (*Legionella* sp., *C. pneumoniae*, and *M. pneumoniae*) were found in 15% of patients.

Woodhead and coworkers examined the aetiology of community-acquired pneumonia in Nottingham, England, from October 1984 to September 1985 (Woodhead et al. 1987). Pneumonia accounted for 5.6% of all lower respiratory tract infections for which antibacterials were prescribed. The incidence of pneumonia was 4.7 per 1000 adult population per year. A pathogen was identified in 55% of cases: *S. pneumoniae* accounted for 36%, *H. influenzae* for 10%, and atypical pathogens including respiratory virus for 16% of cases.

Marrie and coworkers studied all patients with community-acquired pneumonia admitted to the Victoria General Hospital in Halifax, Canada, between November 1981 and March 1987 (Marrie et al. 1989). A definitive aetiological diagnosis was not made in 47% of patients. *S. pneumoniae* was the most common agent isolated and accounted for

8.5% of cases. Atypical organisms (*M. pneumoniae*, *Legionella* sp., and *C. burnetii*) accounted for slightly more than 10% of cases.

Levy and colleagues, working in Paris, reported that an aetiological diagnosis was obtainable in only 65% of 116 patients presenting to hospital between February 1983 and January 1984 (Levy et al. 1988). They found that *S. pneumoniae* was the commonest isolated organism (26%), followed by *H. influenzae* (12%). Collectively, the atypical pathogens accounted for slightly over 8% of cases.

The British Thoracic Society reported that *S. pneumoniae* was the most commonly found causative pathogen (34%), followed by *M. pneumoniae* (18%) [Research Committee of the British Thoracic Society and the Public Health Laboratory Service 1987]. An aetiological agent was found in 67% of cases. These findings are in contrast to a recent study from Barcelona, Spain, where *C. pneumoniae* was the commonest pathogen, followed by *S. pneumoniae* and then *M. pneumoniae* (Almirall et al. 1993). However, the cause of pneumonia was established in less than half of all patients identified with the disease. The incidence of pneumonia was 2.6 cases per 1000 adult population, which is slightly less than the incidence reported by British workers (Woodhead et al. 1987).

From these and other similar studies, several conclusions can be drawn (Bates et al. 1992; Pareja et al. 1992). The aetiological agent is not found in 30 to 50% of cases. Most studies clearly indicate a declining role for *S. pneumoniae*, and the increasing importance of atypical pathogens. The most common pathogens in patients under the age of 65 years and without comorbid illnesses are *M. pneumoniae*, *S. pneumoniae*, respiratory tract viruses, *C. pneumoniae* and *H. influenzae*. Mortality associated with these infections is low, and the majority of patients can be treated on an outpatient basis. Patients over the age of 65 and with comorbid illnesses are likely to be infected with *S. pneumoniae*, respiratory tract viruses, *H. influenzae*, aerobic Gram-negative bacilli, and *S. aureus*. Less common pathogens include *Moraxella catarrhalis*, *Legionella* spp., Mycobacteria and endemic fungi.

### 1.3 Diagnostic Studies in Patients with Community-Acquired Pneumonia

Chest roentgenography should be performed in all patients suspected of having pneumonia. An abnormal chest roentgenogram is the only way to absolutely confirm the diagnosis of pneumonia, and at times may confirm the presence of coexisting conditions such as bronchial obstruction or pleural effusions. Clinicians have used the chest roentgenogram to infer an aetiological diagnosis of pneumonia, but this is fraught with hazard. While homogeneous alveolar infiltration is more common in bacterial aetiologies, other findings such as atelectasis or pleural effusion can be seen in all aetiologies (MacFarlane et al. 1984). No organism consistently produces the same roentgenographic abnormality; conversely, similar roentgenographic patterns may be produced by different organisms. Tew and colleagues found that *M. pneumoniae* was more easily diagnosed roentgenographically than other bacterial and viral pneumonia, but agreement between members of a panel of expert radiologists on aetiological diagnosis was reached in only 29% of cases (Tew et al. 1977).

A properly performed Gram stain of expectorated sputum examined by an experienced observer may be useful in the initial evaluation of a patient with pneumonia. However, false positive and false negative rates of 88 and 38%, respectively, have been reported (Merrill et al. 1973; Rein et al. 1978). Failure to visualise a predominant organism on Gram stain despite the presence of large numbers of leucocytes should suggest the possibility of atypical pathogens (Fang et al. 1990). The results with expectorated sputum cultures are even worse, with fewer than 50% of samples processed by the usual clinical methods yielding reliable results (Bartlett 1987). Blood cultures should be drawn in patients ill enough to require hospitalisation, but positive results are observed in only 15 to 25% of patients with pneumococcal pneumonia, and less frequently in patients infected with other pathogens (Levy et al. 1988). Serological testing and cold agglutinin measurements are not useful in the initial evaluation of patients with community-ac-

quired pneumonia and should not be routinely performed. More invasive procedures such as bronchoscopy, bronchoscopy with a protected brush catheter, bronchoalveolar lavage with or without balloon protection, direct needle aspiration of the lung, or open lung biopsy should be reserved for the more critically ill patient who is not responding to the usual empirical therapy.

#### 1.4 Severe Community-Acquired Pneumonia

The overall mortality rate associated with community-acquired pneumonia continues to be between 10 and 20%. Mortality is higher in patients developing acute respiratory failure and requiring mechanical ventilation. The mortality rate varied from 21 to 54% in patients with community-acquired pneumonia requiring Intensive Care Unit (ICU) management, in 6 studies published between 1985 and 1991 (Feldman et al. 1989; Ortqvist et al. 1985; Pachon et al. 1990; Sorenson et al. 1986; Torres et al. 1991; Woodhead et al. 1985). More than 50% of these patients required mechanical ventilation. The 2 commonest organisms found in this clinical setting were *S. pneumoniae* and *Legionella pneumophila*. The factors associated with mortality included inadequate antibacterial therapy before ICU admission, the requirement for mechanical ventilation, use of positive endexpiratory pressure, inspired oxygen fraction ( $F_iO_2$ ) > 0.6, coexistence of adult respiratory distress syndrome (ARDS), radiographic spread of pneumonia during ICU stay, septic shock, bacteraemia and *Pseudomonas aeruginosa* as the causative agent. Of all the factors listed above, radiographic spread of pneumonia and the presence of septic shock will accurately predict mortality in most patients (Torres et al. 1991).

## 2. Management

For the reasons listed above, the majority of patients will be treated empirically. Given careful consideration of aetiological and epidemiological factors, an approach to rational antimicrobial prescribing can be derived (Mandell et al. 1993). This

approach utilises the severity of illness and the presence of comorbid factors to determine the most likely pathogens. Patients presenting with community-acquired pneumonia without significant comorbid illnesses and not severely ill tend to be infected with *M. pneumoniae*, *S. pneumoniae*, *C. pneumoniae* and *H. influenzae*. An orally administered macrolide antibiotic such as erythromycin or spiramycin should be considered for initial therapy, with tetracycline or its derivatives as alternatives (Hampson et al. 1991). In patients not severely ill but with significant comorbid illness, such as chronic obstructive lung disease, the commonest organisms are *S. pneumoniae*, *H. influenzae*, oral anaerobes, Gram-negative rods, *S. aureus* and, in some specified geographical sites, *Legionella* species. Reasonable choices for these patients would include an orally administered second generation cephalosporin, cotrimoxazole (trimethoprim/sulfamethoxazole), or a  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination with or without a macrolide. A macrolide should be included for *Legionella* infections. A  $\beta$ -lactam antibiotic such as amoxicillin alone may not be successful because of the increasing prevalence of  $\beta$ -lactamase-producing strains of *H. influenzae* throughout the world (Doern et al. 1988).

In patients ill enough to require hospitalisation, the commonest pathogens are identical to the ones listed above. In patients without comorbid illness, a combination of parenteral erythromycin and a second or third generation cephalosporin will cover the most likely pathogens. In patients with comorbidity, the macrolide antibiotic may be omitted if *Legionella* infection is unlikely. For patients with extensive pneumonia requiring ICU admission, the most likely pathogens are *S. pneumoniae* and *Legionella* species (Feldman et al. 1989; Ortqvist et al. 1985; Pachon et al. 1990; Sorenson et al. 1986; Torres et al. 1991; Woodhead et al. 1985). However, to assure broad coverage for critically ill patients, a combination of a macrolide plus a third generation cephalosporin with antipseudomonal activity is appropriate. Alternatives to the latter include imipenem/cilastatin or a quinolone.

While these choices are reasonable for initial

**Table II.** Most frequently isolated pathogens in patients with nosocomial pneumonia in the United States [data from Centers for Disease Control, National Nosocomial Infections Study Report, annual summary, 1984. Morbidity and Mortality Weekly Report 1986: 35 (1SS): 17SS-29SS]

Pathogen	Frequency (% of isolates)
<b>Gram-positive cocci</b>	
<i>Staphylococcus aureus</i>	12.9
<b>Gram-negative bacilli</b>	
<i>Pseudomonas</i> spp.	16.9
<i>Klebsiella</i> spp.	11.6
<i>Enterobacter</i> spp.	9.4
<i>Escherichia coli</i>	6.4
<i>Serratia</i> spp.	5.8
<i>Proteus</i> spp.	4.2

empirical therapy, close follow-up is required to assure that a response is achieved. If further information regarding the aetiology of infection is obtained, then targeted therapy with narrow spectrum antimicrobials is warranted.

### 3. Nosocomial Pneumonia

Nosocomial pneumonia is defined as pneumonia occurring 48 hours or more after admission to hospital. It occurs at a rate of 5 to 10 per 1000 discharges and is the second most common hospital-acquired infection, accounting for 10 to 17% of all hospital-acquired infections (Centers for Disease Control 1985; Wenzel 1989). It extends the length of hospitalisation by 7 to 9 days and costs in excess of \$1 billion annually in the United States alone (Wenzel 1989). The overall mortality associated with nosocomial pneumonia ranges from 28 to 37% in university teaching hospitals (Celis et al. 1988; Graybill et al. 1973; Gross et al. 1980), with approximately one-third of deaths attributed to nosocomial pneumonia (Leu et al. 1989).

#### 3.1 Aetiology and Pathogenesis

With the rapid changes in available technology, the aetiological diagnosis of nosocomial pneumonia has evolved in the past few years (see sec-

tion 3.2). Most studies have found that aerobic Gram-negative bacilli account for 60 to 80% of bacteria isolated, and aerobic Gram-positive cocci, especially *S. aureus*, for a further 20 to 30% (table II). *L. pneumophila*, viruses and fungi may also be causative agents (Hall et al. 1975; Kirby et al. 1980; Klein & Watanakunakorn 1979).

Many risk factors have been associated with nosocomial pneumonia (table III) [Celis et al. 1988; Craven et al. 1986]. Endotracheal intubation and tracheostomy are associated with the highest rates of nosocomial pneumonia. The presence of endotracheal and nasogastric tubes alters natural host defences and increases the rate of entry of microorganisms into the lung. Respiratory therapy devices such as mechanical ventilators, in-line medication nebulisers, and mist tents have all been associated with increased rates of nosocomial pneumonia (Craven et al. 1984; Reinartz et al. 1965). Common to these identified risk factors is access to the lower respiratory tract by Gram-negative and other potential respiratory pathogens after initial colonisation of the upper respiratory tract (Johanson et al. 1969, 1972). Colonisation occurs rapidly in critically ill populations. Attachment of Gram-

**Table III.** Risk factors for nosocomial pneumonia (adapted from Craven et al. 1990)

Endogenous factors	Exogenous factors
<b>Host factors</b>	<b>Environmental factors</b>
Advanced age	Seasonal trends
Male sex	Cross contamination
Chronic disease	Air flow/water supply
Impaired immunity	<b>Hospitalisation</b>
Malnutrition	Teaching hospital
Obesity	Intensive care unit
<b>Life-style factors</b>	Medical/surgical wards
Smoking	Prolonged stay
Ethanol abuse	<b>Therapeutic</b>
<b>Depressed consciousness</b>	Sedatives/hypnotics
<b>Aspiration</b>	Immunosuppressives
<b>Prior infection/antibacterials</b>	Antacid ± H <sub>2</sub> -blocker
<b>Prior surgery</b>	<b>Invasive devices</b>
Head and neck	Endotracheal tube
Thoracic	Tracheostomy tube
Abdominal	Nasogastric tube
	Intracranial pressure monitor

negative rods by adhesins (pili, fimbriae or alginate) is an important step in colonisation, and is inversely related to cell surface fibronectin (Woods et al. 1980, 1981). Once colonisation of the upper respiratory tract has been established, aspiration of bacteria into the tracheobronchial tree from the oropharynx or stomach challenges the intrinsic respiratory defence mechanisms. Aspiration occurs commonly in healthy individuals, but is more common in patients with altered consciousness, inability to protect the upper airway, delayed gastric emptying or decreased gastrointestinal motility (Huxley et al. 1978; Pennington 1984). Host factors such as the extremes of age, male sex, the presence of chronic disease, impaired immunity, malnutrition, obesity, smoking history and ethanol abuse have also been associated with nosocomial pneumonia (Craven et al. 1990).

### 3.2 Diagnosis of Nosocomial Pneumonia

The diagnosis of nosocomial pneumonia is difficult because there is no gold standard. Most studies have used clinical criteria to establish a diagnosis; indeed, the Center for Disease Control recently defined nosocomial pneumonia as including the presence of rales or dullness to percussion on physical examination of the chest, with chest roentgenographic evidence of a new or progressive infiltrate, consolidation, cavitation or pleural effusion with new purulent sputum, positive blood culture, or isolation of an aetiological agent obtained by transtracheal aspirate, bronchial brushing, or biopsy (Centers for Disease Control 1989).

Because of the inherent difficulty of obtaining sputum cultures, as well as problems with their accuracy, reliability and interpretation in diagnosing pneumonia, other techniques have been introduced in order to improve diagnostic accuracy. Fiberoptic bronchoscopy by itself does not eliminate the problem, since aspirates are contaminated as they pass through the suction channel. These new techniques have been introduced to improve the sensitivity and specificity of the diagnosis of nosocomial pneumonia, but none are perfect and all are invasive, which limits their utility (table IV).

In most cases, the diagnosis of nosocomial pneumonia will be established by a synthesis of information obtained from the case history, including comorbid conditions and risk factors, and by physical examination and appropriate laboratory tests and/or procedures. A proper expectorated sputum sample for Gram stain and culture, blood cultures, and blood count should be obtained, and differential and routine chest roentgenography performed. Bronchoscopic specimens or other special tests should be reserved for more critically ill patients, such as those requiring ventilatory support.

### 3.3 Management

For patients with nosocomial pneumonia without particularly severe illness or unique risk factors, the likeliest causative organisms are *Klebsiella* spp., *Enterobacter* spp., *Escherichia coli*, *Proteus* spp., *Serratia marcescens* and *S. aureus* (core organisms). Depending on the severity of illness, oral agents such as amoxicillin/clavulanic acid, a second generation cephalosporin, cotrimoxazole or a quinolone may be used. If parenteral therapy is required, the combination of a first generation cephalosporin and an aminoglycoside, a parenteral second generation cephalosporin, or a nonanti-pseudomonal third generation cephalosporin should suffice.

Patients at risk of aspiration and those who have undergone thoraco-abdominal surgery may be infected with the core organisms plus anaerobes. Therefore, additional antianaerobic therapy, such as clindamycin, may be indicated.

Patients with diabetes mellitus or with a head injury or coma are prone to infection with *S. aureus*, and methicillin-resistant strains may be involved (Rello et al. 1990). A first generation cephalosporin plus an aminoglycoside, a second generation cephalosporin, or a nonanti-pseudomonal third generation cephalosporin will be adequate for infections caused by methicillin-sensitive strains. Vancomycin should be added in institutions where methicillin-resistant staphylococci are prevalent.

**Table IV.** Sensitivity and specificity of diagnostic methods used in patients with suspected nosocomial pneumonia

Diagnostic method	Sensitivity (%)	Specificity (%)	Reference
Clinical/x-ray parameters	34-100	64-90	Andrews et al. (1981) Bell et al. (1983) Chastre et al. (1984) Fagon et al. (1988, 1993)
Blood culture	24	42	Fagon et al. (1988)
Sputum culture	80	45-90	Bartlett (1987) Bryan & Reynolds (1984)
Bronchial washing			
Antibody-coated bacteria	54-73	98-100	Winterbauer et al. (1983)
Protected specimen brushing			
Gram stain	30	100	Higuchi et al. (1982)
Quantitative culture	67-100	67-100	Baughman et al. (1987) Chastre et al. (1984) De Castro et al. (1991) Fagon et al. (1988) Guerra & Baughman (1990) Higuchi et al. (1982) Pham et al. (1991) Torres et al. (1988)
Nonbronchoscopic protected specimen brushing			
Quantitative culture	64	100	Torres et al. (1988)
Bronchoalveolar lavage (BAL)			
Gram stain	79-86	96-100	Chastre et al. (1988)
Quantitative culture	77-88	100	Kahn & Jones (1987) Pugin et al. (1991) Torres et al. (1989)
Protected BAL			
Quantitative culture	84	100	Torres et al. (1989)
Protected mini-BAL			
Semiquantitative culture	70	69	Rouby et al. (1989)
Nonbronchoscopic BAL			
Bacterial culture	55	75	Piperno et al. (1988)

Patients who have been hospitalised for a prolonged period of time, who have received antibacterials during the current hospitalisation period, or who have been admitted to the ICU are prone to infection with resistant Gram-negative rods. These patients should be treated with a broad spectrum  $\beta$ -lactam with activity against *P. aeruginosa*, such as piperacillin, ceftazidime, imipenem/cilastatin, ticarcillin/clavulanic acid or ciprofloxacin plus an aminoglycoside. A similar recommendation ap-

plies to any patient with life-threatening nosocomial pneumonia (requiring ICU admission).

Patients receiving high dose corticosteroids may be infected with the core organisms and *Legionella* spp. Addition of a macrolide to antibacterials covering the core pathogens should be considered.

As with community-acquired pneumonia, the initial empirical regimen should be modified to a more narrow spectrum if specific information regarding the aetiological agent is obtained. Close



follow-up and frequent re-evaluation of therapeutic choices is mandatory.

#### **4. Acute Exacerbation of Chronic Bronchitis**

Acute exacerbations of chronic bronchitis are characterised by an increase in cough, dyspnoea, and alterations in the amount and type of sputum produced. Systemic features suggestive of infection, such as fever, leucocytosis or parenchymal lung infiltrates, are frequently absent. The role of bacterial infection in this condition is controversial and the value of antimicrobial therapy is uncertain.

##### **4.1 Aetiology and Pathogenesis**

Viruses, and to a lesser extent *Mycoplasma*, are implicated in approximately one-third of acute exacerbations (Buscho et al. 1978; Gump et al. 1976; Smith et al. 1980). Bacteria may act either as primary pathogens, or as secondary invaders after other agents have established mucosal injury. *S. pneumoniae*, nontypeable strains of *H. influenzae* and *M. catarrhalis* have been isolated from the sputum of most of these patients at some time in the course of their disease (Hager et al. 1987; Smith et al. 1976; Tager & Speizer 1975). Whether these organisms play a role in the acute exacerbation, or are simply saprophytes, has not been determined. There is evidence that the mere presence of these organisms can elicit and perpetuate an inflammatory response in the airway mucosa. Once cigarette smoke or other initiating factors damage airway mucosa and alter mucociliary clearance, organisms can adhere to airway secretions and colonise the airway. Organisms such as *H. influenzae*, *S. pneumoniae* and *P. aeruginosa* produce substances that can alter mucociliary clearance and damage epithelial surfaces (Munro et al. 1989; Wilson & Cole 1988; Wilson et al. 1985). Once an organism has colonised the airway, there is an inflammatory response involving cytokines and elastolytic enzymes, which can further injure the mucosa (Ras et al. 1990; Read et al. 1991). This may lead to

progressive airway damage and has been termed the 'vicious circle hypothesis' (Cole & Wilson 1989). If this hypothesis is correct, early intervention to eradicate bacteria from the lower respiratory tract, and perhaps steps to interfere with the inflammatory response, might help to prevent progressive airway damage.

##### **4.2 Management**

Antibacterial therapy is only one part of the management of acute exacerbations of bronchitis. The avoidance of respiratory irritants such as tobacco smoke, appropriate use of bronchodilators, corticosteroids and supplemental oxygen may all be beneficial.

Three of 6 randomised, placebo-controlled trials of antimicrobial therapy failed to demonstrate improvement, whereas the other 3 showed accelerated recovery, in patients with acute exacerbations of bronchitis (Anthonisen et al. 1987; Elmes et al. 1957, 1965; Nicotra et al. 1982; Pines et al. 1968, 1972). Importantly, the most recent study by Anthonisen and colleagues also indicated that antibacterial therapy prevented clinical deterioration (Anthonisen et al. 1987). In most published studies, the major pathogens recovered from sputum have been nontypeable *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*. Using a protected specimen brush technique to avoid upper airway contamination, Fagon and coworkers demonstrated that species of *Haemophilus* were the most commonly found organism in the lower respiratory tract of intubated patients with acute exacerbation of chronic bronchitis (Fagon et al. 1990). Prior to 1972, isolates of *H. influenzae* were uniformly susceptible to ampicillin. Since then, there has been a steady increase in the percentage of isolates resistant to ampicillin. Estimates of ampicillin resistance vary; however, rates as high as 15 to 30% have been reported (Jorgensen et al. 1990; Thornsberry 1988). *M. catarrhalis* is the third most commonly found organism in this clinical setting, and up to 75% of strains are  $\beta$ -lactamase producing (Murphy & Sethi 1992). While no antibacterial has been demonstrated to be superior in the management of these

**Table V.** Causes of acute pharyngitis (adapted from Pichichero 1990)

<b>Primary pathogens (30% of cases)</b>
Group A $\beta$ -haemolytic streptococci (common)
Group C streptococci (uncommon)
Group G streptococci (uncommon)
<i>Neisseria gonorrhoeae</i> (uncommon)
<i>Corynebacterium diphtheriae</i> (rare)
<b>Possible primary pathogens (&lt; 1% of cases)</b>
<i>Corynebacterium haemolyticum</i>
<b>No pathogens isolated (30% of cases)</b>
<b>Viruses (40% of cases)</b>
Rhinoviruses
Adenoviruses
Parainfluenzae virus
Coxsackievirus
Coronavirus
Echovirus
Herpes simplex virus
Epstein-Barr virus
Cytomegalovirus

patients, it seems prudent to consider agents that will cover  $\beta$ -lactamase-producing strains of *H. influenzae* and *M. catarrhalis*, such as amoxicillin/clavulanic acid, sulbactam/ampicillin or cefaclor, especially in patients with significantly compromised pulmonary function.

### 5. Acute Tonsillitis and Pharyngitis

Infections involving the pharynx are the most common cause of the 'sore throat'. Pain is aggravated by swallowing and may radiate along the glossopharyngeal nerve to the ear. Associated features commonly include rhinorrhoea, cough, cervical lymphadenopathy and tenderness, tonsillar enlargement, pharyngeal or tonsillar exudate and fever (Lang & Singh 1990). Generally, the symptoms and signs are self-limiting, disappear within a few days and no specific therapy is required. However, it is important to remember that a minority of pharyngeal infections are due to life-threatening diseases (diphtheria, acute epiglottitis or peritonsillar abscess), impending rheumatic fever (caused by  $\beta$ -haemolytic streptococci) or infec-

tious mononucleosis (Gomez-Barreto 1991) [table V; Pichichero 1990].

#### 5.1 Aetiology and Pathogenesis

Group A  $\beta$ -haemolytic streptococci are considered to be the most common cause of bacterial pharyngitis. According to the 1979 US National Health Care Survey, within a given year some 11% of children attending school are treated for pharyngitis, and 25 to 50% of these will be diagnosed as having group A streptococcus infection (Peter 1992; Pichichero 1990). Diagnosis is complicated by the fact that several adenoviruses cause symptoms that are indistinguishable from streptococcal pharyngitis, except where there is an associated conjunctivitis (30 to 50% of cases) [Lang & Singh 1990]. *M. pneumoniae* and *C. pneumoniae* are also relatively common causative organisms, but tend to cause subclinical pharyngitis. Although it is relatively uncommon in countries with an adequate vaccination programme, diphtheria should not be ruled out if a grey-green membrane firmly attached to the mucosa is observed; however mononucleosis should also be considered in this circumstance. Diagnosis of mononucleosis can be confirmed by the presence of a cheesy, creamy-white exudate or membrane confined to the tonsils, disturbed liver function tests, generalised lymphadenopathy, atypical mononuclear lymphocytes and a positive heterophile antibody test at some stage of the illness. Diphtheria, which is commonly accompanied by the classic 'bull-neck', may also involve the uvula and larynx, producing hoarseness and stridor in some cases. Anterior cervical lymphadenopathy is also common in this condition, and may be painful (Lang & Singh 1990).

Although relatively uncommon, the presence of a scarlatiniform rash accompanying a case of pharyngitis indicates the presence of infection caused by *S. pyogenes* or *Corynebacterium haemolyticum* (Lang & Singh 1990).

#### 5.2 Management

Penicillin remains the drug of choice for the treatment of streptococcal pharyngitis in primary care. In penicillin-allergic patients or penicillin-re-

sistant infections, a macrolide antibiotic or a cephalosporin is an appropriate alternative agent (Peter 1992; Pichichero 1990). It is important to note that an increasing number of cases are associated with concomitant colonisation by  $\beta$ -lactamase-producing organisms, which can protect streptococci by inactivating  $\beta$ -lactam antibacterials (Pichichero 1990). Many clinicians stress the need for prompt treatment of sufficient duration, in order to avoid complications such as rheumatic fever.

The treatment of mononucleosis is supportive, with no specific treatment being available. If diphtheria is suspected, treatment should be initiated immediately with either penicillin or erythromycin, and bacteriological confirmation sought (Lang & Singh 1990).

## 6. Otitis Media and Sinusitis

Otitis media is the most commonly diagnosed disease in children, with 25% of antibacterial prescriptions written in the USA each year being for the treatment of this condition (Bluestone 1992; Gomez-Baretto 1991). Sinusitis is also a common disorder, particularly in the paediatric population, and has often been underdiagnosed or under-recognised in the past. If left untreated, otitis media can result in complications such as cholesteatoma and hearing loss, while sinusitis can result in cellulitis, abscess, meningitis, osteomyelitis, or facial deformity, or serve as a trigger for asthma (Bluestone 1992; Gomez-Barreto 1991; Herr 1991).

### 6.1 Aetiology and Pathogenesis

Acute otitis media is defined as a middle-ear effusion accompanied by symptoms of an acute infection such as fever and irritability, and otalgia. Otitis media with effusion is characterised by the presence of an asymptomatic middle-ear effusion. *S. pneumoniae* (35% of cases) and *H. influenzae* (23% of cases) are the more common bacteria found in acute otitis media. *M. catarrhalis* infection is becoming more prevalent (14% of cases in 1992), with most strains being  $\beta$ -lactamase-producing

(Bluestone 1992). It is important to note the increasing emergence of  $\beta$ -lactamase-producing organisms that are implicated in acute otitis media and the consequences of this on the choice of antibacterial therapy (Bluestone 1992).

Sinusitis is an inflammation of the mucosa of the paranasal sinuses that may involve development of a bacterial infection at some stage. Presenting symptoms include nasal discharge and/or daytime cough lasting at least 10 days, or a severe episode of upper respiratory tract infection with high fever accompanied by a purulent nasal discharge (Wald et al. 1986). It is a common complication of upper respiratory tract infections, often involving the same bacteria prevalent in acute otitis media. There are similarities between adults and children in bacteriological characteristics (Giebink 1992). However, sinusitis is difficult to diagnose, as bacterial sinus infection, uncomplicated viral infection and allergic rhinitis are often indistinguishable. In addition, clinicians must decide whether to treat acute bacterial sinusitis during the course of an upper respiratory tract infection, given that the signs and symptoms resolve spontaneously in 40% of patients (Giebink 1992).

### 6.2 Management

Effective antibacterial treatment of both otitis media and sinusitis should be based on a knowledge of the bacterial aetiology. Although some investigators question the need for administering antibacterials in either of these conditions, most experts agree that patients who have signs and symptoms of acute otitis media or acute sinusitis should receive antimicrobial therapy. The antimicrobial regimens recommended for the treatment of acute sinusitis are similar to those used for acute otitis media. Amoxicillin is currently preferred for initial treatment and should be given for 10 to 14 days; however, treatment for up to 21 days is recommended by some clinicians (Lazar & Younis 1992). Doxycycline is also a popular choice and should be given in a dose of 200mg initially, then 100mg daily for 7 to 14 days. If the patient is allergic, or the causative pathogen is resistant to

penicillins or cephalosporins, a macrolide antibiotic or cotrimoxazole would be appropriate. However, the latter may be ineffective in patients with pharyngitis caused by Group A streptococci. In cases of sinusitis where there are signs and symptoms of intraorbital or intracranial complications, surgical drainage in conjunction with antibacterial therapy is recommended (Bluestone 1992; Giebink 1992; Gwaltney et al. 1992; Herr 1991; Lazar & Younis 1992). The use of decongestants, antihistamines and anti-inflammatory agents in the treatment of sinusitis remains controversial. Although decongestants shrink nasal mucous membranes, improve drainage and provide symptomatic relief, they can cause ciliostasis. They may therefore delay clearance of infected material, as well as impairing diffusion of antimicrobial drugs into the sinuses by decreasing bloodflow. Antihistamines can cause inspissation of secretions, and are also implicated in a number of adverse reactions (Giebink 1992).

## 7. Conclusions

Infections of the upper and lower respiratory tract are responsible for more restriction of activity and absence from work than any other category of acute illness. They are the most common reason cited for visits to a physician and a frequent cause for prescription of antibacterial agents. A thorough understanding of the clinical syndromes associated with respiratory tract infections, and the pathogens likely to be involved, is important in the selection of appropriate antimicrobial therapy. Careful monitoring of the patient's response to therapy, in addition to the judicious use of laboratory investigations, should lead to a successful therapeutic intervention.

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