45 Infections of the lower respiratory tract

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Respiratory infections are usually divided into those involving the upper and those involving the lower respiratory tract. The former typically include infections of the sinuses, the tonsillopharyngeal area and the middle ear. Lower respiratory tract infections include acute bronchitis, acute exacerbations of chronic bronchitis and pneumonia. Pneumonia is further subdivided into community-acquired, healthcare-associated and hospital-acquired infections.

Acute lower respiratory tract infections are a significant cause of morbidity and mortality worldwide and most occur in developing countries where poverty and inadequate medical care contribute to the high mortality rates. Pneumonia continues to be the most common cause of death from infectious diseases worldwide. Although our understanding of the various etiological agents and the pathogenic mechanisms involved in various respiratory infections has increased, our ability to diagnose accurately the causative agent(s) has not kept pace. This means that often the physician initiates treatment on an empirical basis and in far too many situations antibiotics are used when the infection is viral in nature.

ACUTE BRONCHITIS

Lower respiratory tract infections are typically divided into either bronchitis or pneumonia. These can also be thought of as infections involving the airways and the pulmonary parenchyma, respectively. Acute bronchitis is very common and can be viewed as one end of a continuum that extends from bronchitis to pneumonia. While it is generally not a particularly serious infection, it still has a considerable economic impact because of the frequency of physician visits and the fact that despite the lack of any compelling evidence supporting antimicrobial therapy, physicians who diagnose acute bronchitis prescribe antibiotics for 66% of such patients.[1]

In the USA it is estimated that acute bronchitis results in approximately 12 000 000 visits to physicians per year at a cost of $200–300 million.[2]

ETIOLOGY AND EPIDEMIOLOGY

The most common infectious agents are viruses, and typically respiratory viruses such as rhinovirus, corona virus, adenovirus and influenza virus are implicated. Other viral agents include respiratory syncytial virus (RSV), parainfluenza virus, measles virus and herpes simplex virus.[3–5]

While the term 'atypical respiratory pathogens' can include a large and diverse number of etiological agents, by convention they usually refer to *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella* species. *Mycoplasma* and *Ch. pneumoniae* and the etiological agent of whooping cough, *Bordetella pertussis*, are the most commonly encountered non-viral causes of acute bronchitis.[6]

Like many other respiratory infections, acute bronchitis is most common during the winter months. The mean attack rate in developed countries is 87 cases per 100 000 persons per week, reaching a peak of 150 cases per 100 000 during the winter season.[7]

PATHOGENESIS

In cases of acute bronchitis the disease process is limited to the mucous membrane lining the tracheobronchial tree. The mucous membrane becomes edematous and hyperemic and increased bronchial secretion is typically seen. Epithelial injury is usually mild to moderate but in cases of influenza virus infection there may be fairly significant epithelial damage.

Studies of pulmonary function during attacks of acute bronchitis have demonstrated abnormal findings in both airway resistance and reactivity. Such results are in keeping with the association that has been described between an increased incidence of mild asthma and patients with a history of recurrent episodes of acute bronchitis.[8]

The increased airway reactivity and resistance may manifest themselves clinically as a persistent cough lasting up to several weeks following the initial infection.

CLINICAL MANIFESTATIONS

The predominant symptom is cough. This may last up to several weeks and, depending upon the etiological agent, may be non-productive or productive of either mucoid or purulent sputum. In some cases the sputum may be mucoid initially, but if secondary bacterial infection results it may become purulent. Patients may also experience a burning retrosternal sensation on inspiration.

Physical examination may reveal the presence of rhonchi or coarse rales but bronchial breath sounds should not be heard.

The patient may be febrile but usually does not appear particularly ill. The exceptions to this are herpes simplex infection or bronchitis complicating influenza, which can produce marked malaise.

DIAGNOSIS

The diagnosis of acute bronchitis in an otherwise well adult is usually obvious from the clinical features. If there is any question of pneumonia, a chest radiograph will exclude the presence of a pulmonary infiltrate.

In general, it is not worth obtaining blood samples for serology or sputum for Gram stain and culture.

TREATMENT

Acute bronchitis is a common condition and most patients are managed at home. The treatment of acute bronchitis can be symptomatic or specific. Symptomatic treatment relies primarily upon maintenance of adequate hydration and cough suppression in those unable to sleep. If bronchospasm is a problem, then inhaled β_2-adrenergic bronchodilators may be used. At present there is no evidence to support the routine use of oral or inhaled steroids. Smokers should be encouraged to stop.

In patients with underlying cardiopulmonary disease, an episode of acute bronchitis may precipitate cardiac failure and the patient may need to be admitted to hospital for appropriate ventilatory and cardiac support.

Antimicrobial chemotherapy is generally not recommended: a number of placebo-controlled trials have evaluated the role of antibiotics in acute bronchitis and there is minimal benefit at best. Antibiotics might be considered in patients with persistent, prolonged and worsening symptoms.

In such situations, doxycycline, or a macrolide (erythromycin, azithromycin or clarithromycin) should be considered.

ACUTE EXACERBATION OF CHRONIC BRONCHITIS

Chronic bronchitis is defined as the presence of a productive cough for at least 3 months of the year for 2 consecutive years. Chronic bronchitis itself constitutes a common component of chronic obstructive pulmonary disease (COPD), a clinical entity characterized by reduced expiratory air flow that is relatively stable over several months of observation. The prognosis for COPD correlates best with the forced expiratory volume in one second (FEV_1), and when this falls below 50% of predicted value the prognosis worsens.

Most physicians do not differentiate among COPD, acute bronchitis and acute exacerbation of chronic bronchitis (AECB). In fact, even pneumonia is often simply included as part of the designation 'lower respiratory tract infections'. It is difficult to obtain accurate data on the exact economic impact of such entities, although COPD has been estimated to afflict one-fifth of the population of the USA.[9] In the UK around 30 million working days are lost every year because of bronchitis, and the disease accounts for approximately 5% of deaths annually.[10]

ETIOLOGY AND EPIDEMIOLOGY

Chronic bronchitis is the result of a variety of insults to the lung over time. These include predominantly cigarette smoke, infection, and environmental pollutants and irritants. Once chronic bronchitis is established, the episodic worsening referred to as acute exacerbations of chronic bronchitis can be triggered by similar causes. For the purposes of this chapter, however, we will focus on infectious triggers.

Viruses account for up to 50% of acute exacerbations of chronic bronchitis and a variety of agents have been implicated: RSV, rhinovirus, influenza virus and parainfluenza virus. The remaining 50% of acute exacerbations are bacterial in nature, with the most common pathogens being *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*. The role of atypical pathogens such as *M. pneumoniae* and *Ch. pneumoniae* is unclear but it is thought that they may account for a small percentage of infections.

Infection results in the release of inflammatory mediators and further impairment of mucociliary clearance. This in turn alters the local milieu, making it easier for pathogens to further colonize the airways. Progressive airway damage is thought to occur as the result of injury caused either by the pathogens themselves or by the host response to the various infective agents.

CLINICAL MANIFESTATIONS

The clinical manifestations of patients with AECB represent a common pathway of underlying pulmonary disease in the form of chronic bronchitis or emphysema and the acute exacerbation triggered by infection or environmental pollutants. Patients may present with any or all of the following: increase in dyspnea, sputum volume or sputum purulence. In 1987, Anthonisen and colleagues demonstrated that patients with at least two of these three findings experienced better clinical outcomes when treated with antibiotics than with placebo.[11]

The Anthonisen classification refers to patients with one of these findings as type 3, two of the findings as type 2 and three of the findings as type 1. Other symptoms that may be noted during an exacerbation include wheezing, elevated temperature and a feeling of malaise.

The duration of an exacerbation can vary from a few days to several weeks. On average, most patients experience approximately three exacerbations annually, although significant variation has been described.

DIAGNOSIS

The diagnosis of AECB is usually clinical. Patients with a known history of chronic bronchitis who suffer periodic flare-ups are usually well aware of the signs and symptoms heralding the onset of an exacerbation. Increasing dyspnea, sputum volume and purulence are the main clues that an exacerbation has occurred.

One of the difficulties in defining etiology is that many, if not most, individuals with chronic bronchitis normally have bacteria in their respiratory secretions. These bacteria colonize the airways but during an exacerbation are present in higher numbers. *H. influenzae*, *Str. pneumoniae* and *Mor. catarrhalis* are the predominant pathogens. However, among those with severe exacerbations requiring admission to an intensive care unit (ICU) and mechanical ventilation, these pathogens seem to be present less frequently and organisms such as *H. parainfluenzae* and *Pseudomonas aeruginosa* are more frequently found, and bacteria in this context are often resistant to antibiotics.[12,13]

In most patients treatment is begun empirically. In those with more severe underlying disease or in whom the exacerbations appear to be more serious, it may be worthwhile obtaining sputum samples for culture and susceptibility testing in order to rule out the presence of a resistant pathogen. Data are available suggesting that as the severity of the illness increases (as indicated by markers such as illness lasting longer than 10 years, more than four exacerbations per year, steroid therapy, recent antibiotics, and severe airway obstruction [FEV_1 <35% predicted]) the microbiology becomes more complex.[14,15]

On the basis of a clinical examination, it may be impossible to differentiate between an acute exacerbation of chronic bronchitis and pneumonia. In such cases, a chest radiograph is necessary.

TREATMENT

Anthonisen was the first to assess response to treatment based upon stratification of patients according to their symptoms.[11] A meta-analysis of nine randomized placebo-controlled trials of patients treated for AECB demonstrated a statistically significant improvement in outcomes in those treated with antibiotics.[16] The effect size favored antibiotics in seven of the nine studies.

Despite such data, however, it is clear that routine antibiotic treatment fails in 13–25% of exacerbations.[17] Such failures carry an economic burden because they require additional visits to physicians, additional treatment regimens and more days lost from work.

A number of risk factors have been defined for treatment failure. These include the presence of cardiopulmonary disease and increased frequency of pulmonary infections during the previous year (>4).[17] A subgroup of patients is at risk, not only of treatment failure but also of respiratory failure. Mortality rates in hospital inpatients of 10–30% have been described, typically in patients older than 65 years, those with co-morbid respiratory and extrapulmonary organ dysfunction, and those residing in hospital before transfer to the ICU.[18,19]

It has been suggested that stratification of patients according to risk factors will allow physicians to treat more appropriately. No single stratification scheme has been agreed upon but those that do exist attempt to rank patients according to increased risk factors for treatment failure and possibly admission to hospital. Three schema have been published to date: Lode – Germany (1991), Balter – Canada (1994), and Wilson – UK (1995).[20–22] Their recommendations are summarized in Table 45.1.

Patients with AECB should be considered as being possibly infected with a 'core' group of pathogens such as *H. influenzae*, *Str. pneumoniae* and *Mor. catarrhalis*; those who are more complicated (such as elderly patients, patients with more frequent exacerbations and those with reduced lung function) may be infected not only by the core pathogens but also by Gram-negative bacilli such as the Enterobacteriaceae and *Ps. aeruginosa* or possibly resistant core pathogens.

The advantage of such an approach lies in the fact that they identify patients at increased risk of failure so that treatment may be initiated with antibiotic regimens most likely to be effective against all of the potential etiological pathogens.

Table 45.1 Stratification and treatment of acute exacerbations of chronic obstructive pulmonary disease[20]

Category	Characteristics	Suggested treatment
Group 1	Postviral tracheobronchitis; previously healthy person	None
Group 2	Simple chronic bronchitis; young person; mild–moderate impairment of lung function (FEV_1 >50% predicted); fewer than 4 exacerbations/year	No treatment or β-lactam antibiotic
Group 3	'Chronic bronchitis plus risk factors' older person; FEV_1 50% predicted or FEV_1 50–60% predicted but concurrent medical illnesses; CHF, diabetes mellitus, chronic renal disease, chronic liver disease, more than 4 exacerbations/year	Fluoroquinolone, amoxicillin–clavulanic acid, group 3 or 4 cephalosporin,[a] azithromycin or clarithromycin
Group 4	'Chronic bronchial sepsis', bronchiectasis, chronic airway colonization	Tailor antimicrobial treatment to airway pathogens

[a]See Ch. 13 for classification of cephalosporins.
CHF, congestive heart failure; FEV_1, forced expiratory volume in 1 second.
From Lode H. Respiratory tract infections: when is antibiotic therapy indicated? **Clin Ther.** 1991;13:149–156.

A variety of adjunctive or supportive measures, including the use of bronchodilators, steroids (oral and/or inhaled) and oxygen therapy, may be necessary. Preventive measures such as cessation of smoking, annual influenza vaccination and administration of the pneumococcal vaccine should be emphasized.

COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) has a significant impact on both individual patients and society, and pneumonia is currently the sixth leading cause of death in the USA with an estimated 3–4 million cases annually, accounting for more than 600 000 hospital admissions and 64 million days of restricted activity.[23]

CAP is not a reportable disease so exact figures are not available. It is clear, however, that it has a significant impact on the individual patient and society as a whole. Most (80%) patients are treated as outpatients while 20% are admitted to hospital; it is these 20% who generate most of the costs. The annual costs of treatment are US$4.8 billion (patients older than 65 years) and $3.6 billion (patients under 65 years).[24]

ETIOLOGY AND EPIDEMIOLOGY

As with many other infections, the incidence rates of CAP are greatest at the extremes of age. Although the overall annual rate of pneumonia in the USA is 12 cases per 1000 the rate is 12–18 cases per 1000 in children below 4 years of age and 20 cases per 1000 in people over 60 years age.[25,26] Between the ages of 5 and 60 years, the annual rate ranges from one to five cases per 1000 and the incidence of CAP requiring admission to hospital in adult patients is 2.6 cases per 1000.[27]

Risk factors for pneumonia have been defined and include the following: alcoholism, asthma, immunosuppression, institutionalization, and age greater than or equal to 70 years versus age 60–69 years.[28] Specific risk factors for pneumococcal infection include dementia, seizure disorders, congestive heart failure, cerebrovascular disease, COPD and HIV infection.[29]

Numerous microbial pathogens are potential etiological agents, and patients may be infected with more than one agent. Such mixed infections are well described in hospital-acquired pneumonia, where multiple pathogens are present in more than half of the nosocomial pneumonia patients studied.[30] In CAP, the incidence of mixed infections is lower, ranging from 2.7% to 13% in well-defined studies of inpatients with CAP.[31–33]

The single most important etiological agent is undoubtedly *Str. pneumoniae*. In a meta-analysis covering a 30-year period and including 7000 cases of pneumonia in which an etiological diagnosis was made, *Str. pneumoniae* accounted for two-thirds of all cases and for two-thirds of fatalities.[34]

At one time it was thought that atypical pathogens such as *M. pneumoniae*, *Ch. pneumoniae* and *Legionella* species were not important causes of pneumonia and that if they did cause infection they were usually mild and affected primarily the young. A study in 1997 of more than 2700 patients admitted to hospital with CAP ranked these pathogens second, third and fourth of all etiological agents meeting the criteria for a 'definite' diagnosis.[35] Another study described three outbreaks of *Ch. pneumoniae* in nursing homes with high attack and mortality rates.[36] These two studies have helped to dispel the earlier misconceptions surrounding infection with the atypical pathogens.

Gram-negative rods such as *Escherichia coli* and *Klebsiella* spp. are not particularly common causes of CAP but are nevertheless important to consider, particularly in elderly people or in those with co-morbid illness, especially if they are ill enough to require hospital treatment.[31,37] There has been considerable debate about whether or not *Ps. aeruginosa* is a significant pathogen requiring treatment. The consensus is that, while it is certainly not common, it can occur in selected patients if risk factors such as a recent course of antibiotics or steroids or a prolonged stay in hospital are present.

PATHOGENESIS

The various etiological pathogens can gain access to the lower respiratory tract by a number of possible routes. These include inhalation, aspiration and hematogenous spread. For bacterial pneumonia, aspiration of organisms colonizing the oropharynx appears to be the most important route.[38] Pneumonia results when innate immunity, including macrophage phagocytosis, fails to eradicate the infecting pathogen, and a neutrophilic infiltrate is recruited.[6]

CLINICAL MANIFESTATIONS

Until relatively recently, physicians tended to divide cases of CAP into typical or atypical pneumonia based upon their clinical presentation. Typical or classic pneumonia refers to infection caused by bacterial pathogens such as *Str. pneumoniae* or *H. influenzae*, whereas atypical pneumonia refers to infection caused by the atypical pathogens (*M. pneumoniae*, *Ch. pneumoniae* and *Legionella* spp.). It was thought that those with classic bacterial pneumonia presented with fairly sudden onset of signs and symptoms with cough productive of purulent sputum, pleuritic chest pain and rigors. In contrast, those with atypical infection presented with an illness of undefined duration, a non-productive cough and often a frontal headache. It has become clear, however, that it is not possible to determine the etiological agent from a careful history, physical examination, and non-specific laboratory tests and chest radiographs.

The symptoms of CAP may be constitutional and non-specific or they may be localized to the respiratory tract and be fairly specific for respiratory infection. The former category includes such findings as malaise, anorexia, myalgias

and arthralgias, chills and rigors; the latter includes shortness of breath, pleuritic chest pain, cough and sputum production.

In elderly patients the findings may be imprecise because constitutional symptoms such as confusion may predominate and there may be fewer findings related to the respiratory tract.

DIAGNOSIS

The problem of the diagnosis of CAP has generated much debate among physicians. Unfortunately, despite extensive testing even in university medical centers, no specific etiological agent may be found in up to one-half of the cases. In routine clinical practice, the etiological agent is determined in approximately 25% of cases but results in a change in antimicrobial therapy in less than 10% of cases.[39] Furthermore, an improvement in clinical outcome does not always result from identification of the etiological agent.

Generally, diagnostic tests fall into two categories: clinical and invasive/quantitative. Clinical testing relies on information obtained from the patient history, physical examination, and selected tests or procedures such as chest radiography, sputum Gram stain, and blood and sputum cultures. Invasive/quantitative methods include bronchoscopic techniques, pleural fluid aspiration and (in selected cases) lung biopsy. As a rule, the clinical method is too sensitive and lacks specificity while the invasive/quantitative methods require special expertise and laboratory support, and are more costly.

CLINICAL EVALUATION

The first step is to determine whether the patient has pneumonia rather than some other infective process such as bronchitis, or whether a non-infectious etiology (e.g. congestive heart failure, pulmonary embolism) is the cause of the patient's problem. If a diagnosis of pneumonia is made, the next step is to determine the etiological agent if possible. Unfortunately, it is impossible to accurately identify the pathogen based on clinical findings, even when multiple clinical variables are used.[31,40] There is significant intraobserver variation in the ability to elicit abnormal physical findings and the sensitivity and specificity of the history and physical examination are currently undetermined.[41]

CHEST RADIOGRAPH

The presence of an infiltrate on the chest radiograph can help to establish the diagnosis of pneumonia but does not determine the causative pathogen. However, the radiograph is important in defining the presence of a lobar or multilobar infiltrate and in assessing the severity of illness and prognosis.

LABORATORY ASSESSMENT

Routine laboratory assessment is unnecessary for ambulatory patients with CAP, who are likely to be managed as outpatients. However, for those ill enough to require admission to hospital (or even for those considered for admission), a complete blood and differential count, serum electrolytes, liver function tests, serum creatinine and an oxygen saturation assessment should be obtained. Significant abnormalities have been identified as risk factors for a complicated course or increased mortality. These abnormalities can be used to assess mortality risk and to help in the site of care decision.[42]

MICROBIOLOGICAL ASSESSMENT

Sputum Gram stain and culture

Of the two tests, the sputum Gram stain is more reliable, but is regarded as neither sensitive nor specific, though in some laboratories the test has made a positive contribution to early diagnosis.[43] Many patients are unable to produce a sputum sample, and of those samples produced a significant percentage may not be adequate. Although current data suggest that atypical pathogens are responsible for 20–25% of all CAP cases, none is detectable by the sputum Gram stain. There is also considerable inter- and intraobserver variation in Gram stain interpretation.[44] The sputum culture also lacks sensitivity and specificity. Even in patients with confirmed pneumococcal pneumonia based upon positive blood cultures, a simultaneously obtained sputum culture tested positive in only one-half of patients.[45]

Blood cultures

The incidence of positive blood cultures in ambulatory patients with CAP is less than 1%.[46] In hospital inpatients it ranges from 6.6% to 17.6% but may reach 27% in patients in ICUs.[32] The most common pathogen is *Str. pneumoniae*, and pneumococcal pneumonia is complicated by bacteremia more frequently than pneumonia caused by other pathogens. It is generally recommended that blood cultures be obtained from all patients who are admitted with CAP but not from those treated in the community.

Serology

To determine the role of a specific micro-organism as a pathogen, serological assessments should be based on the results of paired (acute and convalescent) serum samples. Unfortunately, such results are never available at the time the initial treatment decision is being made. Therefore, other than helping to define the epidemiological role of selected pathogens, serological testing is not helpful and is not recommended for routine use.

Legionella urinary antigen

This test is easy to perform and yields rapid results with a sensitivity of 70% and specificity of 100%. It is limited by the fact that it identifies only *Legionella pneumophila* serogroup 1. However, this serogroup accounts for most *Legionella* infections.

DNA probes and amplification

Polymerase chain reaction-based methods are being used increasingly.[47] Unfortunately, rapid diagnostic techniques are not generally available and simply identifying the presence of a particular micro-organism does not confirm infection. There are, however, a few micro-organisms whose mere presence indicates infection. These include *M. tuberculosis*, *Coxiella burnetii* and *Pneumocystis jirovecii* (formerly *Pn. carinii*).

INVASIVE PROCEDURES

For most patients with CAP, invasive tests such as bronchoscopy, bronchoalveolar lavage, protected specimen brush and percutaneous lung needle aspiration are not required. However, they may be appropriate in certain situations (e.g. patients with fulminant pneumonia or those unresponsive to a standard course of antimicrobials), when it may be necessary to identify a resistant or fastidious pathogen or to rule out a non-infectious cause.

Thoracocentesis should be performed in CAP patients with a significant pleural effusion defined as a collection of greater than 10 mm thickness on the lateral decubitus view. The incidence of pleural effusion with pneumonia varies from 36% to 57% and is most common in patients with pneumococcal infection.[48]

TREATMENT

Therapy can be directed or empirical. Directed therapy implies that the etiological agent is known and that therapy is aimed specifically at that pathogen. Empirical therapy is the more usual; it is, in effect, an educated guess and the physician institutes a course of treatment aimed at the most likely causes. Of these two options, directed therapy is clearly more desirable because it limits the breadth of spectrum required of the treatment agent(s), it may limit the number of drugs, reduces the adverse reactions associated with antibiotics, reduces antibiotic selection pressure and may result in less antimicrobial resistance.

Before discussing the various regimens, it is important to consider how the decision is made in terms of outpatient versus inpatient therapy and the problem of antimicrobial resistance.

SITE OF CARE DECISION

This decision is an important one, with considerable economic implications. The cost of inpatient care exceeds that of outpatient treatment by a factor of 15–20, and the cost of hospital management accounts for most of the money spent annually on CAP in the USA.[49]

In some cases it is immediately obvious that a patient can be treated outside the hospital; in other situations it is equally apparent that a patient requires hospital treatment and possibly admission to an ICU.

Effective prognostic scoring and outcome assessment tools are necessary to help physicians make the site of care decision. Such tools provide objective methods to assess the risk of adverse outcomes, including death.

Studies by Fine and others have attempted to identify patients at increased risk for adverse outcomes and to define independent predictors of mortality or poor outcome.[34,42] However, weaknesses or design flaws were found in each of them.[49]

The use of prediction rules may minimize unnecessary hospital admissions and help to identify patients who will benefit from care and intervention in the hospital and the ICU. The best known and most widely used prognostic tool is that of Fine.[42] This is a two-step rule designed to identify patients at low risk for mortality. Points are given based on age, coexisting disease, and abnormal physical and laboratory findings, and patients are assigned to classes 1–5 based on the total number of points assigned. This scoring system has been used to triage low-risk patients towards outpatient therapy with a high degree of success.[50] Fine's rule has been adopted into recommendations published by the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS) and the European Respiratory Society.[51–53]

An alternative system of assessing severity, the CURB score, has been recommended by the British Thoracic Society[54] and the European Respiratory Society.[53] This score incorporates assessments of pulse rate, respiratory rate, renal function and mental status for the initial evaluation of patients, assigning 1 point for each abnormal feature (plus 1 for patients over 65 years of age in the CURB65 variation) and is much easier to use than the Fine score.

In assessing patients for severity, such scoring systems can only be a guide. Ultimately the physician must decide on grounds of clinical experience whether an individual patient with pneumonia warrants intravenous therapy, admission to hospital or management in an intensive care facility.

ANTIMICROBIAL RESISTANCE

Antimicrobial resistance among respiratory pathogens has become a major concern and it is important that clinicians understand and appreciate the general mechanisms and implications of this phenomenon. The emergence of resistance to penicillin among *Str. pneumoniae* isolates represents a gradual reduction in in-vitro susceptibility. The National Committee for Clinical Laboratory Standards defines strains for which the minimum inhibitory concentration (MIC) of penicillin is <1 mg/L as sensitive, 1.0–2.0 mg/L as

intermediate and ≥4 mg/L as resistant.[55] With *Str. pneumoniae*, the DNA incorporation and remodeling that results in resistance is from the DNA of closely related oral commensal bacteria (*see* Ch. 3). By such a process, our own flora can develop resistance when we are treated with antibiotics and pathogens such as *Str. pneumoniae* can subsequently acquire resistance coding DNA from our own colonizing microflora.[56] Pneumococcal resistance to β-lactams is due solely to the presence of low-affinity penicillin-binding proteins. Macrolide resistance, however, can occur either by target site modification or by an efflux pump (*see* Chs 3 and 22). The relative frequencies of the two mechanisms vary internationally but in North America account for approximately 45% and 55%, respectively, of resistant isolates. Reports of breakthrough pneumococcal bacteremia in patients treated with macrolides have highlighted concerns about resistance to this class of agents.[57,58]

Resistance to ciprofloxacin and to newer fluoroquinolones among pneumococcal isolates has been reported.[59] Pneumococcal resistance to fluoroquinolones may be mediated by changes in one or both target sites (topoisomerase II and IV), usually resulting from mutations in the *gyrA* and *parC* genes, respectively, and possibly also by an efflux pump (*see* Ch. 3).[60] Of greatest concern, however, are the multidrug-resistant isolates, those that are resistant to two or more antibiotics having different mechanisms of action. In the USA, between 1995 and 1998, the proportion of invasive pneumococcal isolates that were resistant to three or more classes of drugs increased from 9% to 14%; there also were increases in the proportions of isolates that were resistant to penicillin (21% to 25%), cefotaxime (10% to 15%), meropenem (10% to 16%), erythromycin (11% to 16%) and trimethoprim–sulfamethoxazole (25% to 29%). These increases in frequency of resistance to multiple antimicrobial agents occurred in penicillin-resistant isolates only.[61] Drug-resistant *Str. pneumoniae* is associated with various risk factors including the presence of co-morbidities, such as chronic heart, lung, liver or renal disease, diabetes, alcoholism, immunosuppression or use of antimicrobials within the previous 3 months.[62] Infection with drug-resistant pneumococci results in invasive disease with higher mortality rates amongst hospitalized individuals.[63]

Pathogens such as *H. influenzae* and the Enterobacteriaceae are also important to consider. *H. influenzae* is the third most common cause of CAP requiring admission to hospital and, while the Enterobacteriaceae are not particularly common, they are important because of the high mortality rates associated with them. Among such pathogens resistance is usually mediated by β-lactamases, and the highest prevalence of β-lactamase genes is found on plasmids rather than chromosomes. Members of the TEM and SHV families are the most successful of the plasmid-encoded β-lactamases, and the TEM-1 β-lactamase accounts for almost 80% of all plasmid-encoded β-lactamases.[64] The extended-spectrum β-lactamases include oxyimino enzymes that are TEM and SHV mutants and cephalosporinases unrelated to TEM and SHV enzymes (*see* Ch. 15).

THERAPEUTIC REGIMENS

Once the diagnosis of pneumonia has been made, the physician must decide whether to treat the patient outside or inside the hospital and this in turn will help to determine the appropriate therapeutic regimen. In most patients an empirical choice must be made; however, where the infecting pathogen is known, antibiotic choice can be guided by local knowledge of antimicrobial sensitivities and policies. The correct choice of antimicrobial(s) for empirical therapy has generated considerable discussion, and a number of societies have produced guidelines to help physicians with the initial management of patients with CAP.[51–54]

Guidelines have served a number of useful functions. They have codified our management of patients with CAP and (at the very least) they have highlighted the gaps in our knowledge and have helped to direct future studies and research. Adherence to guidelines has had a significant pharmaco-economic effect, lowered mortality rates and shortened hospital stay.[65,66]

The joint guidelines of the IDSA and the ATS[51] make recommendations for outpatient and inpatient treatment of pneumonia, and draw a distinction between those individuals who do or do not have risk factors for drug-resistant *Str. pneumoniae* (DRSP) (Table 45.2). For outpatient treatment of previously healthy individuals with no risk factors for DRSP, these guidelines recommend a macrolide (azithromycin, clarithromycin or erythromycin) or doxycycline. In the presence of risk factors for DRSP, outpatients are recommended a 'respiratory' fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin [750 mg]) or a high dose β-lactam plus a macrolide or doxycycline. This latter recommendation also pertains to all inpatients (non-ICU). For inpatients requiring ICU treatment the IDSA/ATS guidelines recommend a β-lactam (cefotaxime, ceftriaxone or ampicillin–sulbactam) plus either azithromycin or a fluoroquinolone, except where *Pseudomonas* infection is suspected, in which case an antipneumococcal, antipseudomonal β-lactam (piperacillin–tazobactam, cefepime, imipenem or meropenem) plus either ciprofloxacin or levofloxacin (750 mg) is the recommended first-line regimen. Where community-acquired methicillin-resistant *Staphylococcus aureus* infection is suspected to be the cause of the pneumonia, these guidelines recommend the addition of vancomycin or linezolid to the regimen.

The recommendation for the use of macrolides in these guidelines relates to the coverage of atypical pathogens. A β-lactam would be the agent of choice for *Str. pneumoniae* but it would be ineffective against any of the atypicals. However, a macrolide provides good-to-excellent coverage for all these likely pathogens.

In North America the fluoroquinolones have assumed an important role in the management of CAP coinciding with rising resistance to β-lactams and macrolides, the appreciation of the potential importance of Gram-negative rods in selected CAP patients and the availability of the 'respiratory' fluoroquinolones which offer once-daily monotherapy, compared with the multiple dosing required if a β-lactam and macrolide regimen is used.[51]

Table 45.2 Empirical antimicrobial selection for community-acquired pneumonia (IDSA/ATS guidelines)

Outpatient treatment

1. Previously healthy and no use of antimicrobials within the previous 3 months
   – A macrolide
   – Doxycycline
2. Presence of co-morbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
   – A respiratory fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin [750 mg])
   – A β-lactam plus a macrolide
3. In regions with a high rate (>25%) of infection with high-level (MIC ≥16 μg/mL) macrolide-resistant *Streptococcus pneumoniae*, consider use of alternative agents listed above in (2) for patients without co-morbidities

Inpatients, non-ICU treatment

A respiratory fluoroquinolone
A β-lactam plus a macrolide

Inpatients, ICU treatment

A β-lactam (cefotaxime, ceftriaxone, or ampicillin–sulbactam) plus either azithromycin or a respiratory fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

Special concerns

If *Pseudomonas* is a consideration
   – An antipneumococcal, antipseudomonal β-lactam (piperacillin–tazobactam, cefepime, imipenem or meropenem) plus either ciprofloxacin or levofloxacin (750 mg), *or*
   – The above β-lactam plus an aminoglycoside and azithromycin, or
   – The above β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for above β-lactam)
If CA-MRSA is a consideration, add vancomycin or linezolid

CA–MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit.
Adapted from Mandell LA , Wunderink RG , Anzueto A , et al. Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community acquired pneumonia in adults. **Clin Infect Dis.** 2007;44(suppl 2): S27–S72.

Many experts feel that penicillin still has a role to play in the treatment of pneumococcal pneumonia and that it is effective against infections caused by susceptible organisms. For strains of *Str. pneumoniae* with intermediate levels of resistance to penicillin higher doses may be used, as recommended in the IDSA/ATS guidelines. Unfortunately, the identity or susceptibility of the etiological agent is unknown in most cases at the time of initial antibiotic treatment.

Efflux resistance to macrolides results in low-level resistance, whereas the target change mechanism results in high-level resistance. Low-level resistance predominates in North America, while the latter is more frequent in Europe. In the USA and Canada, therefore, macrolides are still seen as having a significant role to play in the management of many patients with CAP.

For those treated in hospital, the guidelines divide patients into those treated on a medical ward and those treated in the ICU, and use the risk of infection with *Ps. aeruginosa* as a means of further subdividing ICU patients, reflecting the enhanced mortality rate and constitutive antimicrobial resistance associated with this organism.

The recent British Thoracic Society (BTS) guidelines (Table 45.3) provide an exhaustive evidence-based approach to the management of CAP patients.[54] They differ from the IDSA/ATS guidelines quite extensively. For outpatients, the BTS does not consider that atypical pathogens such as *M. pneumoniae* or *Ch. pneumoniae* are important enough to warrant routine coverage, and therefore treatment is aimed primarily at *Str. pneumoniae*, for which the drug of choice is amoxicillin. For hospital inpatients, the North American document divides patients into those managed on a ward or in the ICU, whereas the British guidelines consider hospital-treated patients under three categories: (1) not severe and admitted for non-clinical reasons or previously treated in the community (CURB65 0–1); (2) moderate severity

Table 45.3 British Thoracic Society recommendations for initial empirical treatment of community-acquired pneumonia

Type of patient	First choice	Second choice
Low severity (i.e. CURB65 = 0–1), home treated	Amoxicillin 500 mg p.o. every 8 h	Doxycycline 200 mg loading dose then 100 mg/day or clarithromycin 500 mg p.o. every 12 h
Hospital treated, not severe (i.e. CURB65 = 0–1)	Amoxicillin 500 mg p.o. or i.v. every 8 h	Doxycycline 200 mg loading dose then 100 mg/day or clarithromycin 500 mg p.o. every 12 h
Hospital treated, moderately severe (i.e. CURB65 = 2)	1. Amoxicillin 500 mg–1 g p.o. every 8 h + clarithromycin 500 mg p.o. every 12 h 2. If oral treatment not possible, amoxicillin 500 mg –1 g i.v. every 8 h or benzylpenicillin 1.2 g i.v. every 6 h + clarithromycin 500 mg i.v. every 12 h	Doxycycline 200 mg loading dose then 100 mg/day or levofloxacin 500 mg p.o. every 12 h or moxifloxacin 400 mg p.o. every 12 h
Hospital treated, severe (i.e. CURB65 = 3–5); consider critical care review	Amoxicillin–clavulanate 1.2 g i.v. every 8 h + clarithromycin 500 mg i.v. every 12 h (if *Legionella* strongly suspected, consider adding levofloxacin)	Benzylpenicillin 1.2 g i.v. every 6 h + either levofloxacin 500 mg i.v. every 12 h or ciprofloxacin 400 mg i.v. every 12 h *or* Cefuroxime 1.5 g i.v. every 8 h or cefotaxime 1 g i.v. every 8 h or ceftriaxone 2 g i.v. per day + clarithromycin 500 mg i.v. every 12 h (if *Legionella* strongly suspected, consider adding levofloxacin)

Adapted from Lim WS , Baudouin SV , George RC , et al. Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. **Thorax.** 2009;64(suppl 3):iii1–iii55.

admitted for non-clinical reasons or previously treated in the community (CURB65 0–1); (2) moderate severity (CURB65 = 2); and (3) severe (CURB65 3–5). The first group is treated with amoxicillin, the second is given amoxicillin plus a macrolide (erythromycin or clarithromycin) and the third group is given a β-lactam (amoxicillin–clavulanate) plus intravenous erythromycin or clarithromycin. Fluoroquinolones are recommended as an alternative only for the second and third categories. In general, the potency and breadth of intravenous antibiotics recommended increases as severity increases. In moderately ill hospitalized patients treated in the UK, a simple β-lactam in combination with a macrolide is likely to be used, if clinicians follow the BTS guidelines. Individual hospital policies will be tailored to balance the requirement for potent therapy, with the need to keep antimicrobial activity as narrow spectrum as possible to avoid potential impacts on hospital ecology.

Initiation of treatment should not be delayed, particularly when dealing with patients over 65 years of age. A study of elderly patients presenting to emergency departments with CAP showed that those who received antibiotics within 8 h of presentation had a significantly lower 30-day mortality rate than those who waited longer for initiation of treatment.[67]

Intravenous to oral sequential treatment is strongly recommended because it reduces costs, encourages patient mobility and allows earlier discharge from hospital. Ancillary measures such as supplemental oxygen, drainage of significant pleural effusions and hydration are also important.

The patient should be followed and objective parameters monitored. These include the resolution of cough, shortness of breath and elevated temperature and (for those in hospital) improvement in the oxygen saturation, C-reactive protein and white blood cell count.

UNUSUAL PATHOGENS

Staphylococcal pneumonia can be associated with a necrotizing pneumonitis, particularly when stains expressing Panton–Valentine leukocidin toxin are implicated. If such organisms are strongly suspected in patients with severe pneumonia, a combination of intravenous linezolid (600 mg every 12 h), intravenous clindamycin (1.2 g every 6 h) and intravenous rifampicin (rifampin) (600 mg every 12 h) should be added to the initial antibiotic regimen.[54]

HEALTHCARE-ASSOCIATED PNEUMONIA

'Healthcare-associated pneumonia' refers to pneumonia in patients who have recently been hospitalized, had hemodialysis or received intravenous chemotherapy, or reside in a nursing home or long-term care facility.[68] They are distinguished by having a different pattern of microbial flora associated with the pneumonia (often Gram-positive organisms with a higher tendency towards antimicrobial resistance) and also more severe disease, longer hospital stay and higher mortality rates. The dominant group in this class of patients generally comprises residents of nursing homes. Nursing home pneumonia or pneumonia in elderly residents of long-term care facilities is an important entity and is only now becoming the subject of serious clinical investigation. Pneumonia is the main cause of death among residents of such facilities, with acute mortality rates ranging from 5% to 40% per infection. It is the most common reason for transfer of nursing home residents to an acute care hospital, with approximately one-third of pneumonia patients requiring hospital admission.[69]

ETIOLOGY AND EPIDEMIOLOGY

The incidence of pneumonia among residents of nursing homes is considerably higher than among persons living in the community, ranging from 1.2 to 2.5 episodes per 1000 resident days with a median incidence of 1 per 1000 resident days.[69] One of the difficulties in establishing the etiology of nursing home pneumonia is the fact that studies in this area have depended almost exclusively on results of sputum cultures. Such studies are compromised from the outset because over half the elderly patients do not produce any sputum. The likely pathogens are somewhat different from those in patients with CAP. In cases of CAP, the predominant etiological agents are *Str. pneumoniae* and the atypicals (in selected cases Gram-negative rods may be encountered). In nursing home pneumonia, *Str. pneumoniae* is still a significant pathogen, but (it is important to note that age >65 years and residence in a nursing home have been identified as risk factors for penicillin-resistant *Str. pneumoniae* infection) there is a greater proportion of cases caused by *Staph. aureus*, *H. influenzae* and Gram-negative rods in this population than in a younger cohort, and a disconcertingly high percentage of the *Staph. aureus* isolates are methicillin resistant.[70] Atypicals are more common in younger patients.

The role of anaerobes is still not definitely settled and appropriately designed studies to substantiate their role as pathogens in the elderly do not appear to have been undertaken.

In addition to aerobic and possibly anaerobic bacterial pathogens, viruses and *M. tuberculosis* must also be considered. Epidemics of influenza, RSV and parainfluenza have been described in such populations, and must always be considered if an institutional outbreak is encountered. The incidence of tuberculosis is substantially higher in the institutionalized elderly and must be included in the assessment of such patients.

PATHOGENESIS

A number of risk factors have been defined in a prospective cohort study of respiratory tract infections in nursing home residents.[69] Older age, male sex, inability to take oral medications

and swallowing difficulties were identified as independent risk factors for the development of pneumonia. Swallowing difficulty, confusion and altered levels of consciousness have often been evoked as surrogate markers for aspiration and by inference as indicators of infection with anaerobes.

Nasogastric tube feeding and tracheostomy have also been identified as potential risk factors for pneumonia, presumably because of the increased risk of aspiration.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The physician must be aware that in an elderly patient with pneumonia rather than a history of elevated temperature, chills and cough with purulent sputum, the story may be that of confusion, weakness, anorexia and falls. The difficulty in making a diagnosis of pneumonia in a nursing home population is enhanced by the fact that nursing homes lack laboratory and radiographic facilities and many often do not have a physician in attendance on a full-time basis.

Ideally, if a patient presents with findings suggestive of pneumonia, he or she should be evaluated by a physician and a chest radiograph obtained. If feasible, an expectorated sputum sample should be sent for Gram stain and culture, and for people with more serious illness in whom parenteral therapy or transfer to a hospital is contemplated, the following additional tests should be done: blood samples for culture and susceptibility testing, complete blood count and differential, serum creatinine, urine for *Legionella* antigen.

If pneumonia occurs in the setting of an influenza outbreak or if a particular case is suggestive of influenza infection, a nasopharyngeal swab should be obtained for rapid detection of viral antigen by polymerase chain reaction. Similarly, if tuberculosis is a possibility, sputum samples for microscopy and rapid culture should be obtained. In both of these circumstances respiratory precautions must be instituted and the patient should be isolated to prevent spread of the disease.

TREATMENT

As with any patient, the use of an antimicrobial directed at a known pathogen is the ideal; however, at the time that the treatment decision is made it is unlikely that a definitive etiological agent will have been identified. As with most cases of pneumonia, an empirical regimen is usually selected, based upon local epidemiology and susceptibility patterns and risk stratification of the patient.

The site of care decision is an important one and nursing home residents with pneumonia can be evaluated using the same prediction rules for hospital admission as are used for other patients with CAP.[42] For most patients who can be treated in the nursing home setting, with no other risk factors for multidrug-resistant pathogens, a 'respiratory fluoroquinolone' such as moxifloxacin, gatifloxacin or levofloxacin (according to availability), or a combination regimen consisting of amoxicillin–clavulanate, is generally recommended as first choice.[70,71]

Influenza outbreaks in an institutional setting can be associated with high attack rates and mortality rates. Annual immunoprophylaxis using vaccines offers protection and is recommended for all residents. Zanamivir and oseltamivir are neuraminidase inhibitors with activity against both influenza A and influenza B. Both of these agents are approved for treatment of uncomplicated influenza and if given within 48 h of onset of symptoms may decrease the severity and duration of the symptoms.

HOSPITAL-ACQUIRED PNEUMONIA

Hospital-acquired or nosocomial pneumonia is by definition infection that occurs 48 h or more after admission to hospital. Although it is the second most common nosocomial infection in the USA, accounting for 13–18% of all hospital-acquired infections, it is the one most frequently associated with a fatal outcome, and is associated with significant morbidity and mortality.[71]

Current figures are based on estimates from hospital records because nosocomial pneumonia is not a reportable disease. It is considered, however, that currently more than 300 000 cases occur annually in the USA, resulting in an average increase in length of hospital stay of 8 days.[71]

Mortality figures range from 15% to 70%; however, the more relevant attributable mortality figures are estimated at 33–50%.

ETIOLOGY AND EPIDEMIOLOGY

The estimated rate of occurrence is 4–8 episodes per 1000 hospital admissions in non-teaching hospitals and 8 per 1000 in teaching hospitals.[71] In patients who are intubated, the rate is up to 20 times higher than in non-intubated patients. Rates of ventilator-associated pneumonia are reported to be approximately 15 per 1000 ventilator days.[72]

Risk factors for nosocomial pneumonia include increasing age, COPD, neuromuscular disease, decreased consciousness, aspiration, endotracheal intubation, thoracic and upper abdominal surgery, and nasogastric intubation. Of the various pathogens, perhaps the most important with defined risk factors are *Staph. aureus* (head injury, coma longer than 24 h and intravenous drug use) and *Ps. aeruginosa* (prior antibiotics, structural lung disease and steroid treatment).[71,73]

The most common pathogens encountered in nosocomial pneumonia are the Gram-negative bacilli, which have been reported in up to 60% of cases, and *Staph. aureus*, which has been reported in up to 40% of patients. In infections occurring during the first 4 days of hospital stay, bacteria typically associated with CAP, such as *Str. pneumoniae* and *H. influenzae*, have also been reported.

The Gram-negative rods of interest are *Esch. coli*, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp. and *Serratia marcescens*. *Esch. coli* is the third most common coliform isolated from patients with nosocomial pneumonia and appears to affect predisposed hosts such as the critically ill. *K. pneumoniae* is the most commonly isolated of the *Klebsiella* species and may cause severe necrotizing lobar pneumonia in the elderly, in alcoholics and in diabetics. *K. pneumoniae* and *Esch. coli* are the bacteria that most commonly carry the extended-spectrum β-lactamases, rendering them resistant to oxyimino β-lactams such as cefotaxime, ceftazidime and aztreonam.

Among *Enterobacter* spp., *E. cloacae* and *E. aerogenes* are the primary cause of nosocomial pneumonia and frequently colonize patients who have received a course of antibiotics. Resistance to group 4 cephalosporins among these pathogens may develop within days of treatment.

Proteus mirabilis and *Proteus vulgaris* can act as opportunistic respiratory pathogens in a manner similar to that of the *Enterobacter* spp. Indole-positive species such as *Pr. vulgaris* may undergo a single-step mutation to become constitutive high-level producers of β-lactamase enzymes, which is manifested as resistance to group 4 cephalosporins. *Ser. marcescens* preferentially colonizes the respiratory and urinary tracts and has been associated with common source outbreaks of pneumonia in the setting of inhalation therapy and contaminated bronchoscopes. Like all Enterobacteriaceae, this organism may spread to patients by hand transfer from healthcare personnel.

The non-fermentative Gram-negative bacilli of importance are *Ps. aeruginosa* and *Acinetobacter* spp. *Ps. aeruginosa* is one of the leading causes of Gram-negative pneumonia. The most common mechanism of infection is direct contact with environmental reservoirs, including respiratory devices such as contaminated nebulizers or humidifiers. *Acinetobacter* spp. can also result in serious nosocomial infection and has been shown to be an important cause of ventilator-associated pneumonia.

H. influenzae frequently colonizes the upper respiratory tract of individuals with predisposing conditions such as COPD. Most adult infections are caused by non-typeable strains and *H. influenzae* (along with *Str. pneumoniae*) can often be isolated from tracheal secretions following intubation. *Str. pneumoniae*, like *H. influenzae*, colonizes the oropharynx and, although it is predominantly a pathogen associated with CAP, *Str. pneumoniae* is being recognized with increasing frequency as a cause of hospital-acquired infection.[71]

Anaerobes may be found as pathogens in patients predisposed to aspiration. The anaerobes that have been implicated in nosocomial pneumonia are those that colonize the oropharynx, such as *Fusobacterium* spp., *Prevotella melaninogenica* and *Bacteroides ureolyticus*.

Legionella pneumophila serogroup 1 is the most common of the *Legionella* spp. to be associated with both CAP and hospital-acquired pneumonia. The exact mode of transmission is controversial and there is evidence for both aspiration and inhalation. Contaminated potable water and contaminated aerosols have been reported as sources of infection in hospitals.

It is important to realize that nosocomial pneumonia may be caused by multiple pathogens in any one patient, emphasizing the need for broad coverage when empirical treatment is initiated. Bartlett and colleagues demonstrated that more than one pathogen could be documented in over half of the cases studied.[30]

PATHOGENESIS

The pathogenesis of nosocomial pneumonia is complex. Pathogens may gain access to the lower respiratory tract by inhalation, microaspiration or silent aspiration of oropharyngeal secretions, gross aspiration of gastric contents, hematogenous spread, translocation from the gastrointestinal tract, spread from a contiguous focus (e.g. pleural space) and direct inoculation during surgery.

For certain pathogens, such as *Mycobacteria* and *Aspergillus* spp., inhalation of aerosols is important. In patients being mechanically ventilated, contamination of a humidification reservoir may result in aspiration of potential pathogens directly into the airways. The most important mechanism, however, particularly for Gram-negative rods, is the microaspiration of bacteria colonizing the oropharynx.

Studies have shown that while oropharyngeal colonization by Gram-negative rods is unusual in healthy people, it occurs with increasing frequency in those with underlying disease.[71] Once oropharyngeal colonization is established, the silent aspiration of these potentially virulent bacteria eventually results in the overwhelming of host defenses in the lung and the development of pneumonia.

In addition to the oropharyngeal–pulmonary route, the gastropulmonary route has also been suggested as a means of introducing pathogens to the distal airways. Normally, the acidic pH of the stomach provides a hostile environment to bacteria, rendering the stomach contents virtually sterile, but above pH 4 bacterial overgrowth may occur. However, studies of stress ulcer prophylaxis have failed to demonstrate a definitive correlation between colonization of the stomach by bacteria and pneumonia.[74,75] A review of the literature concluded that the stomach should be regarded as an amplifier but not as the primary source of pathogens causing pneumonia and that the oropharyngeal–pulmonary route is more important than the gastropulmonary route.[76]

In patients who are being mechanically ventilated, the endotracheal tube plays an important role in the pathogenesis of ventilator-associated pneumonia. The tube itself breaches the upper airway defenses, and the inflated cuff allows the oropharyngeal secretions containing various pathogens to collect until they eventually pass the inflated cuff to the distal airways. In addition, the tube acts as a template upon which a layer of biofilm is deposited.[77] Pieces of this biofilm containing millions of bacteria may subsequently break off and reach the distal airways, thereby seeding remote sites of the lung.

CLINICAL MANIFESTATIONS

Much of what has been said in the discussion of the clinical manifestations of CAP and nursing home-acquired pneumonia applies to nosocomial pneumonia. The findings will vary, depending upon the age of the patient and the severity of the illness. As with CAP and nursing home-acquired infection, the symptoms may be constitutional and non-specific or localized to the respiratory tract.

DIAGNOSIS

As with CAP, two approaches may be used: clinical and invasive/quantitative.

With the clinical approach, pneumonia is defined as the presence of a new pulmonary infiltrate unexplained by other obvious causes plus one of a number of additional features, such as elevated temperature, production of purulent sputum or leukocytosis. While the clinical approach is relatively easy and straightforward and is not associated with significant costs, it is overly sensitive and does not reliably discriminate among the various causes. The invasive/quantitative approach, on the other hand, generally has greater precision but requires special training and laboratory support, is associated with significant costs, and has the potential for serious adverse effects.

Whichever approach is used, every patient with nosocomial pneumonia requires a careful history, including risk factors for specific pathogens, a physical examination, posteroanterior and lateral chest radiographs, complete blood count, blood chemistry, blood cultures, and either oximetry or arterial blood gases.

Chest radiography is useful in helping to determine the extent of the pneumonia and the presence of a pleural effusion. Multilobar involvement, cavitation or rapid radiographic progression indicates the presence of a severe infection.

Routine blood counts and chemistry may indicate evidence of end-organ dysfunction and can be helpful in adjusting treatment regimens. Blood cultures may be useful in identifying the pathogen in up to 20% of patients with nosocomial pneumonia. The presence of a pathogen in blood indicates not only that it is the etiological agent but also that the patient is at increased risk for a complicated course.

Serology is not normally useful in the management of individual patients with nosocomial pneumonia. It may, however, be helpful for epidemiological purposes, although this is more likely to be the case in patients with CAP.

The value of sputum Gram stain and culture is controversial as there are significant problems with both the sensitivity and specificity of these tests. Most studies have been carried out in patients with CAP; however, the results can be extrapolated to patients with nosocomial pneumonia. In selected cases direct staining of sputum samples for fungi or mycobacteria, or direct fluorescent antibody staining for *Legionella pneumophila*, may help in directing therapy.

Invasive techniques are not performed routinely in patients with nosocomial pneumonia. However, invasive techniques should be considered in selected cases, such as:

- patients receiving appropriate empirical antimicrobial coverage but who are failing to respond
- certain immunocompromised patients
- patients in whom an alternative diagnosis (e.g. carcinoma) is suspected.

A number of methods have been developed to obtain samples of lower respiratory tract secretions that are not contaminated by oropharyngeal micro-organisms. They are endotracheal aspirate, protected catheter aspirate, protected specimen brush and bronchoalveolar lavage. The studies that claim to support these techniques suffer from a lack of standardization, which makes comparison difficult at best. The discordant findings among the investigators studying these techniques make it difficult for practitioners to determine the most effective method.

Other invasive tests include transthoracic needle aspiration, transbronchial biopsy, thoracoscopy and open lung biopsy. One study comparing invasive and non-invasive strategies for management of suspected ventilator-associated pneumonia showed that there was a statistically significant reduction in mortality, sepsis-related organ failure and antibiotic-free days in the cohort managed with invasive diagnostic tests.[78]

TREATMENT

When devising an antimicrobial regimen, the patient, the pathogen and the drug should all be considered individually and the interactions among them taken into account.

PATIENT-RELATED FACTORS

These include any previous history of adverse reactions (and, in particular, anything suggesting type 1 hypersensitivity to any antimicrobial) and increasing age (since adverse drug effects are more common in elderly people). Macrolides, lincosamides, chloramphenicol and metronidazole are eliminated via the liver, while most other antibiotics are eliminated by the kidney. When treating women of childbearing age, it is important to determine if the patient is pregnant because teratogenicity and fetotoxicity must be considered.

PATHOGEN-RELATED FACTORS

Ideally, the narrowest spectrum agent associated with the least toxicity and lowest cost should be administered if the pathogen is known. Unfortunately, empirical therapy is usually the norm, and one must consider the likely pathogens based upon

local epidemiology, risk factors for pneumonia and for specific pathogens, and severity of illness. The prevalence of resistance among pathogens to various antimicrobials must also be considered.

DRUG-RELATED FACTORS

When selecting any antibiotic, the first step is to select an agent to which the pathogen is known or likely to be susceptible. Other considerations include pharmacokinetic and pharmacodynamic properties, toxicity, drug interactions and cost. Depending upon the class of antibiotic being used, different pharmacokinetic/pharmacodynamic parameters correlate more or less closely with clinical or therapeutic efficacy. For β-lactam drugs, macrolides and clindamycin, the time during which the antibiotic concentration at the site of action in the tissues is above the MIC for the organism correlates best with efficacy. However, for aminoglycosides, fluoroquinolones and vancomycin, the 24 h area-under-the-curve/MIC ratio correlates best. Higher ratios of peak serum concentrations to MIC (C_{max}/MIC) have been shown to prevent the emergence of resistance during treatment with fluoroquinolones and aminoglycosides. Furthermore, aminoglycosides do not achieve high levels in lung tissue, and this problem is compounded by the fact that they are also relatively inactivated by the acidic pH present at the site of infection in the lung.

The approach to the management of patients with nosocomial pneumonia should take into account the risk factors, severity of illness and time of onset of the illness.[79,80] The risk factors are for infection with specific pathogens; severity of illness is either mild to moderate or severe; time of onset refers to early versus late (i.e. <5 or ≥5 days, respectively). Based upon these variables, a hierarchical approach to the patient with nosocomial pneumonia has been developed. While it is recognized that a large number of bacteria are potential pathogens, there is a 'core' group of organisms that must be considered for each patient for whom antimicrobial coverage must be provided (Table 45.4). This group consists of Gram-negative bacilli (such as *Enterobacter* spp., *Esch. coli*, *Klebsiella* and *Proteus* spp., *Ser. marcescens*), *H. influenzae*, *Staph. aureus* and *Str. pneumoniae*. Depending upon the risk factors present and the severity of illness, anaerobes, methicillin-resistant *Staph. aureus*, *Legionella* spp., *Ps. aeruginosa* and *Acinetobacter* spp. should also be considered.

The American Thoracic Society regimens are presented in Tables 45.4, 45.5 and 45.6.[71] Other countries have produced guidelines for local use which reflect variation in the target pathogens and choice of therapy. Until the evidence base surrounding nosocomial pneumonia improves, variations in practice are likely to continue. The decision to select an agent should be based upon the host, pathogen and drug-related issues outlined earlier. A few specific issues, however, deserve comment. Single-agent therapy is recommended in many situations. Although two drugs should be used to achieve synergistic or additive activity against *Ps. aeruginosa*, there are no

Table 45.4 Initial empirical antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset and any disease severity

Potential pathogen	Recommended antibiotic[a]
Streptococcus pneumoniae[b] *Haemophilus influenzae* Methicillin-sensitive *Staphylococcus aureus* Antibiotic-sensitive enteric gram-negative bacilli	Ceftriaxone or Levofloxacin, moxifloxacin, or ciprofloxacin or
Escherichia coli *Klebsiella pneumoniae* *Enterobacter* spp. *Proteus* spp. *Serratia marcescens*	Ampicillin–sulbactam or Ertapenem

[a]See Table 45.6 for recommended initial doses of antibiotics.
[b]The frequency of penicillin-resistant *Str. pneumoniae* and multidrug-resistant *Str. pneumoniae* is increasing; levofloxacin or moxifloxacin is preferred to ciprofloxacin. The role of other new quinolones, such as gatifloxacin, has not been established. Adapted from the American Thoracic Society.[71]

Table 45.5 Initial empirical therapy for hospital-acquired pneumonia, ventilator-associated pneumonia and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity

Potential pathogens	Combination antibiotic therapy[a]
Pathogens listed in Table 45.4 and multidrug-resistant pathogens *Pseudomonas aeruginosa* *Klebsiella pneumoniae* (ESBL⁺)[b] *Acinetobacter* species[b]	Antipseudomonal cephalosporin (cefepime, ceftazidime) or Antipseudomonal carbapenem (imipenem or meropenem) or β-Lactam/β-lactamase inhibitor (piperacillin–tazobactam) plus Antipseudomonal fluoroquinolone[b] (ciprofloxacin or levofloxacin) or Aminoglycoside (amikacin, gentamicin or tobramycin) plus
Methicillin-resistant *Staphylococcus aureus* (MRSA) *Legionella pneumophila*[b]	Linezolid or vancomycin[c]

[a]See Table 45.6 for adequate initial dosing of antibiotics. Initial antibiotic therapy should be adjusted or streamlined on the basis of microbiological data and clinical response to therapy.
[b]If an extended spectrum β-lactamase-positive (ESBL⁺) strain, such as *K. pneumoniae*, or an *Acinetobacter* species is suspected, a carbapenem is a reliable choice. If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (e.g. azithromycin), or a fluoroquinolone (e.g. ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.
[c] If MRSA risk factors are present or there is a high incidence locally.
Reproduced from the American Thoracic Society. From American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. **Am J Respir Crit Care Med.** 2005;171:388–416.

data to support the routine use of combination therapy for other bacterial pathogens in non-neutropenic patients.[81]

In patients who are either severely ill with risk factors and early onset or severely ill without risk factors but with late onset, combination therapy should be instituted. If the patient was not receiving any prior antibiotics and deep suction

Table 45.6 Initial intravenous, adult doses of antibiotics for empirical therapy of hospital-acquired pneumonia, including ventilator-associated pneumonia and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens

Antibiotic	Dosage[a]
Antipseudomonal cephalosporin	
Cefepime	1–2 g every 8–12 h
Ceftazidime	2 g every 8 h
Carbapenems	
Imipenem	500 mg every 6 h or 1 g every 8 h
Meropenem	1 g every 8 h
β-Lactam/β-lactamase inhibitor	
Piperacillin–tazobactam	4.5 g every 6 h
Aminoglycosides	
Gentamicin	7 mg/kg per day[b]
Tobramycin	7 mg/kg per day[b]
Amikacin	20 mg/kg per day[b]
Antipseudomonal quinolones	
Levofloxacin	750 mg/day
Ciprofloxacin	400 mg every 8 h
Vancomycin	15 mg/kg every 12 h[c]
Linezolid	600 mg every 12 h

[a] Dosages are based on normal renal and hepatic function.
[b] Trough levels for gentamicin and tobramycin should be <1 μg/mL; for amikacin they should be <4–5 μg/mL.
[c] Trough levels for vancomycin should be 15–20 μg/mL.
Reproduced from the American Thoracic Society. From American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. **Am J Respir Crit Care Med.** 2005;171:388–416.

aspirates or bronchoscopy samples fail to yield *Ps. aeruginosa* or other often-resistant pathogens such as *Acinetobacter* spp., treatment may be modified to a single-drug regimen.

Enterobacter spp. are among the most common causes of Gram-negative bacillary hospital-acquired pneumonia. A major concern with infection caused by this organism is that in the presence of a group 4 cephalosporin it can become a hyperproducer of β-lactamase.[82]

The final issue is that of duration of therapy. Unfortunately, there are no appropriately designed randomized controlled trials that specifically address this issue. The general consensus, however, is that patients with severe infection caused by pathogens such as *Ps. aeruginosa* or *Acinetobacter* spp. should be treated for a minimum of 14 days, whereas patients with less severe infection may only require 7–10 days of treatment.

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