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Chapter 27

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Community-acquired pneumonia

INTRODUCTION

Pneumonia is a respiratory infection of the alveolar space, which can vary from a mild outpatient illness to a severe illness necessitating hospitalization and intensive care. In 2004, pneumonia, along with influenza, was the eighth leading cause of death in the USA, the sixth leading cause of death in those over age 65, and the principal cause of death from infectious diseases.[1] When the infection occurs in patients who are living in the community it is termed community acquired pneumonia (CAP), while it is called nosocomial pneumonia if it arises in patients who are already in hospital.[2,3] However, the distinction between these two forms of infection is becoming increasing blurred because of the complexity of patients who are now living outwith hospital, including those in nursing homes, those receiving chronic hemodialysis and those recently admitted to hospital, all of whom have contact with the health-care environment and may import multidrug-resistant (MDR) organisms when they come to the hospital with 'healthcare-associated pneumonia' (HCAP). Thus, the relationship between bacteriology and the site of origin of infection is a reflection of several factors, including the co-morbid illnesses present in the patient who develops pneumonia, their host-defense status and their environmental exposure to specific pathogens.[4] This discussion focuses on patients who develop pneumonia out of the hospital (including CAP and HCAP), who are not HIV infected and who do not have traditional immune suppression (cancer chemotherapy, immune suppressive medications).

The complexity of CAP management has increased in recent years, not only because of the presence of more co-morbid illness in at-risk individuals, but also because the etiologic pathogens are changing. Historically, CAP was regarded as a bacterial illness caused by one pathogen, *Streptococcus pneumoniae*, but now the number of identified pathogens has expanded to include not only bacteria, but also viruses (influenza), fungi and a number of other recently identified organisms (e.g. *Legionella* spp. and *Chlamydophila pneumoniae*). In addition to an expanding number of etiologies, the ability to treat CAP is being challenged by the rising frequency of antimicrobial resistance among many bacteria, including pneumococcus.

EPIDEMIOLOGY

In 1994, over 5.6 million people were diagnosed with CAP in the USA, but the majority, 4.6 million, were treated out of the hospital.[5] Data from 2005 showed that there were 1.3 million hospitalizations for pneumonia in the USA, more in females than males, and approximately 60% in those over the age of 65.[1] Community-acquired pneumonia has a seasonal variability, with a rise in frequency during the winter months, paralleling the times of influenza and viral infection, illnesses which can interfere with host defense and predispose to secondary bacterial pneumonia. Certain pathogens, such as *Legionella* spp., are more common in the late summer and early fall, reflecting the water-borne sources of this organism.

The cost of care for patients with CAP in the USA was estimated to be over $40 billion in 2005, including both direct and indirect costs.[1] The elderly account for a disproportionate amount of this cost, largely because they often require inpatient treatment, reflecting a high frequency of co-morbid illness. Although those over age 65 account for only about one-third of all cases of CAP, they are responsible for 60% of those hospitalized with CAP.

The elderly have both an increased incidence of pneumonia and an increased mortality, compared to younger populations. The high frequency and enhanced mortality of pneumonia in older patients are well known, but controversy still continues about whether this is a consequence of aging itself or the result of the co-morbid illnesses that become increasingly common in the aging population.

PATHOLOGY AND PATHOGENESIS

Pneumonia is an infection of the gas exchanging units of the lung, most commonly caused by bacteria, but occasionally by viruses, fungi, parasites and other infectious agents. In the immunocompetent individual, it is characterized by a brisk filling of the alveolar space with inflammatory cells and fluid. If the alveolar infection involves an entire anatomic lobe of the lung, it is termed 'lobar pneumonia'. Multilobar illness can be present in some instances and may lead to more severe clinical manifestations. When the alveolar process occurs in a distribution that is patchy, and adjacent to bronchi, without filling an entire lobe, it is termed a 'bronchopneumonia'.

Pneumonia occurs when a patient's host defenses are overwhelmed by an infectious pathogen. This can happen because the patient has an inadequate immune response, often as the result of underlying chronic medical diseases (congestive heart failure, diabetes, renal failure, chronic obstructive lung disease, malnutrition), because of anatomic abnormalities (endobronchial obstruction, bronchiectasis), as a result of acute illness-associated immune dysfunction (as can occur with sepsis or acute lung injury) or because of therapy-induced dysfunction of the immune system (corticosteroids, endotracheal intubation). Some commonly used therapies may actually reduce the mortality risk of pneumonia, including angiotensin-converting enzyme (ACE) inhibitors and statins.[6] Admission hyperglycemia may increase mortality risk in CAP, but it is unclear if therapy can mitigate this risk.[7]

Pneumonia can even occur in patients who have an adequate immune system if the host defense system is overwhelmed by a large inoculum of micro-organisms, which can occur in a patient with massive aspiration of gastric contents. Patients with impaired gastrointestinal or neurologic function may also aspirate, and this process

involves failure to protect the lower respiratory tract from the entry of oropharyngeal secretions, which are often overgrown with potentially pathogenic Gram-negative bacteria.[8] In patients outside the hospital, a normal immune system can also be overcome by a particularly virulent organism to which the patient has no pre-existing immunity (such as certain bacteria or viruses) or to which the patient has an inability to form an adequate acute immune response. The epidemic spread of severe acute respiratory syndrome (SARS), due to a virulent virus, is one example of this phenomenon.

Bacteria can enter the lung via several routes, but aspiration from a previously colonized oropharynx is the most common mechanism for pneumonia.[9] Although most pneumonias result from microaspiration, some patients can also aspirate large volumes of bacteria if they have impaired neurologic protection of the upper airway (stroke, seizure) or if they have intestinal illnesses that predispose to vomiting. Other routes of entry include inhalation, which applies primarily to viruses, *Legionella pneumophila* and *Mycobacterium tuberculosis*; hematogenous dissemination from extrapulmonary sites of infection (right-sided endocarditis); and direct extension from contiguous sites of infection (such as liver abscess).

Based on these mechanisms, previously healthy individuals often develop infection with virulent pathogens such as viruses, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Strep. pneumoniae* (pneumococcus). On the other hand, chronically ill patients can be infected by these organisms, as well as by organisms that commonly colonize the oropharynx (primarily enteric Gram-negatives) but only cause infection when immune responses are inadequate. These organisms include enteric Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp.), as well as fungi.

Severe forms of pneumonia develop when the infection is not contained (inadequate immune response) or, alternatively, if the inflammatory response to infection is unable to be localized to the site of infection (excessive immune response) and it 'spills over' into the systemic circulation (sepsis) or to the rest of the lung (acute respiratory distress syndrome). The normal lung immune response to infection is generally 'compartmentalized' and thus most patients with unilateral pneumonia have an inflammatory response that is limited to the site of infection. In patients with localized pneumonia, tumor necrosis factor (TNF), interleukin (IL)-6 and IL-8 levels are increased in the pneumonic lung and generally not increased in the uninvolved lung or in the serum.[10] Patients with severe pneumonia have increased serum levels of TNF and IL-6. It remains uncertain why localization does not occur in all individuals, but it is likely that genetic polymorphisms in the immune response may explain some of these differences, with patients who have certain inherited patterns of response being more prone than others to severe forms of pneumonia, and even mortality from this illness.[11,12] For example, CAP severity is increased with genetic changes in the IL-10 1082 locus, which are often present along with changes in the TNF 308 locus.[11,12] Currently, there are a large number of genes that have been identified as being able to affect the severity and outcome of CAP, but the ability to use this information to impact patient management does not currently exist.

ETIOLOGY

Etiologic pathogens (overview)

An etiologic pathogen is identified in only about half of all CAP patients, reflecting the limited value of even extensive diagnostic testing and the likelihood that we do not know all the organisms that can cause this illness. For example, in the past three decades, a variety of new CAP pathogens have been identified, including *Legionella pneumophila*, *Chlamydophila pneumoniae*, hantavirus, metapneumoviruses and coronaviruses (including the SARS virus). In addition, antibiotic-resistant variants of common pathogens such as drug-resistant *Streptococcus pneumoniae* (DRSP) and methicillin-resistant *Staphylococcus aureus* (MRSA) have become more prominent.

The number one pathogen for all patient populations with CAP is *Strep. pneumoniae*, or pneumococcus (including DRSP), and some studies have suggested that it may be responsible for many of the patients with no established etiologic diagnosis using standard diagnostic methodology.[13] In addition, atypical pathogens such as *M. pneumoniae*, *C. pneumoniae* and *Legionella pneumophila* are also common in patients with CAP, but may exist as co-pathogens, along with bacterial organisms.[14] Viruses may be present in up to 20% of all patients, particularly influenza, parainfluenza, adenovirus and respiratory syncytial virus.[15] Because a diagnosis of viral pneumonia requires specialized testing, usually acute and convalescent titers, this diagnosis is often not established. *Haemophilus influenzae* is a common organism in patients who smoke cigarettes and in those with chronic obstructive lung disease. Enteric Gram-negatives are not common causes of CAP, being found in only a few patients, and most of those with these organisms actually have HCAP which is treated similarly to nosocomial pneumonia.[3,16] Seasonal variations of pathogens may also be seen – pneumococcus and respiratory viruses are more common in winter in temperate countries.

In approaching management, it is important to stratify patients into different populations that are at risk for infection with specific pathogens (Table 27.1). The classification is based on the severity

Table 27.1 Common pathogens causing CAP and HCAP in specific patient populations (in order of decreasing frequency)

Outpatient, no cardiopulmonary disease or modifying factors	*Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* (alone or as mixed infection), *Haemophilus influenzae*, respiratory viruses, others (*Legionella* spp., *Mycobacterium tuberculosis*, endemic fungi)
Outpatient, with cardiopulmonary disease and/or modifying factors, or HCAP with no resistance risk factors	All of the above plus DRSP, enteric Gram-negatives and possibly anaerobes (with aspiration)
Inpatient, with cardiopulmonary disease and/or modifying factors, or HCAP with no resistance risk factors	*Strep. pneumoniae* (including DRSP), *H. influenzae*, *Mycoplasma pneumoniae*, *C. pneumoniae*, mixed infection (bacteria plus atypical pathogen), enteric Gram-negatives, anaerobes (aspiration), viruses, *Legionella* spp., others (*Mycobacterium tuberculosis*, endemic fungi, *Pneumocystis jirovecii*)
Inpatient, with no cardiopulmonary disease or modifying factors	All of the above, but DRSP and enteric Gram-negatives are unlikely
Severe CAP, with no risks for *Pseudomonas aeruginosa*	*Strep. pneumoniae* (including DRSP), *Legionella* spp., *H. influenzae*, enteric Gram-negative bacilli, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, respiratory viruses, others (*C. pneumoniae*, *Mycobacterium tuberculosis*, endemic fungi)
Severe CAP, with risks for *P. aeruginosa*, or HCAP with resistance risk factors	All of the above pathogens, plus *P. aeruginosa*

DRSP, drug-resistant *Streptococcus pneumoniae*; HCAP, health-care-associated pneumonia.

of illness and the presence of clinical risk factors for specific pathogens, referred to as 'modifying factors'. Patients with severe CAP may have a slightly different spectrum of organisms, being commonly infected with pneumococcus, atypical pathogens (especially *Legionella* spp.), enteric Gram-negatives (including *P. aeruginosa*), *Staph. aureus* and *H. influenzae*. As mentioned, HCAP patients are often at risk for infection with MDR Gram-negatives and Gram-positives, but not all HCAP patients are at the same risk (Table 27.1). In fact, these organisms are only a consideration for the HCAP patient with at least two of three risk factors, which include severe illness, poor functional status and prior antibiotic therapy.[16] Table 27.2 shows that certain clinical conditions are associated with specific pathogens and these associations should be considered in all patients when obtaining a history. One common, and important, association is infection with MRSA in patients with recent influenza infection.[17]

Table 27.2 Clinical associations with specific pathogens

Condition	Commonly encountered pathogens
Alcoholism	*Streptococcus pneumoniae* (including DRSP), anaerobes, Gram-negative bacilli (possibly *Klebsiella pneumoniae*)
Chronic obstructive pulmonary disease/ current or former smoker	*Strep. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella* spp., enteric Gram-negatives
Residence in nursing home	*Strep. pneumoniae*, Gram-negative bacilli, *H. influenzae*, *Staphylococcus aureus*, anaerobes, *Chlamydophila pneumoniae*; consider *Mycobacterium tuberculosis*
Poor dental hygiene	Anaerobes
Bat exposure	*Histoplasma capsulatum*
Bird exposure	*Chlamydia psittaci*, *Cryptococcus neoformans*, *Histoplasma capsulatum*
Rabbit exposure	*Francisella tularensis*
Travel to south-west USA	Coccidioidomycosis, hantavirus in selected areas
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
Travel to South East Asia	*Mycobacterium tuberculosis*, *Burkholderia pseudomallei*, SARS virus
Suspected bioterrorism	Anthrax, smallpox, pneumonic plague
Endobronchial obstruction	Anaerobes
Post influenza pneumonia	*Strep. pneumoniae*, *Staph. aureus*, *H. influenzae*
Structural disease of lung (bronchiectasis, cystic fibrosis, etc.)	*Pseudomonas aeruginosa*, *P. cepacia* or *Staph. aureus*
Recent antibiotic therapy	Pneumococcus resistant to the class of agents to which the patient was recently exposed, enteric Gram-negatives

DRSP, drug-resistant *Streptococcus pneumoniae*; SARS, severe acute respiratory syndrome.

SPECIFIC ORGANISMS

Streptococcus pneumoniae

Streptococcus pneumoniae is the most common pathogen for CAP in all patient populations, possibly even among those without an etiology recognized by routine diagnostic testing. In one study, when no etiologic pathogen was defined by conventional testing, transthoracic needle aspirates, analyzed with polymerase chain reaction (PCR) probes, identified pneumococcus in half of the patients in whom the needle provided a diagnosis.[13] The organism is a Gram-positive, lancet-shaped diplococcus, of which there are 84 different serotypes, each with a distinct antigenic polysaccharide capsule, but 85% of all infections are caused by one of 23 serotypes, which are now included in a vaccine.

Infection is most common in the winter and early spring, which may relate to the finding that up to 70% of patients have a preceding viral illness. The organism spreads from person to person and commonly colonizes the oropharynx before it causes pneumonia. Pneumonia develops when colonizing organisms are aspirated into a lung that is unable to contain the aspirated inoculum. Patients at risk include the elderly; those with asplenia, multiple myeloma, congestive heart failure, alcoholism; after influenza; and in patients with chronic lung disease. Individuals with HIV infection develop pneumococcal pneumonia with bacteremia more commonly than in healthy populations of the same age.

The classic radiographic pattern is a lobar consolidation; however, bronchopneumonia can also occur and is a common pattern in some series. Bacteremia is present in up to 20% of hospitalized patients with this infection, and although the impact of this finding on mortality is uncertain, its presence probably does not lead to a worse outcome. Extrapulmonary complications include meningitis, empyema, arthritis, endocarditis and brain abscess.

Drug-resistant pneumococci (DRSP)

Since the mid-1990s, antibiotic resistance among pneumococci has become increasingly common in the USA and penicillin resistance, along with resistance to other common antibiotics (macrolides, trimethoprim-sulfamethoxazole, selected cephalosporins), is present in over 40% of these organisms, using older definitions of resistance. Fortunately, in the USA, a large number of penicillin-resistant organisms are of the sensitive and 'intermediate' type. In other parts of the world (e.g. the UK) rates of DRSP have remained low over the last decade. Recently, the definitions of resistance have changed for nonmeningeal infection, with sensitive being defined by a penicillin minimum inhibitory concentration (MIC) ≤2 mg/L, intermediate as an MIC of 4 mg/l and resistant as an MIC ≥8 mg/l.[18] While the clinical impact of resistance on outcomes such as mortality was hard to show using older definitions, with the new definitions of resistance very few pathogens will be defined as resistant; however, those that are may affect outcome. In fact, most experts believe that CAP caused by organisms with a penicillin MIC of ≥4 mg/l, still an uncommon finding, can lead to an increased risk of death.[19]

Later studies have shown that higher levels of resistance can affect outcomes such as mortality and the development of suppurative complications such as empyema. The relationship of resistance to illness severity is complex and in some studies severity of illness may be reduced in patients with resistant organisms, implying a loss of virulence among organisms that become resistant.

Resistance of pneumococcus has even been reported to the quinolones, which are ordinarily a reliable class of antibiotic for these organisms. In general, one important risk factor for resistance is repeated use of a given agent in the same patient. In fact, pneumococcal resistance to β-lactams (penicillins and cephalosporins), macrolides and quinolones is more likely if a patient has received the same agent in the past 3 months.[20] With these data in mind, new guidelines have

suggested that CAP patients not receive the same antibiotic as in the recent past, with the cutoff of defining this time interval being within the past 3 months.

Atypical pathogens

Originally the term 'atypical' was used to describe the nonclassic clinical features of infection with certain organisms, but recent studies have suggested that the term does not accurately describe a unique pneumonia syndrome related to specific pathogens. However, the term has been retained to refer to a group of organisms which includes *M. pneumoniae*, *C. pneumoniae* and *Legionella*, a group of organisms that cannot be reliably eradicated by β-lactam therapy (penicillins and cephalosporins) but must be treated with a macrolide, a tetracycline or a quinolone. The frequency of these organisms as CAP pathogens has varied in studies, with recent data from North America and elsewhere suggesting that they may be present in up to 60% of CAP episodes, and that they can serve as co-pathogens, along with bacteria, in up to 40% of patients.[14] When mixed infection is present, particularly with *C. pneumoniae* and pneumococcus, it may lead to a more complex course and a longer length of stay than if a single pathogen is present. In patients with severe CAP, atypical pathogens can be present in almost 25% of all patients, but the responsible organism may vary over time. While atypical pathogens have been thought to be most common in young and healthy individuals, some population data have shown that they are present in patients of all ages, including the elderly in nursing homes.[21]

Studies reporting a high frequency of atypical pathogens have made the diagnosis with serologic testing, which may not be as accurate and specific as culture and antigen identification. The importance of atypical pathogens has been suggested by a number of studies of inpatients, including those with bacteremic pneumococcal pneumonia, showing a mortality benefit from therapies that include a macrolide or quinolone, agents that would be active against these organisms.[22,23] Atypical organism pneumonia may not be a constant phenomenon, and the frequency of infection may vary over the course of time and with geography. In one study, the benefit of providing empiric therapy directed at atypical pathogens was variable, being more important in some calendar years than in others.[23] Differing views about the importance of atypical pathogens have led to disparate recommendations about whether they should be covered by empiric therapy, with some CAP guidelines recommending routine coverage, while others, particularly from the UK and Europe, suggest otherwise.

Legionella pneumophila

This small, weakly staining, Gram-negative bacillus was first characterized after an epidemic in 1976, and can occur either sporadically or in epidemic form. At present, although multiple serogroups of the species *L. pneumophila* have been described, serogroup 1 is the most commonly diagnosed and can be identified with a urinary antigen test. The other species that commonly causes human illness is *Legionella micdadei*. *Legionella* is a water-borne pathogen that can emanate from air conditioning equipment, drinking water, lakes and river banks, water faucets, saunas and shower heads. Infection is more common in the summer and early fall, and is generally caused by inhalation of an infected aerosol generated by a contaminated water source. When a water system becomes infected in an institution, endemic outbreaks may occur, as has been the case in some nursing homes and hospitals. In its sporadic form, *Legionella* may account for 7–15% of all cases of CAP, being a particular concern in patients with severe forms of illness.

The varying incidence of *Legionella* infection among admitted patients is a reflection of geographic and seasonal variability in infection rates, as well as the extent of diagnostic testing. For a serologic diagnosis, it is necessary to collect both acute and convalescent titers. The urinary antigen test is the single most accurate acute diagnostic test for *Legionella*, but is specific to serogroup 1 infection. In recent years, most cases have been diagnosed with urinary antigen and there has been less reliance on serology and culture.[24] With this increased reliance on urinary antigen testing, the case fatality rate of *Legionella* has fallen, possibly reflecting diagnosis of less severe illness than in the past.[24]

It is difficult to identify the microbial etiology of CAP on the basis of clinical and radiographic features and a unique presentation of *Legionella* is uncommon. The classic clinical syndrome is characterized by high fever, chills, headache, myalgias and leukocytosis, along with a history of preceding diarrhea, early onset of mental confusion, hyponatremia, relative bradycardia and liver function abnormalities. Symptoms are rapidly progressive, and the patient may appear to be quite toxic, so this diagnosis should always be considered in patients admitted to the intensive care unit (ICU) with CAP.

Mycoplasma pneumoniae

Mycoplasma pneumoniae can cause CAP year-round, with a slight increase in the fall and winter. All age groups are affected, and although it is common in those less than 20 years of age, it is also seen in older adults. Respiratory infection occurs after the organism is inhaled and then binds via neuraminic acid receptors to the airway epithelium. An inflammatory response with neutrophils, lymphocytes and macrophages then follows, accompanied by the formation of IgM and then IgG antibody. Some of the observed pneumonitis may be mediated by the host response to the organism rather than by direct tissue injury by the organism. Up to 40% of infected individuals will have circulating immune complexes.

Although *Mycoplasma* causes pneumonia, the infection is often characterized by its extrapulmonary manifestations such as upper respiratory tract symptoms, including sore throat and earache (with hemorrhagic or bullous myringitis). Pleural effusion is seen in at least 20% of patients although it may be small. Other manifestations include neurologic illness such as meningoencephalitis, meningitis, transverse myelitis and cranial nerve palsies. The most common extrapulmonary finding is an IgM autoantibody that is directed against the I antigen on the red blood cell and causes cold agglutination of the erythrocyte. Although up to 75% of patients may have this antibody and a positive Coombs' test, clinically significant autoimmune hemolytic anemia is uncommon. The extrapulmonary manifestations may follow the respiratory symptoms by as long as 3 weeks.

Gram-negative bacteria

The most common Gram-negative organism causing CAP is *H. influenzae,* an organism seen in the elderly and in those who smoke cigarettes, or who have a history of alcoholism or chronic bronchitis. *H. influenzae* is a coccobacillary rod that can be either a typeable (encapsulated) or nontypeable organism, and can lead to bronchopneumonia and rarely empyema. Encapsulated organisms require a more elaborate host response and thus are more virulent than unencapsulated organisms. However, several studies have shown that in adults, particularly those with chronic obstructive pulmonary disease (COPD), infection with unencapsulated bacteria is common. The encapsulated type of organism may cause bacteremic pneumonia in some patients, particularly in those with segmental pneumonias as opposed to those with bronchopneumonia.

Enteric Gram-negatives are generally not common in CAP unless the patients are elderly and have chronic cardiac or pulmonary disease, have HCAP or are alcoholic. In one study, the identified risk factors for Gram-negative CAP were probably aspiration, prior hospitalization, prior antibiotic therapy and pulmonary co-morbidity.[25] In these patients, organisms such as *E. coli* and *K. pneumoniae* can be found. Although *P. aeruginosa* is an uncommon cause of CAP, it can be isolated from patients with bronchiectasis, in those with severe forms of CAP and in patients with pulmonary co-morbidity and prior hospitalization.[2,25] Gram-negative CAP was often a severe illness, with septic shock and hyponatremia, and occurred especially in patients with malignancy, cardiac disease and a history of cigarette smoking.[26]

While the frequency of enteric Gram-negatives in CAP has been controversial, many of the patients at risk for these organisms would now be re-classified as HCAP. It is still important to identify patients at risk, since infection with a Gram-negative increased the chance of dying by more than threefold, with a mortality rate of 32% in one study.[25] These patients also need ICU admission and mechanical ventilation more often than patients infected with other organisms. Patients with HCAP severe enough to require mechanical ventilation, admitted from a nursing home and with risk factors for aspiration (intestinal or neurologic risk factors), are particularly at risk for infection with enteric Gram-negatives, more than any other pathogens, including anaerobes.

Anaerobes

These organisms have always been a concern in patients with poor dentition who aspirate oral contents, and those at risk have been patients with neurologic or swallowing disorders, as well as individuals who abuse alcohol and opiate drugs. As mentioned, these patients may also be at risk for infection with enteric Gram-negatives and in the study cited above, many of the aspiration-prone patients who had anaerobes recovered, had them along with aerobic Gram-negatives and their presence did not correlate with poor oral hygiene. Many of these patients received inadequate therapy for anaerobes, yet most recovered, raising a question about whether these organisms really need to be treated. These findings suggest that anaerobes may not always be pathogens but may be colonizers in the institutionalized elderly, including those with aspiration risk factors.

Staphylococcus aureus

Community-acquired pneumonia can also be caused by this organism, which can lead to severe illness and to cavitary pneumonia. This organism can also seed the lung hematogenously from a vegetation in patients with right-sided endocarditis or from septic venous thrombophlebitis (from central venous catheter or jugular vein infection). When a patient develops postinfluenza pneumonia, *Staph. aureus* can lead to secondary bacterial infection, along with pneumococcus and *H. influenzae*. In the past several years, community-acquired strains of methicillin-resistant *Staph. aureus* (CA-MRSA) have emerged, primarily in skin and soft tissue infections, but also as a cause of severe CAP. CA-MRSA is a clonal disease, emanating from the USA 300 clone of *Staph. aureus*, and is clinically and bacteriologically different from the strains of MRSA that cause nosocomial pneumonia.[17] In addition, it can infect previously healthy individuals, and the classic clinical presentation of this pathogen causing CAP is as a complication of a preceding viral or influenza infection. The illness is characterized by a severe, bilateral, necrotizing pneumonia. Since the pathogenesis of pneumonia due to this organism may be related to toxin production by the bacteria, therapy may need to involve both an antibacterial agent and an antitoxin-producing agent.[27]

Viruses

Although the incidence of viral pneumonia is difficult to define, during epidemic times influenza should be considered as it can lead to primary viral pneumonia or to secondary bacterial pneumonia. One careful study of over 300 nonimmunocompromised CAP patients looked for viral pneumonia by paired serologies and found that 18% had viral pneumonia, with about half being pure viral infection and the others being mixed with bacterial pneumonia.[15] Influenza (A more than B), parainfluenza and adenovirus were the most commonly identified viral agents.

Although influenza A and B are the most common causes of viral pneumonia, they can be prevented to a large extent by vaccination. There are also other viruses that can cause severe forms of pneumonia, as evidenced by the recent experience with SARS, which demonstrated the potential of epidemic, person-to-person spread of a virulent respiratory viral infection.

CLINICAL FEATURES

Symptoms and physical findings

Patients with an intact immune system who develop CAP generally have 'typical' respiratory symptoms such as cough, sputum production and dyspnea, along with fever and other complaints. Cough is the most common finding and is present in up to 80% of all patients, but is less common in those with impaired immune responsiveness, such as the elderly, those with serious co-morbidity or individuals coming from nursing homes (HCAP).[4] Pleuritic chest pain is also a common symptom in CAP and its absence has been identified as a poor prognostic finding.[28]

When pneumonia occurs in elderly patients, it can have a non-respiratory presentation with symptoms of confusion, falling, failure to thrive, altered functional capacity or deterioration in a pre-existing medical illness, such as congestive heart failure. Patients with advanced age often have a longer duration of symptoms such as cough, sputum production, dyspnea, fatigue, anorexia, myalgia and abdominal pain than younger patients. In addition, they have delirium or acute confusion more often than younger patients. Very few elderly patients with pneumonia are considered well nourished, with kwashiorkor-like malnutrition being the predominant type of nutritional defect and the one associated with delirium on initial presentation.[29]

Physical findings of pneumonia include tachypnea, focal crackles, rhonchi and signs of consolidation (egophony, bronchial breath sounds, dullness to percussion). Other physical findings can be signs of pleural effusion, metastatic infection (arthritis, endocarditis, meningitis) or extrapulmonary manifestations that can occur with *M. pneumoniae* or *C. pneumoniae*. One of the most important physical assessments in CAP is a careful measurement of respiratory rate, which can have both diagnostic and prognostic relevance. In the elderly, an elevation of respiratory rate may be the initial presenting sign of pneumonia, preceding other clinical findings by as much as 1–2 days.[30] In general, tachypnea is the most common finding in elderly patients; it is present in over 60% of all patients, but occurs more often in the elderly than in younger patients with pneumonia. Measurement of respiratory rate also has prognostic significance and the presence of a respiratory rate greater than 30 per minute is one of several factors associated with increased risk of mortality.

Typical vs atypical pneumonia syndromes

In the past, the clinical and radiographic features of CAP were characterized as fitting into a pattern of either 'typical' or 'atypical' symptoms which could be used to predict a specific etiologic agent. The typical pneumonia syndrome, attributed to pneumococcus and other bacterial pathogens, is characterized by sudden onset of high fever, shaking chills, pleuritic chest pain, lobar consolidation and a toxic-appearing patient with the production of purulent sputum. The atypical pneumonia syndrome, which is characterized by a subacute illness, nonproductive cough, headache, diarrhea or other systemic complaints, can be the result of infection with *M. pneumoniae*, *C. pneumoniae*, *Legionella* spp. or viruses, but bacterial pneumonia can present in this fashion if the patient has an impaired immune response.

Recent studies have shown that this approach is not highly accurate and there is only a weak relationship between clinical features and the etiologic pathogen, primarily because host, as well as pathogenic, factors play a role in defining patient symptoms. Clinical features have been shown to be only about 40% accurate in differentiating pneumococcus, *M. pneumoniae* and other pathogens from one another.[2,31] The limitations of clinical features in defining the microbial etiology also apply to evaluations of radiographic patterns.

Clinical assessment of pneumonia severity

Careful evaluation of illness severity is necessary to guide decisions about whether to hospitalize a patient, and if so, whether to admit the

patient to the ICU. Although a number of models have been developed to predict mortality, and they have been proposed to guide the admission decision, the decision to admit a patient to the hospital should be based on social as well as medical considerations and remains an 'art of medicine' determination. In general the hospital should be used to observe patients who have multiple risk factors for a poor outcome, those who have decompensation of a chronic illness or those who need therapies not easily administered at home (oxygen, intravenous fluids, cardiac monitoring).

Risk factors for a poor outcome include a respiratory rate ≥30/min, age ≥65 years, systolic blood pressure <90 mmHg, diastolic BP ≤60 mmHg, multilobar pneumonia, confusion, blood urea nitrogen (BUN) >19.6 mg/dl, Pa_{O_2} <60 mmHg (on room air), Pa_{CO_2} >50 mmHg, respiratory or metabolic acidosis, or signs of systemic sepsis.[2] The two best-studied and most widely used prediction rules for pneumonia severity are the Pneumonia Severity Index (PSI) and the CURB-65 rule, a modification of a prognostic model developed by the British Thoracic Society.[28,32] The PSI uses multiple demographic and historic findings, physical findings and laboratory data, each assigned a point score, and the total score is used to categorize patients into one of five classes, each with a different risk of death. Although this tool has worked well to define mortality risk, it has had variable success in predicting site of care and is limited by its complexity and its failure to always recognize the most severely ill patients, especially if they do not have underlying co-morbid illness.[33] The CURB-65 rule is simpler, using only five assessments: **C**onfusion (due to the pneumonia), blood **U**rea nitrogen >7 mmol/l, **R**espiratory rate ≥30/min, **B**lood pressure of <90 mmHg systolic or ≤60 mmHg diastolic, and age ≥**65** years. Each of the five criteria receives 1 point, and the score falls between 0 and 5, with mortality risk rising with the score.

In recent studies, both tools have worked equally well to identify patients at low risk of dying, but the CURB-65 has been more discriminating in recognizing patients who need ICU care (score of at least 3) and who have the highest risk of death.[34] On the other hand, the CURB-65 does not account well for patients with decompensated chronic illness that results from the presence of CAP. This is because the PSI weights advanced age and chronic illness very heavily, whereas the CURB-65 model includes age as only one of several risk factors and co-morbid illness is not measured, but instead most of the score is based on acute physiologic abnormalities. Neither prediction model includes 'social factors' and clearly these issues need to be included in patient assessment, paying attention to whether the patient has a stable home environment for outpatient care, an ability to take oral medications, the absence of acute alcohol or drug intoxication, and stability of other acute and chronic medical problems.

There is no specific rule for who requires intensive care, but in general ICU admission (in the USA) is associated with a mortality rate of at least 30%, compared to a mortality rate of 12% for all admitted patients and a 1–5% mortality rate for outpatients.[35] When the ICU is used early in the hospital stay, the mortality rate is lower than if patients are first admitted to the ward, then deteriorate and move to the ICU.[36] Earlier studies that suggested a limited benefit from ICU admission generally found that patients were admitted too late in the course of illness to benefit, thus emphasizing the need for accurately assessing mortality risk when the patient is first evaluated.

Radiographic abnormalities

Most patients are diagnosed and treated for CAP after the physician obtains a chest radiograph which shows the presence of a new infiltrate, although not all outpatients have access to this evaluation. However, even when the radiograph is negative, if the patient has appropriate symptoms and focal physical findings, pneumonia may still be present. When CT scanning has been used in patients with clinical signs and symptoms of CAP, it can demonstrate abnormalities in some patients with a negative chest radiograph and the abnormalities are generally more extensive on CT scan than on chest radiograph.[37] Thus, if a symptomatic patient has an initially negative chest radiograph, it should be repeated after 24–48 hours. It is uncertain why a chest film would initially be negative, but the idea that hydration, especially in the elderly, is the explanation is not proven and falls into the realm of anecdotal reports.

Numerous studies have documented that the pattern of radiographic abnormality cannot reliably be used to predict the etiology of infection. Pleural effusion may appear on the initial chest radiograph and if present, it is necessary to distinguish empyema from a simple parapneumonic effusion by sampling the pleural fluid.

DIAGNOSTIC TESTING

Recommended testing (Table 27.3)

History

Historic data should be collected to suggest the presence of specific unusual pathogens, in addition to the likely organisms[2] (see Tables 27.1 and 27.2). For example, if the presentation is subacute following contact with birds, rats or rabbits, then the possibility of psittacosis, leptospirosis, tularemia or plague should be considered. *Coxiella burnetii* (Q fever) is a concern with exposure to parturient cats, cattle, sheep or goats; *Francisella tularensis* is a concern with rabbit exposure; hantavirus with exposure to mice droppings in endemic areas; *Chlamydia psittacii* with exposure to turkeys or infected birds; and *Legionella* with exposure to contaminated water sources (saunas). Following influenza, superinfection with pneumococcus, *Staph. aureus* (including MRSA) and *H. influenzae* should be considered. The onset of respiratory failure after a preceding viral illness should lead to suspicion of a viral pneumonia. Endemic fungi, (coccidioidomycosis, histoplasmosis and blastomycosis) occur in well-defined geographic areas and may present acutely with symptoms which overlap with acute bacterial pneumonia.

Radiography

Once the clinical evaluation suggests the presence of pneumonia, the diagnosis should be confirmed by chest radiograph. Although a radiograph is recommended in all outpatients and inpatients, it may be impractical in some settings outside of the hospital. A chest radiograph not only confirms the presence of pneumonia, but can also be used to identify complicated illness and to grade severity of disease by noting such findings as pleural effusion and multilobar illness. As mentioned above, there is no specific radiographic pattern that can be used to define the etiologic pathogen of CAP but certain findings can be used to suggest specific organisms (see above).

Table 27.3 Recommended diagnostic testing for CAP

- Diagnose the presence of pneumonia with a chest radiograph and clinical data
- Look for specific pathogens that alter therapy, based on historic and epidemiologic clues
- Outpatient testing optional
- Blood cultures only with severe illness
- Sputum Gram stain and culture prior to therapy if good quality and rapid transport and processing in the laboratory (especially valuable if a drug-resistant or unusual pathogen is suspected, but not to narrow empiric therapy)
- *Legionella* and pneumococcal urinary antigen for severe CAP
- Endotracheal aspirate or sputum culture for severe CAP
- No routine serologic testing for atypical pathogens or viruses

Other testing

Even with extensive testing, at least half of all patients do not have an etiologic diagnosis established and thus therapy is usually empiric. In addition, recent studies have emphasized the mortality benefit of prompt administration of effective antibiotic therapy for those with moderate to severe illness, and therapy should never be delayed for the purpose of diagnostic testing. While several studies have shown that establishing an etiologic diagnosis does not improve the outcome of patients with severe CAP, diagnostic testing may have value for the purpose of narrowing and focusing therapy and for guiding management in the patient who is not responding to empiric therapy.[38]

Recommended testing for outpatients is limited to a chest radiograph and pulse oximetry, if available, with sputum culture being considered in patients suspected of having an unusual or drug-resistant pathogen. For admitted patients, current guidelines recommend that diagnostic testing should include a chest radiograph, assessment of oxygenation (pulse oximetry or blood gas, the latter if retention of carbon dioxide is suspected) and routine admission blood work. If the patient has a pleural effusion, this should be tapped and the fluid sent for culture and biochemical analysis. In addition, the patient should have blood cultures only in the presence of severe illness, while sputum Gram stain and culture have their greatest value when the sample is of good quality and can be transported to the laboratory rapidly. Culture is particularly valuable if the patient has risk factors for a drug-resistant or unusual pathogen. In the patient with severe CAP, an endotracheal aspirate should be obtained, along with urinary antigen testing for pneumococcus and *Legionella*.[2]

Although blood cultures are positive in only 10–20% of CAP patients, most often showing pneumococcus, they can be used to identify a specific pathogen and to define the presence of drug-resistant pneumococci. However, they should be limited to patients with a reasonable likelihood of having a true-positive result. If low-risk patients routinely have blood cultures, it is possible that the frequency of false-positives could exceed the true-positives and lead to inaccurate and unnecessary therapy. Thus, blood cultures are only recommended for patients who are severely ill, especially if they have not received antibiotic therapy prior to admission.[39]

The role of Gram stain of sputum to guide initial antibiotic therapy is controversial, but this test has its greatest value in guiding the interpretation of sputum culture and can be used to define the predominant organism present in the sample. The role of Gram stain in focusing initial antibiotic therapy is uncertain since the accuracy of the test to predict the culture recovery of an organism such as pneumococcus depends on the criteria used.[2] Even if Gram stain findings are used to focus antibiotic therapy, this would not allow for empiric coverage of atypical pathogens which might be present even in patients with pneumococcus as part of a mixed infection. However, Gram stain can be used to broaden initial empiric therapy by enhancing the suspicion for organisms that are not covered in routine empiric therapy (such as *Staph. aureus* being suggested by the presence of clusters of Gram-positive cocci, especially during a time of epidemic influenza).

Routine serologic testing for viruses and atypical pathogens is not recommended. However, in patients with severe illness, the diagnosis of *Legionella* can be made by urinary antigen testing, which is the single test that is most likely to be positive at the time of admission, but is specific only for serogroup 1 infection. Commercially available tests for pneumococcal urinary antigen have been developed and may have value to identify pneumococcus; however, as mentioned, the impact of a positive test on therapy choices is uncertain. Bronchoscopy is not indicated as a routine diagnostic test and should be restricted to immunocompromised patients and to selected individuals with severe forms of CAP.

THERAPY

Initial therapy should be focused on the administration of antibiotics and the use of supportive care. Since it is not possible to know the etiology of CAP on the basis of clinical and laboratory findings, and because of the need to administer therapy as quickly as possible, once the diagnosis is made antibiotic choice is empiric, focusing on the pathogens most likely to be present for a given type of patient. Supportive care includes oxygen if needed, hydration, control of hyperglycemia and possibly chest physiotherapy, as well as administration of bronchodilators and expectorants. For more severely ill patients, the management is similar to severe sepsis, as CAP is a common cause of this syndrome. This means evaluating the need for vasopressors in the presence of hypotension, the use of corticosteroids if relative adrenal insufficiency is suspected and consideration of the use of drotrecogin alpha in selected patients. In addition, the routine use of corticosteroids in patients with severe pneumonia is advocated by some, because of limited data showing a survival benefit with this anti-inflammatory intervention.[40]

In the past 15 years, a variety of professional societies have developed guidelines for the management of CAP and included in the recommendations are antibiotic choice, along with other strategies. Several studies have shown that when therapy is concordant with guideline recommendations, outcomes such as mortality and rate of treatment failure are improved, while for severely ill patients duration of mechanical ventilation is reduced.[41–43] However, the presence of a guideline by itself is not usually enough to lead to these benefits because the guideline requires an implementation strategy in order to be successful. In one study, the benefit of a guideline to reduce length of stay in the hospital was greatest when an implementation strategy was employed that relied on real-time intervention with case managers who identified variances from recommended management.[44]

Antibiotic therapy

Initial empiric therapy for CAP is selected by categorizing patients on the basis of place of therapy (outpatient, inpatient, ICU), severity of illness and the presence or absence of cardiopulmonary disease or specific 'modifying' factors that make certain pathogens more likely.[2] By using these factors, a set of likely pathogens can be predicted for each type of patient (see Table 27.1) and this information can be used to guide therapy. If a specific pathogen is subsequently identified by diagnostic testing, then therapy can be focused. In this scheme, it is also important to identify patients with HCAP and to exclude them from CAP management, as these patients require their own management approach.[2,3,16]

In choosing empiric therapy of CAP, certain principles should be followed. However, the principles that guide therapy in North America are not the same as those used in parts of Europe and the UK.[2,45–47] Although in general guidelines emphasize an empiric approach (without extensive microbiologic testing) and treatment in the community rather than in hospital, the North American guidelines suggest broad-spectrum agents reflecting a recommendation for routine atypical pathogen coverage. In contrast, the UK and European guidelines generally recommend an initial use of penicillins, avoid routine quinolone use and do not advocate therapy for both 'typical' and 'atypical' pathogens except in more severely ill patients. These regional differences reflect variability in the frequency and importance of atypical pathogens and of DRSP, and differing concerns about the importance of empiric broad-spectrum CAP therapy to the rise in resistant health-care-associated infection such as MRSA and *Clostridium difficile* infection. Table 27.4 highlights the principles for CAP management for the North American and UK approaches.

In North American guidelines, for outpatients with no co-morbid cardiopulmonary disease and no history of recent antibiotic use, therapy can be with an advanced macrolide (azithromycin or clarithromycin) or doxycycline. If the patient has co-morbid illness or a history of recent antibiotic therapy (in the past 3 months), then DRSP is a concern and therapy should be with a selected oral β-lactam (amoxicillin, amoxicillin-clavulanate, cefuroxime or cefpodoxime) combined with a macrolide or doxycycline.[2] Alternatively, these patients at risk for DRSP can be treated with an oral fluoroquinolone as monotherapy (gemifloxacin, levofloxacin or moxifloxacin). If the patient has received an

Table 27.4 Principles of antibiotic therapy for CAP: differences between North American and UK guidelines for treatment

Clinical situation	North American approach	UK approach
Timing of antimicrobials	Administer initial antibiotic therapy as soon as possible, after firmly establishing the presence of pneumonia	Antibiotics should be given as soon as possible and within 4 h of clinical diagnosis
Initial choice of antimicrobials	Treat all patients for pneumococcus (including DRSP) and for the possibility of atypical pathogen co-infection (if endemic rates in the community support a role for these organisms)	Treat all patients for pneumococcus. Other pathogens should be considered only in more severe cases or specific clinical situations
Initial antibiotic choice for adults hospitalized with low-moderate severity CAP treated in the community	Use either a macrolide alone (selected patients with no cardiopulmonary disease or modifying factors) or for those outpatients with cardiopulmonary disease or 'modifying factors': • use monotherapy with a quinolone • *or* the combination of a selected β-lactam (cefpodoxime, cefuroxime, high dose ampicillin (3 g/24 h) or amoxicillin-clavulanate) • with a macrolide or tetracycline. A macrolide alone should only be used in outpatients or inpatients with no risk factors for DRSP, enteric Gram-negatives or aspiration	Most patients can be adequately treated with oral antibiotics Oral therapy with amoxicillin is preferred When oral therapy is contraindicated, recommended parenteral choices include iv amoxicillin or benzylpenicillin, or clarithromycin
Initial antibiotic choice for adults hospitalized with moderate severity CAP	Provide initial therapy for hospitalized patients with an iv agent, or if oral only, use a quinolone because of its high bioavailability For inpatients at risk for DRSP: • use quinolone monotherapy • *or* the combination of a selected iv β-lactam (ceftriaxone, cefotaxime, ertapenem, ampicillin-sulbactam) • with a macrolide or tetracycline. Limit antipseudomonal therapy to patients with risk factors	Oral therapy with a combined β-lactam/macrolide regimen is recommended When oral therapy is inappropriate, parenteral amoxicillin or penicillin G are alternatives to oral amoxicillin, with clarithromycin, q12h, as the preferred macrolide for parenteral therapy Levofloxacin iv once daily or a combination of iv second- (e.g. cefuroxime) or third- (e.g. cefotaxime or ceftriaxone) generation cephalosporin with iv clarithromycin are also appropriate alternative choices
Initial antibiotic choice for adults hospitalized with severe CAP	If no pseudomonal risk factors use a selected β-lactam plus a macrolide or antipneumococcal quinolone New antipneumococcal quinolones, in order of decreasing antipneumococcal activity are: gemifloxacin (oral only), moxifloxacin (oral and intravenous), levofloxacin (oral and intravenous) In the combination regimens for severe CAP, consider a quinolone rather than a macrolide for suspected or proven *Legionella* infection For those with pseudomonal risk factors, use an antipseudomonal β-lactam *plus* either ciprofloxacin/high-dose levofloxacin *or* the combination of an aminoglycoside with *either* a macrolide or antipneumococcal quinolone (antipseudomonal β-lactams include cefepime, imipenem, meropenem, piperacillin-tazobactam) Never use monotherapy (including with a quinolone) for patients with severe CAP Empiric therapy for CA-MRSA should be confined to patients with severe pneumonia and evidence of necrotizing infection, particularly after a viral infection Consider using an antitoxin-producing agent with an antibiotic, either vancomycin combined with clindamycin or linezolid monotherapy	Patients with high severity pneumonia should be treated immediately after diagnosis with parenteral antibiotics An iv combination of a broad-spectrum β-lactamase stable antibiotic such as amoxicillin-clavulanic acid together with a macrolide such as clarithromycin is preferred Alternatively, in penicillin-allergic patients, a second- (e.g. cefuroxime) or third- (e.g. cefotaxime or ceftriaxone) generation cephalosporin can be used instead of co-amoxiclav, together with clarithromycin If *Legionella* is strongly suspected, consider adding levofloxacin

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; DRSP, drug-resistant *Streptococcus pneumoniae*.

antibiotic in the past 3 months, then ideally an agent from a different class should be chosen to avoid the risk of repeated use of the same agent, which can promote the emergence of pneumococcal resistance. In contrast to these recommendations, European and UK guidelines rely more on oral penicillins for these patients and place less emphasis on the need for macrolides, except for the more severely ill hospitalized patients, and discourage the routine use of quinolones (see Table 27.4).[45,46] As noted, this reflects different views on the frequency and importance of DRSP and atypical pathogens in the management and outcome of CAP.

The majority of inpatients will have cardiopulmonary disease or other risks for DRSP, and sometimes Gram-negatives, and North American guidelines suggest they should be treated with either a selected intravenous β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam or ertapenem) combined with a macrolide or doxycycline; alternatively, they can receive monotherapy with an intravenous antipneumococcal quinolone (levofloxacin or moxifloxacin).[2] From the available data, either regimen is therapeutically equivalent, but an effort should be made to avoid repeating an agent in the same antibiotic class in the same patient, within a 3-month period. The antipneumococcal

quinolones are being widely used in North America because as a single drug, given once daily, it is possible to cover pneumococcus (including DRSP), Gram-negatives and atypical pathogens. In addition, quinolones penetrate well into respiratory secretions and are highly bioavailable, achieving the same serum levels with oral or intravenous therapy. There are differences among the available agents in their intrinsic activity against pneumococcus and, based on MIC data, these agents can be ranked from most to least active as: gemifloxacin (available only in oral form), moxifloxacin and levofloxacin. Some data suggest a lower likelihood of both clinical failures and the induction of pneumococcal resistance to quinolones if the more-active agents are used in place of the less-active agents.[2,20] UK and European guidelines do not recommend fluoroquinolones as initial therapy in severe pneumococcal CAP because of residual concerns regarding the clinical effectiveness of these agents, as well as concerns about their contribution to healthcare-associated infection (e.g. *Clostridium difficile*). Although oral quinolones may be as effective as intravenous quinolones for admitted patients with moderately severe illness, most admitted patients should receive initial therapy intravenously to be sure that the medication has been absorbed. Once the patient shows a good clinical response, oral therapy can be started.

In the ICU population, all individuals should be treated for DRSP and atypical pathogens, but only those with appropriate risk factors (see above) should have coverage for *P. aeruginosa* (see Table 27.4). In addition, no ICU-admitted patient should receive monotherapy with any agent, including a quinolone. While patients with severe CAP can receive either a macrolide or a quinolone as a second agent, several studies have shown a remarkably high efficacy of levofloxacin and moxifloxacin for documented *Legionella* infection, and thus a quinolone may be the preferred agent if this organism is suspected or proven.[48]

In addition to the therapy regimens discussed, some patients with severe CAP need added coverage for *Staph. aureus*, including MRSA. However, not all patients with severe CAP require this therapy, but most experts recommend that this organism be targeted empirically only in patients with severe necrotizing CAP following a viral illness, particularly influenza. Optimal therapy has not been defined and vancomycin alone may not be sufficient, having led to clinical failure, presumably since it is not active against the PVL toxin that accompanies community-acquired MRSA. For that reason, it may be necessary to add clindamycin to vancomycin or to use linezolid, with rifampin (rifampicin) in severe illness, since both of these latter agents can inhibit toxin production.[27]

Patients with HCAP are a heterogeneous group, with some at risk for MDR Gram-negatives and MRSA, and others not. As discussed earlier, the risks for drug-resistant pathogens in this population include recent antibiotic therapy and poor functional status, as well as severe illness.[16] An HCAP patient (from a nursing home, dialysis center or a patient who was recently hospitalized) who is not severely ill, and who has no or only one risk factor for resistance, can still be treated as non-severe CAP. Similarly, an HCAP patient with severe illness, but 0–1 risk factors for MDR pathogens can be treated with a severe CAP regimen.[16] On the other hand, a patient with severe HCAP and two risk factors for MDR pathogens should be treated for drug-resistant Gram-negatives, MRSA and other pathogens seen in those with nosocomial pneumonia. For these patients, the therapy should be with an aminoglycoside (amikacin, gentamicin or tobramycin) plus an antipseudomonal β-lactam (cefepime, imipenem, meropenem or piperacillin-tazobactam) plus linezolid or vancomycin[2,16] (see Chapter 28 for management of nosocomial pneumonia). If the severely ill HCAP patient has come from a nursing home that is known to have patients with atypical pathogen infection, then additional coverage of these agents is needed.

Other therapy issues

In addition to the general approach to antibiotic therapy outlined above, there are several other therapeutic issues in the management of CAP as highlighted in Table 27.4. These include the need for timely administration of initial antibiotic therapy, the findings of improved outcomes when pneumococcal bacteremia patients receive dual therapy rather than monotherapy, and the use of adjunctive therapies, especially in severely ill patients.

When a patient has CAP, administration of antibiotics as soon as possible has benefit for patient outcome and some retrospective data have suggested that mortality is reduced if the first dose of antibiotics is given within 4 hours of the patient's arrival to the hospital when compared to later administration.[49] These data led to widespread efforts in the USA to provide antibiotics as soon as possible to all CAP patients, with sometimes unintended consequences. While focus on this issue led to more patients receiving antibiotics sooner than before there was a focus on timely antibiotic administration, there was also more use of antibiotics before pneumonia was clearly known to be present, and in some instances patients without pneumonia were treated unnecessarily, occasionally leading to antibiotic-related complications such as *Clostridium difficile* colitis.[50,51]

As discussed, the antibiotic regimens used in North America provide routine therapy for atypical pathogens using either a macrolide or a quinolone, based on data that such an approach reduces mortality, especially in those with severe illness.[22,23] However, even in patients with documented pneumococcal bacteremia, the use of combination therapy (generally with the addition of atypical pathogen coverage to pneumococcal coverage) has been associated with reduced mortality compared to monotherapy.[52] In one study, the benefit of adding a second agent applied to those pneumococcal bacteremia patients who were critically ill, but not to other populations.[53] Rodriguez and colleagues found a benefit to adding a second agent for all patients with severe CAP and shock, and the benefit applied if the agent added was either a macrolide or a quinolone.[54]

For some patients, certain adjunctive therapies should be considered, including oxygen, chest physiotherapy (if at least 30 ml of sputum daily and a poor cough response are present), aerosolized bronchodilators and corticosteroids (if hypotension and possible relative adrenal insufficiency is suspected).

Response to therapy and duration of treatment

The majority of outpatients and inpatients will respond rapidly to empiric therapy, with clinical improvement usually occurring within 24–72 hours. Clinical improvement is measured by following the symptoms of cough, sputum production and dyspnea, along with documenting the ability to take medications by mouth and the presence of an afebrile status on at least two occasions 8 hours apart.[2] When a patient has met these criteria for clinical response, it is appropriate to switch to an oral therapy regimen and to discharge the patient, if he is otherwise medically and socially stable. Radiographic improvement lags behind clinical improvement and in a responding patient a chest radiograph is not necessary until 2–4 weeks after starting therapy.

There are few data about the proper duration of therapy in patients with CAP, especially those with severe illness. Even in the presence of pneumococcal bacteremia, short durations of therapy may be possible, with a rapid switch from intravenous to oral therapy in responding patients. Generally, CAP of unknown etiology and CAP due to *Strep. pneumoniae* can be treated for 5–7 days if the patient is responding rapidly, has been afebrile for 48–72 hours and has received accurate empiric therapy at the correct dose. The presence of extrapulmonary infection (such as meningitis and empyema) and the identification of certain pathogens (such as bacteremic *Staph. aureus* and *P. aeruginosa*) may require longer durations of therapy.[2] Traditionally, identification of *Legionella pneumophila* pneumonia prompted therapy for 14 days, although recent data have shown that quinolone therapy as short as 5 days with levofloxacin 750 mg may be effective.[48]

If the patient fails to respond to therapy in the expected time interval, then it is necessary to consider infection with a drug-resistant or unusual pathogen (tuberculosis, anthrax, *Coxiella burnetii*, *Burkholderia*

pseudomallei, *Pasteurella multocida*, endemic fungi or hantavirus), a pneumonic complication (lung abscess, endocarditis, empyema) or a noninfectious process that mimics pneumonia (bronchiolitis obliterans with organizing pneumonia, hypersensitivity pneumonitis, pulmonary vasculitis, bronchoalveolar cell carcinoma, lymphoma, pulmonary embolus). The evaluation of the nonresponding patient should be individualized but may include CT scanning of the chest, pulmonary angiography, bronchoscopy and occasionally open lung biopsy.

PREVENTION

Prevention of CAP is important for all groups of patients but especially the elderly, who are at risk for both a higher frequency of infection and a more severe course of illness. Appropriate patients should be vaccinated with both pneumococcal and influenza vaccines and cessation of cigarette smoking should be a goal for all at-risk patients. Immunization can be effective even for the patient who is recovering from CAP and hospital-based immunization is an effective and efficient way to promote vaccine utilization.

Pneumococcal vaccine

Pneumococcal capsular polysaccharide vaccine can prevent pneumonia in otherwise healthy populations, as was initially demonstrated in South African gold miners and American military recruits. The benefits in those of advanced age or with underlying conditions in nonepidemic environments are less clearly proven and have been demonstrated in case–control studies rather than in randomized trials. In immunocompetent patients over the age of 65, effectiveness has been estimated to be 75%, while it ranges from 65% to 84% in patients with chronic diseases including diabetes mellitus, coronary artery disease, congestive heart failure, chronic pulmonary disease and anatomic asplenia.[2,55] Its effectiveness has not been proven in immunodeficient populations such as those with sickle cell disease, chronic renal failure, immunoglobulin deficiency, Hodgkin's disease, lymphoma, leukemia and multiple myeloma. A single revaccination is recommended in patients over age 65 who initially received the vaccine more than 5 years earlier and were under age 65 on first vaccination. If the initial vaccination was given at age 65 or older, repeat is only indicated (after 5 years) if the patient has anatomic or functional asplenia or has one of the immunocompromising conditions listed above.

The available pneumococcal vaccine is generally underutilized and the 23-valent pneumococcal vaccine carries the serotypes causing the majority of clinical infection seen in the USA. A protein-conjugated pneumococcal vaccine has been licensed and appears more immunogenic than the older vaccine; however, it contains only seven serotypes and although recommended for healthy children, it has not yet been shown to be effective in adults. Nonetheless, the vaccine has had benefit for adults, even when given only to children, demonstrating a 'herd immunity' effect. More recently, however, children who have received the 7-valent pneumococcal polysaccharide vaccine have developed infection with strains not included in the vaccine, leading to a higher frequency of severe necrotizing pneumonia, especially with serotype 3.[56]

Influenza vaccine

The current vaccine includes three strains: two influenza A strains (H3N2 and H1N1) and one influenza B strain. Vaccination is recommended for all patients over age 65 and for those with chronic medical illness (including nursing home residents) and for those who provide health care to patients at risk for complicated influenza. When the vaccine matches the circulating strain of influenza, it can prevent illness in 70–90% of healthy persons over age 65. For older persons with chronic illness, the efficacy is less, but the vaccine can still attenuate the influenza infection and lead to fewer lower respiratory tract infections and the associated morbidity and mortality that follow influenza.

REFERENCES

References for this chapter can be found online at http://www.expertconsult.com