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Community Acquired Pneumonia, Bacterial and Other Common Pathogens

M S Niederman, State University of New York, Stony Brook, NY, USA

Abstract

Community-acquired pneumonia (CAP) is the number one cause of death from infectious diseases in the US, and the patient population that is affected is becoming increasingly more complex due to the presence of chronic illness which is commonly managed in outpatients who are at risk for pneumonia. The number one pathogen causing CAP is pneumococcus, which is commonly resistant to multiple antibiotics, thus complicating management. Other common pathogens include atypical organisms (*Chlamydophila pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*), *Hemophilus influenzae*, enteric Gram-negatives (especially in those with chronic illness and aspiration risk factors), and *Staphylococcus aureus*. Successful management requires careful assessment of disease severity so that a site-of-care decision can be made (outpatient, inpatient, intensive care unit), appropriate samples for diagnostic testing collected, and antibiotic therapy initiated in a timely and accurate fashion. Initial antibiotic therapy is empiric, but even with extensive diagnostic testing, less than half of all patients have an etiologic pathogen identified. All patients with CAP require therapy for pneumococcus, atypical pathogens, and other organisms, as dictated by the presence of specific risk factors. Because pneumonia has both short-term and long-term impact on mortality, it is also important to focus on prevention of this illness, which requires smoking cessation, and giving at-risk individuals both pneumococal and influenza vaccines.

Introduction

Pneumonia, a respiratory infection of the alveolar space, can vary from a mild outpatient illness to a severe illness necessitating hospitalization and intensive care. It is the sixth leading cause of death in the US and the number one cause of death from infectious diseases. 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 the hospital. Presently, the distinction between community-acquired and nosocomial infection is less clear because the 'community' includes

complex patients such as those who have recently been hospitalized, those in nursing homes, and those with chronic diseases who are commonly managed in such facilities as dialysis centers or nursing homes. When this latter group develops pneumonia, it has been termed healthcare associated pneumonia (HCAP) and this illness shares clinical features with CAP, but the etiologic pathogens may overlap with those seen in more traditional nosocomial pneumonia. Thus, the relationship between bacteriology and the site of origin of infection is a reflection of several factors, including: the types of patients who develop the illness, their host defense related predisposition to infection with specific pathogens, and their environmental exposure to certain organisms. This discussion focuses on pneumonia arising out of the hospital in immune-competent individuals, but excludes discussion of patients with human immunodeficiency virus (HIV) infection or traditional immune suppression (cancer chemotherapy, immune suppressive medications).

In 1994, over 5.6 million people were diagnosed with CAP in the US, but the majority, 4.6 million, were treated out of the hospital. Although the majority of cases of CAP are managed in the outpatient setting, the greater part of the cost of treatment is focused on hospitalized patients. Those who are admitted to the hospital commonly tend to be older and have a high frequency of comorbid illness. In the US, the population of elderly patients is increasing, and those aged over 65 make up about one-third of all CAP patients, but this group accounts for more than half of the cost because of the frequent need for elderly CAP patients to be hospitalized.

The reported mortality of CAP varies with the population being evaluated, ranging from less than 5% among outpatients, to 12% among all hospitalized CAP patients, but rising to over 30% among those admitted to the intensive care unit (ICU). While most studies have focused on the in-hospital mortality of CAP, one recent evaluation of CAP patients over the age of 65 found that while the short-term risk (in-hospital mortality) of illness was an 11% death rate, the mortality rate at 1 year was over 40%, emphasizing that for many patients, CAP is a marker of underlying serious comorbidity, and a predictor of poor outcome, even after hospital discharge, for a variety of reasons. These findings add to the emphasis on pneumonia prevention, especially through the use of available vaccines.

The complexity of CAP management is also increasing because the etiologic pathogens are changing. Historically, CAP was regarded as a bacterial illness caused by one pathogen, *Streptococcus pneumoniae*. Today, the number of etiologic pathogens has mushroomed to include not only bacteria, but also viruses (influenza, severe acute respiratory syndrome (SARS)), fungi, and a number of other recently identified organisms (such as *Legionella*, *Chlamydophila pneumoniae*). Not only is the number of pathogens expanding, but our ability to treat is being challenged by the rising frequency of resistance among bacteria to a wide range of commonly used, and often overused, antimicrobial agents.

Pathology and Pathogenesis

Pneumonia is an infection of the gas-exchanging units of the lung, most commonly caused by bacteria, but occasionally caused 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', and multilobar illness can be present in some instances. When the alveolar process occurs in a distribution that is patchy, and adjacent to bronchi, without filling an entire lobe, it is termed as '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 a result of underlying comorbid illness (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). Pneumonia can also occur in patients who have an adequate immune system, if the host defense system is overwhelmed by a large inoculum of microorganisms, which can occur in a patient with massive aspiration of gastric contents. In patients outside the hospital, a normal immune system can 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.

Bacteria can enter the lung via several routes, but aspiration from a previously colonized oropharynx is the most common way that organisms lead to pneumonia. Although most pneumonias result from microaspiration, 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).

Keeping these concepts in mind, it is easy to understand why previously healthy individuals develop infection with virulent pathogens such as viruses, *L. pneumophila*, *Mycoplasma pneumoniae*, *C. pneumoniae*, and *S. pneumoniae*. On the other hand, chronically ill patients can be infected by these organisms, as well as by organisms that commonly colonize patients, but only cause infection when immune responses are inadequate. These organisms include enteric Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp.) and fungi. Recent studies have evaluated the normal lung immune response to infection and have shown that it is generally 'compartmentalized', and thus most patients with unilateral pneumonia have an inflammatory response that is limited to the site of infection, not spilling over to the uninvolved lung or to the systemic circulation. In patients with localized pneumonia, tumor necrosis factor (TNF) and interleukins 6 and 8 (IL-6, IL-8) levels were increased in the pneumonic lung and generally not increased in the uninvolved lung or in the serum. In patients with severe pneumonia, the immune response is characterized by a spillover of the immune response into the systemic circulation, reflected by increases in serum levels of TNF and IL-6. It remains uncertain why localization does not occur in all individuals, and why some patients develop diffuse lung injury (acute respiratory distress sydrome, ARDS) or systemic sepsis as a consequence of pneumonia. Recent studies have suggested that genetic polymorphisms may explain some of these differences, with patients who have certain inherited patterns of immune response being more prone than others to severe forms of pneumonia, and even mortality from this illness. For example, certain genetic polymorphisms are associated with a greater risk of death from sepsis but not CAP. Specifically, TNF-308 polymorphisms increase sepsis mortality, but not mortality from CAP. In addition, 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. Another genetic change associated with an increased risk of septic shock from CAP is a modification in heat shock protein 70-2. Currently, we are aware of the large number of genes that can affect the severity and outcome of CAP, but much more must be learned to put these findings into a true clinical context.

Etiology

Etiologic Pathogens

Even with extensive diagnostic testing, an etiologic agent is defined in only about half of all patients with CAP, pointing out the limited value of diagnostic testing, and the possibility that we do not know all the organisms that can cause CAP. For example, in the past three decades, a variety of new pathogens for this illness have been identified, including *L. pneumophila*, *C. pneumoniae*, hantavirus, and the SARS virus (a coronavirus). In addition, antibiotic resistant variants of common pathogens such as *S. pneumoniae* (pneumococcus) have become increasingly common and are referred to as drug-resistant *S. pneumoniae* (DRSP).

For all patients with CAP, pneumococcus (including DRSP) is the most common pathogen, and some studies have suggested that it may be responsible for many of the patients with no established etiologic diagnosis, using standard diagnostic methodology. Recent studies have also suggested that atypical pathogens (*M. pneumoniae*, *C. pneumoniae*, and *L. pneumocphila*) are common in patients with CAP, often as copathogens, along with bacterial organisms. Viruses may be present in up to 20% of all patients, but specialized diagnostic testing, usually involving acute and convalescent titers, is needed, thus explaining the ordinary low frequency of documenting these organisms. *Hemophilus 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, but can be present in up to 10% of hospitalized patients, particularly those with advanced age, comorbid illness, or a high likelihood of aspiration.

In general, certain specific patients are at risk for infection with specific pathogens, in different frequencies. Table 1 summarizes the common pathogens causing CAP in both outpatients and inpatients. The classification is based on the severity 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 than less severely affected individuals, being commonly infected with pneumococcus, atypical pathogens, enteric Gram-negatives (including *P. aeruginosa*), *Staphylococcus aureus*, and *H. influenzae*. The modifying factors that increase the risk of infection with DRSP are: age over 65 years, beta-lactam therapy within the past 3 months, alcoholism, immune suppressive illness (including therapy with corticosteroids), multiple medical comorbidities, and exposure to a child in a day care setting. The modifying factors for enteric Gram-negatives include: residence in a nursing home,

Table 1 Common Pathogens Causing CAP in specific patient populations (in order of decreasing frequency)

Outpatient, no cardiopulmonary disease or modifying factors
S. pneumoniae, M. pneumoniae, C. pneumoniae (alone or as mixed infection), H. influenzae, respiratory viruses, others (Legionella sp., M. tuberculosis, endemic fungi)

Outpatient, with cardiopulmonary disease and/or modifying factors
All of the above plus: DRSP, enteric Gram-negatives, and possibly anaerobes (with aspiration)

Inpatient, with cardiopulmonary disease and/or modifying factors
S. pneumoniae (including DRSP), H. influenzae, M. pneumoniae, C. peumoniae, mixed infection (bacteria plus atypical pathogen), enteric Gram-negatives, anaerobes (aspiration), viruses, Legionella sp., others (M. tuberculosis, endemic fungi, Pneumocystis jerovici)

Inpatient, with no cardiopulmonary disease or modifying factors
All of the above, but DRSP and enteric Gram-negatives are not likely

Severe CAP, with no risks for P. aeruginosa
S. pneumoniae (including DRSP), Legionella sp., H. influenzae, enteric Gram-negative bacilli, S. aureus, M. pneumoniae, respiratory viruses, others (C. pneumoniae, M. tuberculosis, endemic fungi)

Severe CAP, with risks for P. aeruginosa
All of the pathogens above, plus P. aeruginosa

Table 2 Clinical associations with specific pathogens

Condition	Commonly encountered pathogens
Alcoholism	S. pneumoniae (including DRSP), anaerobes, Gram-negative bacilli (possibiy K. pneumoniae)
Chronic obstructive pulmonary disease (COPD)/current or former smoker	S. pneumoniae, H. influenzae, Moraxella catarrhalis, Legionella
Residence in nursing home	S. pneumoniae, Gram-negative bacilli, H. influenzae, S. aureus, anaerobes, C. pneumoniae; consider M. tuberculosis
Poor dental hygiene	Anaerobes
Bat exposure	Histoplasma capsulatum
Bird exposure	Chlamydia psittaci, Cryptococcus neoformans, H. capsulatum
Rabbit exposure	Francisella tularensis
Travel to Southwest US	Coccidioidomycosis; hantavirus in selected areas
Exposure to farm animals or parturient cats	Coxiella burnetii (Q fever)
Travel to Southeast Asia	M. tuberculosis, Burkholderia pseudomallei, SARS virus
Suspected bioterrorism	Anthrax, smallpox, pneumonic plague
Endobronchial obstruction	Anaerobes
Post influenza pneumonia	S. pneumoniae, S. aureus, H. influenzae
Structural disease of lung (bronchiectasis, cystic fibrosis, etc.)	P. aeruginosa, P. cepacia, or S. aureus
Recent antibiotic therapy	Pneumococcus resistant to the class of agents to which the patient was recently exposed

underlying cardiopulmonary disease, multiple medical comorbidities, and recent antibiotic therapy. The risk factors for P. aeruginosa infection are: structural lung disease (bronchiectasis), corticosteroid therapy ($>10\,\mathrm{mg\,day}^{-1}$ prednisone), broad-spectrum antibiotic therapy for >7 days in the past month, and malnutrition. Table 2 shows that certain clinical conditions are associated with specific pathogens, and these associations should be considered in all patients when obtaining a history.

Streptococus pneumoniae

As mentioned, S. pneumoniae is the most common pathogen for CAP, in any patient population, possibly even among those without an etiology recognized by routine diagnostic testing. In one study, transthoracic needle aspirates were used to define the etiology of CAP in patients with no identified organisms by conventional diagnostic testing, using a polymerase chain reaction (PCR) probe analysis of the samples, and in half of the patients in whom the needle provided a diagnosis when other methods had failed, pneumococcus was identified.

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 leads to pneumonia. Pneumonia develops when colonizing organisms are aspirated into a lung that is unable to contain the aspirated inoculum. Infection is more common in the elderly; those with asplenia, multiple myeloma, congestive heart failure, or alcoholism; after influenza; and in patients with chronic lung disease. In patients with HIV infection, pneumococcal pneumonia with bacteremia is more common than in healthy populations of the same age. The classic radiographic pattern is a lobar consolidation, but bronchopneumonia can also occur, and in some series, this is the most common pattern. Bacteremia is present in up to 20% of hospitalized patients with this infection, but the impact of this finding on mortality is uncertain. Extrapulmonary complications include meningitis, empyema, arthritis, endocarditis, and brain abscess.

Since the mid-1990s, antibiotic resistance among pneumococci has become increasingly common, and penicillin resistance, along with resistance to other common antibiotics (macrolides, trimethoprim/sulfamethoxizole, selected cephalosporins), is present in over 40% of these organisms. Fortunately, in the US, a large number of penicillin-resistant organisms are of the intermediate type (penicillin minimum inhibitory concentration, or MIC, of $0.1–1.0\,mg\,l^{-1}$) and not of the high-level type (penicillin MIC of $2.0\,mg\,l^{-1}$ or more). It is difficult to show a clinical impact of *in vitro* resistance on outcomes such as mortality in large numbers of patients, but most experts believe that organisms with a penicillin MIC of $\geqslant 4\,mg\,l^{-1}$, still an uncommon finding, can lead to an increased risk of death.

In an early study of the topic, there was no impact of resistance on mortality, after adjusting for severity of illness in a population with nearly a 30% frequency of *in vitro* resistance. More recently, some studies have shown that resistance can affect outcome. In a group of patients with pneumococcal bacteremia, of which more than half were HIV-positive, high-level resistance was a predictor of mortality. Other investigators did not find an increased risk of death from infection with resistant organisms, but did find an enhanced likelihood of suppurative complications (empyema), and a more prolonged length of stay in hospital. These conflicting data may have been the result of studying relatively few patients, many of whom did not have high levels of *in vitro* resistance. One large study evaluated more than 5000 patients with pneumococcal bacteremia and CAP and found an increased mortality for patients

with a penicillin MIC of at least $4\,mg\,l^{-1}$ or greater, or with a cefotaxime MIC of $2.0\,mg\,l^{-1}$ or more. However, this increased mortality was only present if patients who died in the first 4 days of therapy were excluded from analysis. Fortunately, very few organisms are currently at this level of resistance, which may explain the conflicting findings in various studies. More recently, another study using both a cohort and matched control methods found that severity of illness, and not resistance or accuracy of therapy, was the most important predictor of mortality. In some studies, severity of illness was greater in patients without resistant organisms, implying a loss of virulence among organisms that become resistant, a finding echoed in other studies that have found that the absence of invasive illness is a risk factor for pneumoccal resistance.

There are also conflicting data on the impact of discordant therapy in patients infected with DRSP. In one study of bacteremic infection, the only antibiotic associated with a poor outcome, in the presence of *in vitro* resistance, was cefuroxime. In another study, discordant therapy in general was associated with an increased risk of mortality, as was multilobar illness, underlying chronic obstructive pulmonary disease (COPD), and hospitalization within the past 3 months, but these latter factors did not have as much of a risk of death as did discordant therapy. Also in this study, discordant therapy was less likely if patients were treated with ceftriaxone or cefotaxime, compared to other therapies.

Macrolide-resistant pneumococcus is also occurring with increasing frequency, and up to 40% of organisms may be resistant to these agents *in vitro*. However, it is important to understand that most macrolide resistance in the US is low level, and due to an efflux mechanism, and thus it is a type of resistance that may not be clinically relevant, because local concentrations of macrolides at respiratory sites of infection may be adequate for effective therapy. However, some resistance is higher level and due to an inability of the antibiotic to bind to its ribosomal site of action, and this form of resistance may be much higher level and more likely to be clinically relevant. There are however, very few reports of macrolide failures in CAP, especially considering the widespread use of these agents. Reports of breakthrough bacteremia have appeared, but have been due to organisms that were resistant by either the efflux or ribosomal mechanism. It is likely that higher levels of resistance will become more likely in the future, and the impact on outcome is likely to be more apparent.

Resistance of pneumococcus has even been reported to the quinolones, which are ordinarily a

reliable class of antibiotics for these organisms. In general, one important risk factor for resistance is repeated use of these agents in the same patient. In fact, pneumococcal resistance to beta-lactams (penicillins and cephalosporins), macrolides, and quinolones is more likely if a patient has received the same agent in the recent past. It remains uncertain how long after antibiotic exposure that there is still risk of resistance, but 3–6 months has been reported for beta-lactams, up to 6 months for macrolides, and up to 12 months for quinolones. With these data in mind, new guidelines have suggested that CAP patients should not receive the same antibiotic as in the recent past, with a relatively arbitrary cutoff of defining this time interval as 'within the past 3 months'.

Atypical Pathogens

Originally the term 'atypical' was used to describe the unusual clinical features of infection with certain organisms, but recent studies have suggested that the term does not accurately describe a unique clinical 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*, and this group of organisms cannot be reliably eradicated by beta-lactam therapy (penicillins and cephalosporins), but must be treated with a macrolide, ketolide (telithromycin is the only one currently available), tetracycline, or a quinolone. Some recent studies have shown that these infections are common in patients of all ages, not just young and healthy individuals as originally described, and these organisms have even been reported among the elderly in nursing homes. In addition, they can occur as either primary pathogens, or may be part of a mixed infection, along with traditional bacterial pathogens. When mixed infection is present, it may lead to a more complex course and a longer length of stay than if a single pathogen is present. There may be a particular synergy between *C. pneumoniae* and pneumococcus, with either sequential, or mixed infection with *C. pneumoniae* leading to a more severe course for pneumococcus. The frequency of atypical pathogens can be as high as 60% of all CAP patients, in some series, with as many as 40% of patients having mixed infection identified. Although these high incidence numbers have been derived with serologic testing, which is of uncertain accuracy, the importance of these organisms is suggested by studies of inpatients, which have shown a reduced mortality and length of stay when patients receive empiric therapy that accounts for these organisms, compared to regimens that do not

account for these organisms. In fact, several studies of patients with pneumococcal bacteremia have even suggested a mortality benefit to combination therapy that provides coverage for atypical pathogens, as well as pneumococcus.

Atypical organism pneumonia may not be a constant phenomenon, and the frequency of infection may vary over the course of time and with geographical location. 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. The incidence of *Legionella* infection among admitted patients has varied from 1% to 15% or more, and is also a reflection of geographic and seasonal variability in infection rates, as well as a reflection of the extent of diagnostic testing. For *Legionella* to be identified, it is necessary to collect both acute and convalescent serologic studies. In patients with severe CAP, atypical pathogens can be present in almost 25% of all patients, but the responsible organism may vary over time. In one series, *Legionella* was the most common atypical pathogen leading to severe CAP, but in the same hospital a decade later, it had been replaced by *Mycoplasma* and *Chlamydophila* infection.

L. pneumophila is a small, weakly staining, Gram-negative bacillus 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 causes the most cases of pneumonia. The other species that commonly causes human illness is *Legionella micdadei*. *Legionella* is a water-borne pathogen and 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 hospitals, particularly in patients who are receiving corticosteroid therapy. 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.

As mentioned, it is very difficult to use clinical features to predict the microbial etiology of CAP; however, the classic *Legionella* syndrome is characterized by high fever, chills, headache, myalgias, and leukocytosis. The diagnosis is also suggested by the presence of a pneumonia with preceding diarrhea, along with early onset of mental confusion, hyponatremia, relative bradycardia, and liver function abnormalities, but this syndrome is usually not

present. 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 ICU with CAP.

M. 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 a common cause of CAP, even 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 immunoglobulin M (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 *Mycoplasma*. Up to 40% of infected individuals will have circulating immune complexes.

Although *Mycoplasma* causes pneumonia, infection is often characterized by its extrapulmonary manifestations. Up to half of patients will have upper respiratory tract symptoms, including sore throat and earache (with hemorrhagic or bullous myringitis). Pleural effusion is quite common, being seen in at least 20% of patients with pneumonia, although it may be small. Other extrapulmonary 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. Other systemic complications include myocarditis, pericarditis, hepatitis, gastroenteritis, erythema multiforme, arthralgias, pancreatitis, generalized lymphadenopathy, and glomerulonephritis. 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* (see below). Enteric Gram-negatives are generally not common in CAP, unless the patient is elderly and has chronic cardiac or pulmonary disease, has healthcare associated pneumonia, or is alcoholic. In these patients, organisms such as *E. coli* and *K. pneumoniae* can be found. *P. aeruginosa* is an uncommon cause of CAP, but can be isolated from patients with CAP and bronchiectasis, and in those with severe forms of CAP, particularly in the elderly patient aged over 75.

Controversy has persisted about how commonly enteric Gram-negative bacteria are a cause of CAP. However, in one large study of hospitalized CAP patients, careful diagnostic testing identified Gram-negative enterics in 11%, with more than half of these being *P. aeruginosa*. Identified risk factors for Gram-negative infection were: probable aspiration, previous hospital admission within 30 days of admission, previous antibiotics within 30 days of admission, and presence of pulmonary comorbidity. Risk factors for *P. aeruginosa* were pulmonary comorbidity and previous hospitalization. Infection with a Gram-negative increased the chance of dying by more than threefold, with a mortality rate of 32%, and these patients also need ICU admission and mechanical ventilation more often than patients with other organisms.

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. Several recent studies have questioned whether these organisms are really common in patients with risk factors for aspiration. In one evaluation of residents of long-term care facilities who had severe aspiration pneumonia (defined by the presence of risk factors for oropharyngeal aspiration), requiring ICU admission, bacteriology was determined by protected bronchoalveolar lavage (BAL) within 4 h of admission. When a pathogen was identified, the organisms were: enteric Gram-negatives in 49%, anaerobes in 16%, and *S. aureus* in 12%. Many of the anaerobes were recovered with aerobic Gram-negatives, and their presence did not correlate with oral hygiene, but the presence of Gram-negatives did correlate with functional status, being more common in patients who were totally dependent. Many patients received inadequate therapy for anaerobes, yet most recovered, raising a question about whether infection with these organisms really needs 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.

Haemophilus influenzae

This Gram-negative coccobacillary rod can occur in either a typable, encapsulated form or a nontypable, unencapsulated form. The encapsulated organism can be one of seven types, but type B accounts for 95% of all invasive infections. Encapsulated organisms require a more elaborate host response, and

thus they are more virulent than unencapsulated organisms. However several studies have shown that in adults, particularly those with COPD, infection with unencapsulated bacteria is more common than infection with encapsulated organisms. The organism may cause bacteremic pneumonia in some patients, particularly in those with segmental pneumonias as opposed to those with bronchopneumonia. The encapsulated type B organism is more common in patients with segmental pneumonia than in those with bronchopneumonia. Most patients with this infection have some underlying illness such as alcoholism, smoking history, or COPD.

Staphylococcus aureus

CAP can also be caused by *S. aureus*, which can lead to severe illness and to cavitary lung infection. 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 post influenza pneumonia *S. aureus* can lead to secondary bacterial infection, along with pneumococcus and *H. influenzae*. Most recently, there have been reports of CAP caused by methicillin-resistant *S. aureus* (MRSA), and if this becomes a more common occurrence, it may change the way this disease is treated empirically. To date, most patients with MRSA CAP have had a severe necrotizing pneumonia, generally following influenza or another viral infection. The organism responsible has had a specific virulence factor, the Panton–Valentine leukocidin, and all the organisms causing pneumonia appear to be genetically related.

Viruses

The incidence of viral pneumonia is difficult to define, but during epidemic times, influenza should be considered, and it can lead to a primary viral pneumonia, or to secondary bacterial pneumonia. One careful study of over 300 non-immune-compromised CAP patients collected paired sera for respiratory viruses, and found that 18% had viral pneumonia, with about half being pure viral infection and the others being mixed with bacterial pneumonia. Patients with congestive heart failure were at more risk of pure viral pneumonia than they were of pneumococcal infection. Influenza (A more than B), parainfluenza, and adenovirus were the most commonly identified viral causes of CAP.

While influenza A and B still remain the most common causes of viral pneumonia, vigilance to new agents is essential as evidenced by the recent experience with SARS, which demonstrated the potential of epidemic, person-to-person spread of virulent respiratory viral infection. Continued concern about epidemic viral pneumonia remains, with the current worry being focused on avian influenza, and bioterrorism with agents such as smallpox.

Clinical Features

Symptoms and Physical Findings

Patients with an intact immune system who develop CAP generally have 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 who are elderly, those with serious comorbidity, or individuals coming from nursing homes. The elderly generally have fewer respiratory symptoms than a younger population, and the absence of clear-cut respiratory symptoms and an afebrile status have themselves been predictors of an increased risk of death. This may be the consequence of nonrespiratory presentations being an indication of an impaired immune response, as well as a factor leading to delayed presentation to medical attention and recognition of the correct diagnosis. Pleuritic chest pain is also commonly seen in patients with CAP, but its absence has been identified as a poor prognostic finding.

In the elderly patient, pneumonia can have a nonrespiratory 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. In general, overall symptoms are less prominent in those above age 65 than in those who are younger. Patients with advanced age generally also have a longer duration of symptoms such as cough, sputum production, dyspnea, fatigue, anorexia, myalgia, and abdominal pain than younger patients. Studies have found no association between the type of etiologic microorganisms and the clinical presentation of CAP, except for pleuritic chest pain, which is likely to be more common in pneumonia caused by bacterial pathogens such as *S. pneumoniae* than in nonbacterial pneumonia. Delirium or acute confusion can be more frequent in the elderly patients with pneumonia than in age-matched controls who do not have pneumonia. 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.

Physical findings of pneumonia include tachypnea, crackles, rhonchi, and signs of consolidation

(egophony, bronchial breath sounds, dullness to percussion). Patients should also be examined for signs of pleural effusion. In addition, extrapulmonary findings should be sought to rule out metastatic infection (arthritis, endocarditis, meningitis), or to add to the suspicion of an 'atypical' pathogen such as *M. pneumoniae* or *C. pneumoniae*.

One of the most important evaluations in any patient suspected of having pneumonia is a measurement of respiratory rate. 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. In prospective evaluations in a long-term care setting, most patients who were diagnosed with lower respiratory tract infection had a respiratory rate above the normal range of 16–25 min^{-1}, and in general the elevated rate preceded other clinical findings. Although this finding is certainly not specific, it appears to be a very sensitive indicator of the presence of respiratory infection. In general, tachypnea is the most common finding in elderly patients with pneumonia, being present in over 60% of all patients, and being present more often in the elderly than in younger patients with pneumonia. Measurement of respiratory rate not only has diagnostic value, but also prognostic significance. In evaluating patients with CAP, the finding of a respiratory rate $>30 \, min^{-1}$ is one of several factors associated with increased mortality.

Typical versus Atypical Pneumonia Syndromes

In the past, the clinical and radiographic features of CAP have been characterized as fitting into a pattern of either 'typical' or 'atypical' symptoms, and the pattern was used to predict a specific etiologic agent. 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 pathogen factors play a role in defining patient symptoms.

The typical pneumonia syndrome is characterized by sudden onset of high fever, shaking chills, pleuritic chest pain, lobar consolidation, a toxic appearing patient, with the production of purulent sputum. Although this pattern has been attributed to pneumococcus and other bacterial pathogens, these organisms do not always lead to such classic symptoms, especially in the elderly, as discussed above. The atypical pneumonia syndrome, which is characterized by a subacute illness, nonproductive cough, headache, diarrhea, or other systemic complaints, is usually the result of infection with *M. pneumoniae*, *C. pneumoniae*, *Legionella* sp., or viruses. However, patients with impaired immune responses (especially the elderly with chronic illness) may present in this fashion, even with bacterial pneumonia. Clinical features have been shown to be only about 40% accurate in differentiating pneumococcus, *M. pneumoniae*, and other pathogens from one another. In addition, careful comparisons of patients with *S. pneumoniae*, *H. influenzae*, *L. pneumophila*, and *C. pneumoniae* have shown no significant differences in their clinical presentations. The limitations of clinical features in defining the microbial etiology also apply to evaluations of radiographic pattern.

Clinical Assessment of Severity of Pneumonia

One of the most important patient assessments is to define severity of illness, which can be used to guide decisions about whether to hospitalize a patient, and if so, whether to admit the patient to the ICU. While a number of prediction models have been developed to predict severity of illness and to guide the admission decision, no rule is absolute and the decision to admit a patient 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 $\geqslant 30 \, min^{-1}$, age $\geqslant 65$ years, systolic blood pressure $<90 \, mmHg$, diastolic blood pressure $\leqslant 60 \, mmHg$, multilobar pneumonia, confusion, blood urea nitrogen $>19.6 \, mg \, dl^{-1}$, PaO_2 $<60 \, mmHg$, $PaCO_2$ $>50 \, mmHg$, respiratory or metabolic acidosis, or signs of systemic sepsis. The two best-studied and widely regarded 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. The PSI uses a number of demographic and historical findings, physical findings, and laboratory data to assign a score to each patient, and the score is used to categorize patients into one of five classes, each with a different risk of death. This tool has worked very well to define mortality risk, but has had variable success in predicting need for admission, is cumbersome to use, and does not discriminate very well among the most severely ill patients. The CURB-65 rule is simpler, using only five assessments: <u>c</u>onfusion, <u>u</u>rea $>7 \, mmol \, l^{-1}$, <u>r</u>espiratory <u>r</u>ate $\geqslant 30 \, min^{-1}$, <u>b</u>lood pressure $<90 \, mmHg$ systolic or $\leqslant 60 \, mm$ diastolic, and age $\geqslant 65$ years. Each of the five criteria is scored and as the score rises from 0 to 5, mortality risk rises. 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. A major difference between the two models is that the PSI weights advanced age and chronic illness very heavily, while the CURB-65 model includes age as only one of several risk factors, and comorbid illness is not measured, but instead most of the score is based on acute physiologic abnormalities. None of the prediction models includes social factors in the scoring system, 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 should be admitted to the ICU, but in general the ICU is used for approximately 10% of all CAP patients, and this population has 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. There is some debate about the benefit of ICU care for patients with CAP, but the benefit seems most certain if patients are admitted early in the course of severe illness, making assessment of mortality risk an important clinical assessment. Criteria for ICU admission, in addition to need for mechanical ventilation and septic shock, are the presence of at least two of the following: PaO_2/FiO_2 ratio <250, multilobar infiltrates, systolic blood pressure <90 mmHg.

Radiographic Features

The entry point into most treatment algorithms for CAP is the presence of a new radiographic infiltrate, but not all patients with this illness will have this finding when first evaluated. Even when the radiograph is negative, if the patient has appropriate symptoms and focal physical findings, pneumonia may still be present. In one study, nearly 50 patients with clinical signs and symptoms of CAP were evaluated with both a chest radiograph and a high-resolution computed tomography (CT) scan of the chest and there were almost 20% of patients identified by CT scan to have pneumonia who had a negative chest radiograph. In addition, more extensive abnormalities were found on CT scan in many patients than were present on the chest radiograph. The findings of this study confirm the need to repeat the chest film after 24–48 h in certain symptomatic patients with an initially negative chest film. The reason for an initially negative chest film is not clear, but some

studies have suggested that febrile and dehydrated patients can have a normal radiograph when first admitted, although the idea of hydrating a pneumonia is in the realm of 'conventional wisdom' and anecdotal reports.

Although a variety of radiographic patterns can be seen in pneumonia, and radiographic findings cannot generally be used to predict microbial etiology in CAP, there are certain patterns that have been associated with specific pathogens. Focal consolidation can be seen with infections caused by pneumococcus, *K. pneumoniae* (with upper lobe consolidation and the classic bulging down of the upper lobe fissure), aspiration (especially if in the lower lobes or other dependent segments), *S. aureus*, *H. influenzae*, *M. pneumoniae*, and *C. pneumoniae*. Interstitial infiltrates should suggest viral pneumonia as well as infection due to *M. pneumoniae*, *C. pneumoniae*, *Chlamydia psittaci*, and *Pneumocystis jerovici*. Lymphadenopathy with an interstitial pattern should raise concerns about anthrax, *Francisella tularensis*, and *C. psittaci*, while adenopathy can be seen with focal infiltrates in tuberculosis, fungal pneumonia, and bacterial pneumonia. Cavitation can be the result of an aspiration lung abscess, or infection with *S. aureus*, aerobic Gram-negatives (including *P. aeruginosa*), tuberculosis, fungal infection, nocardia, and actinomycosis.

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. Pneumococcal pneumonia is the infection most commonly complicated by effusion (36–57% of patients), but other pathogens causing effusion include *H. influenzae*, *M. pneumoniae*, *Legionella*, and tuberculosis.

Diagnostic Testing

Once the clinical evaluation suggests the presence of pneumonia, the diagnosis should be confirmed by chest radiograph. Although some patients may have clinical findings of pneumonia (focal crackles, bronchial breath sounds), and a negative chest radiograph, the need for antibiotic therapy of CAP has been established in studies of patients with a radiographic infiltrate. In some populations, such as the elderly and chronically ill, the clinical diagnosis is difficult, and for these individuals, a chest radiograph is essential to define the presence of parenchymal lung infection. 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 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, such as anaerobes if a cavitary infiltrate is found, or tuberculosis if a posterior upper lobe infiltrate is present.

Even with extensive testing, most patients do not have a specific pathogen identified, and many who do, have this diagnosis made days or weeks later, as the results of cultures or serologic testing become available. In addition, recent studies have emphasized the mortality benefit of prompt administration of effective antibiotic therapy, with a goal of administering intravenous antibiotics within 4 h of admission to the hospital, for those with moderate to severe illness. Thus, therapy should never be delayed for the purpose of diagnostic testing, and the diagnostic workup should be streamlined, with all patients receiving empiric therapy based on predicting the most likely pathogens, as soon as possible.

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, 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.

Although blood cultures are positive in only 10–20% of CAP patients, they can be used to define a specific diagnosis and to define the presence of drug-resistant pneumococci. One concern with blood cultures is that they be limited to patients with a reasonable likelihood of being positive. If low-risk patients routinely have blood cultures, it is possible that the frequency of false positives may exceed the true positives, and lead to inaccurate and unnecessary therapy. One study of a large Medicare database found that predictors of bacteremia, among admitted patients, were: absence of prior antibiotics, comorbid liver disease, systolic blood pressure <90 mmHg, fever <35 or $>40°C$, pulse $>125\,\text{min}^{-1}$, blood urea nitrogen $>30\,\text{mg}\,\text{dl}^{-1}$, serum sodium <130, white blood cell count <5000 or $>20\,000$. Based on these findings, blood cultures will have the greatest yield of true positive results in patients who have at least one of these risk factors above, or if none, when there is also no history of receiving antibiotics prior to admission.

Sputum culture should be limited to patients suspected of infection with a drug-resistant or unusual pathogen. The role of Gram's 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's 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. Investigators have shown the practical limitations of the test, because fewer than half of all patients can even produce a sputum sample, only about half of these are valid, and very few are diagnostic, and thus it is uncommon to choose an antibiotic directed to the diagnostic result. Even if Gram's stain findings are used to focus antibiotic therapy, this would not allow for empiric coverage of atypical pathogens which might be present with pneumococcus, as part of a mixed infection. In spite of these limitations, Gram's 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 *S. aureus* being suggested by the presence of clusters of Gram-positive cocci, especially during a time of epidemic influenza).

Routine serologic testing is not recommended. However, in patients with severe illness, the diagnosis of *Legionella* can be made by urinary antigen testing, which is the test that is most likely to be positive at the time of admission, but a test that is specific only for serogroup 1 infection. Commercially available tests for pneumococcal urinary antigen have been developed, but their role in the clinical management of CAP is still being defined. Bronchoscopy is not indicated as a routine diagnostic test, and should be restricted to immune-compromised patients, and to selected individuals with severe forms of CAP.

Therapy

The initial therapy for patients with CAP should be focused on the provision of antibiotics and supportive care. Antibiotics are given on a empiric basis, since it is virtually impossible to rely on clinical or laboratory data to provide an exact etiologic pathogen, at the time of initial diagnosis, and thus therapy must be focused on the pathogens most likely to be present for a given type of patient. Supportive care includes oxygen as needed, hydration, possibly chest physiotherapy, as well as bronchodilators and expectorants. For more severely ill patients, it may be necessary to support the blood pressure with pressors, use corticosteroids for possible relative adrenal insufficiency, and provide other therapies directed at signs of sepsis (such as drotrecogin alpha in selected

patients). There may also be benefit from the routine use of corticosteroids in severe pneumonia, for unclear reasons, because some studies have shown a survival benefit to this intervention.

Antibiotic Therapy

Initial empiric therapy 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. By using these factors, a set of likely pathogens can be predicted for each type of patient (Table 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 choosing empiric therapy of CAP, certain principles should be followed (Table 3). Empiric therapy for outpatients with no cardiopulmonary disease or modifying factors should be with a new oral macrolide (azithromycin or clarithromycin) or a tetracycline. Although erythromycin has been used for these patients, its value is limited by its lack of coverage of *H. influenzae*, and a higher frequency of intestinal complications (nausea, vomiting) than with the newer macrolides. Therapy with an antipneumococcal quinolone (gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin) is not necessary in these outpatients, because they are not at risk for organisms such as DRSP and enteric Gram-negatives. However, outpatients with cardiopulmonary disease and/or modifying factors, should not receive macrolide monotherapy, but should be treated with either a selected oral beta-lactam (Table 3) with a macrolide or with monotherapy using an oral antipneumococcal quinolone (gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin) alone. The ketolide telithromycin can also be used in this population as oral monotherapy for patients at risk for DRSP, but with no risk factors for aspiration or for enteric Gram-negatives.

For the non-ICU inpatient, therapy can be with an intravenous macrolide (azithromycin) alone, provided that the patient has no underlying cardiopulmonary disease, and no risk factors for infection with DRSP, enteric Gram-negatives, or anaerobes. Although very few patients of this type are admitted to the hospital, macrolide monotherapy has been documented to be effective in this population. The majority of inpatients will have cardiopulmonary disease and/or modifying factors, and they can be treated with either a selected intravenous beta-lactam (Table 3) combined with a macrolide, or they can receive an intravenous antipneumococcal quinolone (gatifloxacin, levofloxacin, moxifloxacin) alone. From the available data, it appears that either regimen is therapeutically equivalent, and although not proven, it may be useful to use these two types of regimens interchangeably, striving for 'antibiotic heterogeneity', selecting an agent in a different class from what the patient received in the past 3–6 months. Although oral quinolones may be as effective as intravenous quinolones for admitted patients

Table 3 Principles of antibiotic therapy

Administer initial antibiotic therapy within 4 h of arrival to the hospital

Treat all patients for pneumococcus and for the possibility of atypical pathogen coinfection: 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, a ketolide (if no risk factors for enteric Gram-negatives), or the combination of a selected beta-lactam with a macrolide or ketolide or tetracycline

Limit macrolide monotherapy to outpatients or inpatients with no risk factors for DRSP, enteric Gram-negatives, or aspiration

Limit ketolide monotherapy to outpatients with risk factors for DRSP, but no risk factors for enteric Gram-negatives

Provide initial therapy for hospitalized patients with an intravenous agent, or if oral only, use a quinolone

For patients at risk for DRSP, acceptable oral beta-lactams are: cefpodoxime, cefuroxime, high-dose ampicillin ($3 \, \text{g day}^{-1}$) or amoxicillin/clavulanate (up to $4 \, \text{g day}^{-1}$)

For inpatients at risk for DRSP, the selected acceptable intravenous beta-lactams include: ceftriaxone, cefotaxime, ertapenem, ampicillin/sulbactam

Limit antipseudomonal therapy to patients with risk factors: Antipseudomonal agents include: beta-lactams such as cefepime, imipenem, meropenem, piperacillin/tazobactam; quinolones such as ciprofloxacin or high-dose levofloxacin ($750 \, \text{mg day}^{-1}$); and aminoglycosides such as amikacin, gentamicin, or tobramycin; aztreonam is a monobactam that is also active, but cannot be used alone

The new antipneumococcal quinolones, in order of decreasing antipneumococcal activity are: gemifloxacin (oral only), moxifloxacin (oral and intravenous), gatifloxacin (oral and intravenous), levofloxacin (oral and intravenous)

Never use monotherapy for patients with severe CAP. If no pseudomonal risk factors use a selected beta-lactam (above) plus a macrolide or antipneumococcal quinolone. For those with pseudomonal risk factors, use an antipseudomonal beta-lactam (above) plus either ciprofloxacin/high-dose levofloxacin or the combination of an aminoglycoside with either a macrolide or antipneumococcal quinolone (above)

Vancomyin and linezolid should be used rarely and only in those with severe CAP and either meningitis (vancomycin) or severe necrotizing pneumonia after influenza (either agent)

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. Selected inpatients with mild to moderate disease can initially be treated with the combination of an intravenous beta-lactam and an oral macrolide, switching to exclusively oral therapy once the patient shows a good clinical response.

In the ICU population, all individuals should be treated for DRSP and atypical pathogens, but only those with appropriate risk factors (above) should have coverage for *P. aeruginosa*. Since the efficacy, dosing, and safety of quinolone monotherapy has not been established for ICU-admitted CAP patients, the therapy for such patients, in the absence of pseudomonal risk factors, should be with a selected intravenous beta-lactam, combined with either an intravenous macrolide or an intravenous quinolone. For patients with pseudomonal risk factors, therapy can be with a two-drug regimen, using an anti-pseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus ciprofloxacin or high-dose levofloxacin, or alternatively, with a three-drug regimen, using an anti-pseudomonal beta-lactam plus an aminoglycoside plus either an intravenous non-pseudomonal quinolone or macrolide.

The antipneumococcal quinolones are being widely used in both inpatients and outpatients as monotherapy because as a single drug, given once daily, it is possible to cover pneumococcus (including DRSP), Gram-negatives, and atypical pathogens. Quinolones penetrate well into respiratory secretions, and are highly bioavailable, achieving the same serum levels with oral or intravenous therapy, thereby allowing moderately ill outpatients to be managed effectively with oral antibiotics. 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, gatifloxacin, and levofloxacin. Some data suggest a lower likelihood of both clinical failures and the induction of pneumoccal resistance to quinolones, if the more active agents are used in place of the less active agents.

In addition to the general approach to therapy outlined above, there are several other therapeutic issues in the management of CAP, which are highlighted in Table 3. These include the need for timely administration of initial antibiotic therapy, the limited use of therapy directed at methicillin-resistant *S. aureus*, the need for routine atypical pathogen coverage for all patients, and the emphasis on using highly active agents in all patients with risk factors

for infection with DRSP. The reason for this last recommendation is because if a patient is at risk for infection with DRSP, use of a highly active agent is not only likely to minimize the risk of treatment failure, but may also rapidly and reliably eradicate pneumococcal organisms that have low levels of resistance, so that there is less selection pressure for emergence of organisms with high level of resistance.

Response to Therapy

The majority of outpatients and inpatients will respond rapidly to the empiric therapy regimens suggested above, with clinical response usually occurring within 24–72 h. Clinical response for inpatients is defined as improvement in symptoms of cough, sputum production, and dyspnea, along with ability to take medications by mouth, and an afebrile status for at least two occasions 8 h apart. 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.

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, *C. 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 cigarette smoking should be stopped in all at-risk patients. Even for the patient who is recovering from CAP, immunization while in the hospital is appropriate to prevent future episodes of infection, and the evaluation of all patients for vaccination need and the provision of information about

smoking cessarion are now performance standards used to evaluate the hospital care of CAP patients.

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 defined. In immunocompetent patients over the age of 65, effectiveness has been documented to be 75%. The vaccine efficacy has ranged from 65% to 84% in patients with diabetes mellitus, coronary artery disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia. Its effectiveness has not been proven in immune-deficient 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 indicated in a person who is aged over 65 years who initially received the vaccine >6 years earlier and was less than 65 years old on first vaccination. If the initial vaccination was given at age 65 or older, repeat is only indicated (after 6 years), if the patient has anatomic or functional asplenia, or has one of the immune compromising conditions listed above.

The available pneumococcal vaccine is widely underutilized, and the 23-valent pneumococcal vaccine carries the pneumococcal serotypes causing the majority of clinical infection seen in the US. A protein-conjugated pneumococcal vaccine has been licensed and it appears more immunogenic than the older vaccine, but it contains only seven serotypes, and is recommended for healthy children, and has not yet been shown to be effective in adults for preventing both pneumococcal bacteremia and hospitalization for pneumonia. Hospital-based immunization for most admitted patients could be highly effective, since over 60% of all patients with CAP have been admitted to the hospital, for some indication, in the preceding 4 years, and hospitalization could be defined as an appropriate time for vaccination.

Influenza vaccination The current vaccine includes three strains: two influenza A strains (H3N2 and H1N1) and one influenza B strain. Vaccination is recommended for all patients aged over 65, and to those with chronic medical illness (including nursing home residents), and to those who provide healthcare to patients at risk for complicated influenza. It is given yearly, usually between September and mid November (in the northern hemisphere). When the vaccine matches the circulating strain of influenza, it can prevent illness in 70–90% of healthy persons aged over 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.

See also: **Endotoxins**. **Leukocytes**: Neutrophils. **Pleural Effusions**: Pleural Fluid Analysis, Thoracentesis, Biopsy, and Chest Tube; Parapneumonic Effusion and Empyema. **Pneumonia**: Overview and Epidemiology; Parasitic. **Stem Cells**. **Systemic Disease**: Sickle Cell Disease. **Ventilation, Mechanical**: Ventilator-Associated Pneumonia.

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Fungal (Including Pathogens)

R Boyton and D M Altmann, Imperial College London, London, UK

Abstract

Fungal infection generally originates from an exogenous, environmental source acquired by inhalation, ingestion, or trauma. Fungi are rarely associated with significant disease in the normal host, although many more cause serious disease in the immunocompromised host. Opportunistic fungal infections have become increasingly common, especially in AIDS patients, and constitute a major cause of morbidity and mortality in this group. Pathogenicity depends on the interplay between components of the host immune system and specific features of the fungal strain. Considerable efforts are underway to conduct genetic characterization of fungal virulence and host susceptibility factors in disease. Genome projects have been undertaken for a number of the key fungal pathogens. Here we consider the etiology, pathology, clinical features, management, and molecular mycology of Blastomycosis, Coccidioidomycocis, Histoplasmosis, Paracoccidioidomycosis, Aspergillosis, Candidosis, Cryptococcosis, and Mucormycosis.

Introduction

Fungi are a diverse group of eukaryotic organisms that have cell walls and no chlorophyll. They exist in nature as parasites or saprobes, dependent on living or dead organic matter for nutrition. About 250 000 species of fungi have been described, but less than 200 have been associated with human disease. Fungal infection usually originates from an exogenous, environmental source acquired by inhalation, ingestion, or trauma. Very few fungi cause significant disease in the normal host, but many more can cause disease in the immunocompromised host. Thus,

pathogenicity can be considered to depend on the interplay between aspects of the host immune system and specific features of the fungal strain. Considerable efforts are underway to conduct genetic characterization of fungal virulence and host susceptibility factors in disease. Genome projects have been undertaken for a number of key pathogens (see 'Relevant websites').

Systemic mycoses often start in the lung, but may spread to other organs. They are usually acquired by inhaling spores of organisms growing as saprobes in the soil or decomposing organic material, or as plant pathogens. The organisms that cause systemic fungal infection in humans can be divided into two groups, true pathogens and opportunists. True pathogens, able to invade and grow in tissues of a normal host, include *Histoplasma capsulatum*, *Coccidoides immitis*, *Blastomyces dermatidis* and *Paracoccidioides braziliensis* (Table 1). In general, infections with true pathogenic fungi are asymptomatic or mild, of short duration, occur in regions endemic for the fungus, and follow inhalation of spores from the environment. Individuals either recover from infection with protective immunity to re-infection or sometimes develop chronic granulomatous disease. In the immunocompromised host, however, true pathogenic fungi may cause significant, relapsing, life-threatening disease that is difficult to treat. Opportunist fungi, such as *Aspergillus fumigatus*, are less virulent and less well-adapted organisms that are only able to invade the tissues of a debilitated or immunocompromised host. Resolution of infection does not confer protection and re-infection or reactivation may occur. Many of these organisms are ubiquitous saprobes found in the soil, decomposing organic

Table 1 Pathogens that cause fungal pneumonia according to the immunological status of the host

Normal host
Blastomyces dermatidis
Coccidoides immitis
Histoplasma capsulatum
Paracoccidioides braziliensis
Normal and immunocompromised host
Aspergillus spp.
Cryptococcus neoformans
Geotrichum spp.
Penicillium marneffei
Sporothrix schenckii
Immunocompromised host
Candida spp.
Fusarium spp.
Hansenula spp.
Mucormycosis
Penicillium spp.
Pneumocystis jiroveci
Pseudoallescheria boydii