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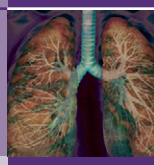


Chapter 28
Pneumonia in the Non-HIV-Infected Immunocompromised Patient

Jennifer Quint • Jeremy S. Brown

OVERVIEW

The respiratory tract is continually exposed to a range of microorganisms that normal immune responses generally prevent from causing infection. Hence, it is not surprising that patients with significantly impaired immunity frequently develop lung infections. Immunodeficient patients also frequently have several other risk factors that contribute to an increased risk for development of pneumonia, including low-level microaspiration of oropharyngeal contents, mucosal damage caused by cytotoxic therapy, underlying lung damage, and poor nutrition. As a consequence, lung infections are a common and frequently serious complication in patients with significant impairment of the immune system. Pulmonary infiltrates occur in 25% of patients with neutropenia developing after chemotherapy, and up to 5% of patients undergoing hematopoietic stem cell transplantation (HSCT) will die as a result of pneumonia. The range of potential pathogens causing lung infections in immunocompromised patients is much broader than for the usual pathogens causing community-acquired pneumonia and includes organisms such as *Aspergillus fumigatus* and human cytomegalovirus (CMV); the diagnosis of infections due to these microbes can be difficult, and the required therapies frequently are toxic. The large number of potential pathogens and the background disease together make management of lung infection in immunocompromised patients considerably more complex, and the use of invasive diagnostic tests such as bronchoscopy frequently is necessary. This chapter focuses on the common causative pathogens and the clinical approach to pulmonary infections in patients who have been severely immunocompromised by chemotherapy, organ transplantation, or hematologic disease (**Box 28-1**) but not human immunodeficiency virus (HIV) infection (discussed in Chapter 29). Pneumonia in patients with milder degrees of immunosuppression due to myeloma, low-dose cytotoxic therapy, or disease-modifying agents administered for rheumatologic conditions generally should be managed as community- or hospital-acquired pneumonia, but with recognition that the disease could be due to various opportunistic pathogens, as discussed in this chapter.

GENERAL PRINCIPLES OF THE CLINICAL APPROACH

Potential pathogens causing lung infection in the immunocompromised patient are listed in **Table 28-1**. Empirical therapy that is active against all these possible pathogens is not feasible, especially given the potential toxicity of some treatments. Hence, the challenge in managing these patients is to (1) reduce the scope of the differential diagnosis to include the most likely problems and thus allow relatively targeted empirical therapy and (2) identify when and which type of invasive diagnostic test(s) should be used to provide the most useful data. The likely potential causative pathogens can be defined by ascertaining the following:

- The clinical and radiologic presentation
- The speed of onset of the infection
- The type, duration, and severity of the patient's immune defect
- Positive results on microbiologic studies
- Associated factors of importance, including any recent local infective epidemics and the patient's prophylaxis regimen, ethnic background, and travel history

The exact type of immune defect is determined by a combination of the disease and the treatment received and, fortunately, can generally be predicted (**Table 28-2**). The three main categories of immune defect are absolute or functional neutropenia, defects in cell-mediated immunity, and deficiencies in antibody responses (a clinically less severely affected category). Each is associated with a particular range of pathogens (see Table 28-2). Patients with neutropenia are mainly at risk for infection with extracellular pathogens such as pyogenic bacteria and filamentous fungi. Defects in cell-mediated immunity tend to predispose affected patients to development of infections with intracellular pathogens such as viruses and mycobacteria, as well as some unusual extracellular infections such as *Pneumocystis* pneumonia (PCP). Deficiencies in antibody responses result in a high incidence of infections due to encapsulated bacteria such as *Streptococcus pneumoniae* and to herpesviruses. Individual patients may have a combination of these immune defects; for example, lymphoma can cause impairment of cell-mediated immunity that can be combined with neutropenia if the patient receives chemotherapy.

HSCT, especially for allograft recipients, is particularly associated with lung complications, including infections with a daunting range of pathogens. The immune defects associated with HSCT depend on the conditioning regimen and type of graft, and evolve with time. In phase I, the preengraftment phase (15 to 45 days after transplantation), prolonged neutropenia and breaks in the mucocutaneous barrier increase the risk of bacterial and fungal infections. Herpes simplex virus reactivation also can occur during this phase. In phase II, the

Box 28-1 Diseases and Conditions Associated With Severe Immunocompromise*

Lymphoma/leukemia
Hematopoietic stem cell transplantation (HSCT)
Aplastic anemia
Solid organ transplantation
Other causes of neutropenia (fewer than 1500 cells/mL)
Inherited disorders of immune function (e.g., chronic granulomatous disease, recent chemotherapy)
High-dose corticosteroid treatment (greater than 30 mg prednisolone for 21 days or longer)
Treatment with immunosuppressive therapy (e.g., tacrolimus, cyclosporine)
Treatment with cytotoxic therapy (e.g., cyclophosphamide, mycophenolate)

*As defined in this chapter.

immediate post-engraftment phase at around 30 to 100 days after transplantation, infections relate primarily to impaired cell-mediated immunity and include those due to herpesviruses (particularly CMV) and PCP unless the patient is given prophylaxis. During phase III, the late phase (beyond 100 days), common pathogens again include herpesviruses, but there is also a marked increased incidence of infection with encapsulated bacteria such as *S. pneumoniae,* perhaps relating to impaired humoral immunity. Graft-versus-host disease also is associated with ongoing susceptibility to *Aspergillus* during phases II and III. For recipients of nonmyeloablative hematopoietic stem cell transplants, substantial differences may be observed during phase I, but susceptibility to infections during phases II and III is about the same. The risk of disease from community-acquired respiratory viruses is elevated in all three phases.

By combining the clinical pattern of presentation with knowledge of the patient's immune defect, a differential diagnosis of likely pathogens can be suggested. For example, infections developing rapidly over 1 to 3 days with a marked rise in serum inflammatory markers such as C-reactive protein (CRP), pronounced fever, and focal radiologic changes are very likely to be due to infection with pyogenic bacteria. In a patient with a defect in cell-mediated immunity, however, widespread ground glass infiltrations in both lungs developing over several days could represent CMV pneumonitis or PCP. In general, the more severe and prolonged the immune defect, the greater the range of possible causative pathogens and the less typical the clinical presentation for a particular pathogen, prompting the need for early invasive investigation if the initial therapy is failing to effect improvement. Furthermore the character of the disease can be dictated by the severity of the immune defect. For example, infections due to filamentous fungi such as *Aspergillus* progress faster with increasing severity of neutropenia, but may regress and become more focal when the neutrophil count recovers. Table 28-3 shows the common conditions that should be considered for different presentations of lung complications in immunocompromised patients. Many patients will be found to have dual pathologic processes, either involving two separate pathogens or with simultaneous noninfective (fluid overload being the most common) and infective problems, which will be responsible for separate elements of the clinical picture.

Previous results of microbiologic tests need to be reviewed, because these may provide a strong indication of the cause of the present lung infection. For instance, infected indwelling vascular and urinary catheters can form foci of infection that can metastasize to the lungs, and previous *Aspergillus* infection may recur during new episodes of immunosuppression. Knowledge of previous and present CMV status identifies patients at risk for development of CMV pneumonitis, and positive

Table 28-1 Range of Pathogens Commonly Associated With Pneumonia in the Non-HIV-Infected Immunocompromised Patient

Pathogen	Cases (%)
Gram-Negative Pyogenic Bacteria	
Escherichia coli	6
Proteus, *Enterobacter*, *Serratia*, and *Citrobacter* spp.	2
Haemophilus influenzae	<1
Klebsiella pneumoniae	<1
Pseudomonas aeruginosa	8
Acinetobacter spp.	2
Stenotrophomonas maltophilia	<1
Gram-Positive Pyogenic Bacteria	
Streptococcus pneumoniae	2
Viridans streptococci	<1
Staphylococcus aureus	12
Enterococcus spp.	4
Other Bacteria	
Anaerobes	<1
Legionella pneumophila	2
Chlamydia spp.	2
Mycoplasma pneumoniae	<1
Mycobacterium tuberculosis	4
Nontuberculous mycobacteria	<1
Nocardia spp.	2
Fungi	
Pneumocystis jirovecii	3
Candida spp.	9
Aspergillus spp.	24
Rarer molds (e.g., *Mucor*, *Penicillium*, *Fusarium*)	2
Endemic fungi (e.g., *Histoplasma*, *Coccidioides*)	<1
Protozoa	
Toxoplasma gondii	<1
Helminths	
Strongyloides stercoralis	<1
Viruses	
Cytomegalovirus	6
Herpes simplex virus, varicella-zoster virus	2
Respiratory viruses (respiratory syncytial virus, adenovirus, influenza virus, parainfluenza virus, human metapneumovirus)	8

Modified from Rañó A, Agustí C, Jimenez P, et al: Pulmonary infiltrates in non-HIV immunocompromised patients: a diagnostic approach using non-invasive and bronchoscopic procedures, *Thorax* 56:379-387, 2001.

Table 28-2 Type of Immune Defect According to Disease/Treatment and Range of Pathogens Commonly Associated With Infections in Patients with Such Immune Defects

Immune Defect	Cause	Associated Pathogens
Neutropenia/functional neutrophil defects	Chemotherapy Early HSCT* Acute leukemia Chronic myelocytic leukemia Aplastic anemia Marrow infiltrations Azathioprine/mycophenolate† High-dose corticosteroids† Chronic granulomatous disease† Other inherited phagocyte defects†	Pyogenic bacteria and anaerobes Filamentous fungi (*Aspergillus*, rarer molds) *Candida* spp.
Cell-mediated immunity	HSCT Chronic lymphocytic leukemia Lymphoma Tacrolimus/sirolimus for organ transplant recipients Cyclosporine for organ transplant recipients Azathioprine/mycophenolate High-dose corticosteroids Graft-versus-host disease Inherited disorders of lymphocyte function	*Pneumocystis jirovecii* Herpesviruses Respiratory viruses *L. pneumophila* Mycobacteria and *Nocardia* Agents of endemic mycoses *T. gondii* *S. stercoralis*
Antibody deficiency	HSCT Chronic lymphocytic leukemia Lymphoma Myeloma	Encapsulated bacteria (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*), herpesviruses

*Allografts up to 1 month, autografts usually less than 14 days.
†Patients usually have a normal neutrophil count but have defects in their function and/or a poor response to infection.
HSCT, hematopoietic stem cell transplantation.

sputum surveillance cultures for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* may indicate likely causes of a new pneumonia. In addition, positive samples from other patients also may be helpful, because local epidemics of respiratory virus infections are not uncommon in hospitals, and more rarely, clusters of nosocomial *Aspergillus*, *Nocardia* (both of which may be associated with ongoing construction on the hospital site), or *Legionella* infection can occur.

Other important factors that need to be taken into account include the patient's present antibiotic prophylaxis regimen, travel history, and ethnic background. A patient compliant with co-trimoxazole prophylaxis will rarely develop PCP, and fluconazole prophylaxis predisposes to non-albicans *Candida* infection. Patients with certain ethnic backgrounds or a pertinent travel history are more at risk of TB, endemic mycoses such as histoplasmosis, or parasitic diseases such as disseminated strongyloidiasis. Finally, the patient's background lung structure and function should be considered, because existing structural abnormalities may make certain pathogens more likely. For example, bronchiectasis could predispose affected persons to pneumonia caused by *P. aeruginosa* (**Figure 28-1**), and preexisting lung cavities to *Aspergillus* infection.

CLINICAL ASSESSMENT AND DIAGNOSTIC PROTOCOLS

The combination of new respiratory symptoms and/or new radiologic findings with pyrexia suggests lung infection, although incidental radiologic or microbiology results may also identify active lung infection in an asymptomatic patient. The patient should undergo careful clinical assessment, including a review of previous laboratory and radiologic findings; the high mortality associated with lung infections in immunocompromised patients requires that this is initiated rapidly. The level of oxygenation will characterize the immediate risk to the patient and can also suggest likely pathogens as severe hypoxia is more likely with a bacterial lobar pneumonia, extensive PCP or viral infections. Chest radiographs are an essential first line investigation and are useful for monitoring progress. However, with the exception of lobar consolidation chest radiographs may not be sufficiently sensitive to make an accurate assessment of the pattern of lung shadowing. Ultimately a computed tomography (CT) scan of the thorax often is required. CT scans are approximately 20% more sensitive than chest radiographs at identifying lung involvement and also define whether new changes on a chest radiograph represent consolidation, nodules, ground glass infiltrates, or "tree-in-bud" changes.

All patients with suspected new lung infection require blood and sputum cultures, as well as routine blood tests, and in many cases nasopharyngeal aspirate studies for identification of viruses, assessment of CMV status, and serum testing for fungal antigens (galactomannan or β-D-glucan). An important question for the respiratory physician is when to utilize more invasive investigations, either bronchoscopy with bronchoalveolar lavage (BAL) and possibly transbronchial biopsy, percutaneous radiologically guided biopsy, or, on occasion, surgical biopsy, usually video-assisted thoracoscopic surgery (VATS). Which test should be used and when will depend to a large extent on the type of radiologic presentation—consolidation, diffuse ground glass infiltrates, tree-in-bud changes, and nodules—in accordance with the algorithms for each provided in Figures 28-2, 28-4, 28-6, and 28-7, respectively. These suggested protocols balance the likelihood and necessity of a positive yield against the clinical probability that a particular disease will be identified with the potential complications of the investigations. These protocols are for general guidance; atypical presentations and dual pathology are not uncommon, and an individual patient often will require a modified approach. Immunocompromised patients are also at high risk for development of a range of noninfective causes of lung disease, including pulmonary edema, idiopathic pneumonia syndrome (IPS), and diffuse alveolar hemorrhage (see Chapter 59). These conditions should always be considered in the differential diagnosis for new lung disease. The protocols are discussed in detail next.

INVESTIGATION OF CONSOLIDATION

Rapidly developing focal consolidation usually is due to bacterial pneumonia and initially can be treated empirically with broad-spectrum antibiotics (**Figure 28-2**). The most likely reason for a lack of improvement in the patient's condition within 48 to 96 hours is infection with bacteria resistant to

Table 28-3 Differential Diagnosis for Computed Tomography (CT) Pattern and Rate of Development of Clinical Problem

Predominant CT Pattern	Rate of Progression		
	Acute (days)	**Subacute (days to weeks)**	**Chronic (weeks)**
Consolidation/focal ground glass infiltration	Bacterial pneumonia Aspiration Diffuse alveolar hemorrhage Acute respiratory distress syndrome (ARDS)*	Cryptogenic organizing pneumonia Aspiration Mycobacteria† *Nocardia*† Invasive filamentous fungi†	Cryptogenic organizing pneumonia Lymphoma Mycobacteria† *Nocardia*†
Diffuse ground glass infiltration	CMV pneumonia Viral pneumonia Diffuse alveolar hemorrhage ARDS*	CMV pneumonia PCP Idiopathic pneumonia syndrome (IPS) Drug reactions	Drug reaction
Nodules	Metastatic infection Invasive filamentous fungi	Metastatic infection Invasive filamentous fungi *Nocardia* Mycobacteria	Lymphoma Lymphoproliferative disease *Nocardia* Mycobacteria
Multiple nodules (>10)	Metastatic infection	Metastatic infection Mycobacteria	Lymphoma Lymphoproliferative disease Mycobacteria
Bronchiolitis/"tree-in-bud" changes	Viral bronchiolitis *Chlamydia pneumoniae* *Mycoplasma pneumoniae* Bacterial exacerbation bronchiectasis	Viral bronchiolitis *C. pneumoniae* *M. pneumoniae* Nontuberculous mycobacteria *Aspergillus* tracheobronchitis† Bacterial exacerbation bronchiectasis	Bronchiectasis Nontuberculous mycobacteria

*Extensive, patchy, mainly posterior.
†Usually focal patches.

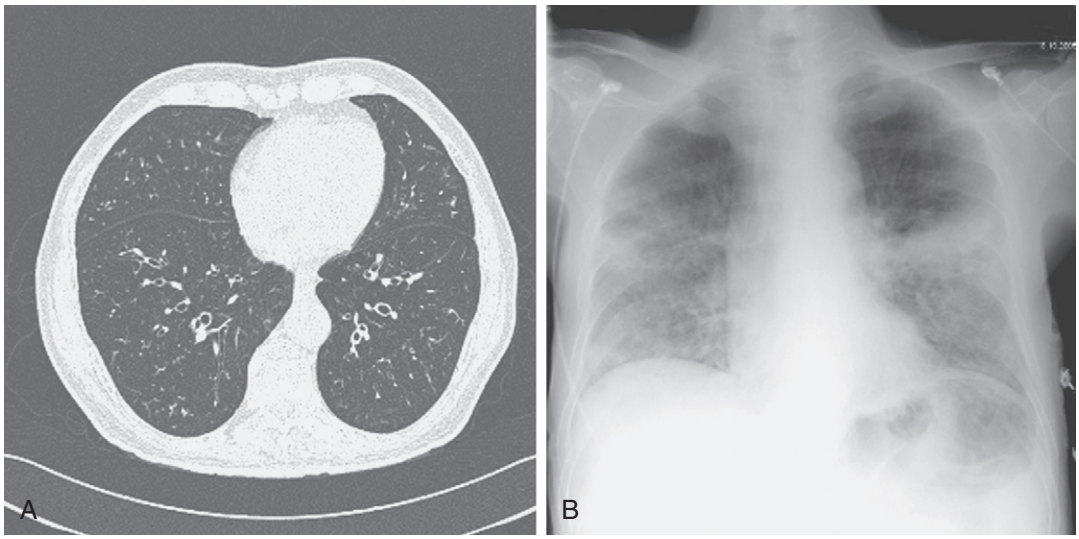


Figure 28-1 A, Computed tomography (CT) scan of thorax shows dilated, thick-walled bronchi, characteristic of bronchiectasis. The patient, who had a long history of chronic lymphatic leukemia and immunoglobulin deficiency, produced purulent sputum daily, culture of which grew *Pseudomonas aeruginosa.* **B,** A chest radiograph obtained in the same patient, whose clinical presentation included high fever, productive cough, and marked hypoxia, shows consolidation (most marked in the left middle zone) due to *P. aeruginosa* pneumonia.

first-line antibiotics. At this point, treatment with second-line antibiotics effective against likely resistant organisms should be started. Consideration also should be given to starting antibiotics that are effective against MRSA and anaerobic pathogens if this has not been done already. In patients at high risk for invasive fungal infection, especially those with CT evidence of associated nodular disease or patchy or infarct-shaped consolidation, failure of first-line therapy warrants testing for fungal antigens (galactomannan or β-D-glucan) and either fiberoptic bronchoscopy (FOB) with BAL or percutaneous CT-guided biopsy (mainly for evaluation of dense consolidation adjacent to the pleura). These investigations also will be necessary in patients whose pneumonia fails to respond to second-line antibiotic therapy or those with subacute or chronic consolidation in whom sputum microbiologic or cytologic testing is nondiagnostic. With progressive disease and lack of a definitive diagnosis after the foregoing tests, surgical biopsy should be seriously considered.

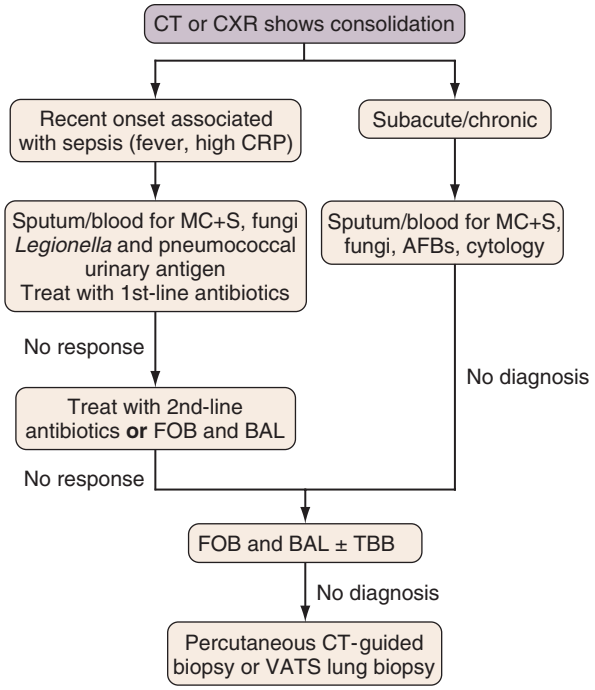


Figure 28-2 Investigation of consolidation in the immunocompromised patient. *AFBs*, acid-fast bacilli; *BAL*, bronchoalveolar lavage; *CRP*, C-reactive protein; *CT*, computed tomography; *FOB*, fiberoptic bronchoscopy; *MC+S*, microbial culture and sensitivity [testing]; *TBB*, transbronchial biopsy; *VATS*, video-assisted thoracoscopic surgery.

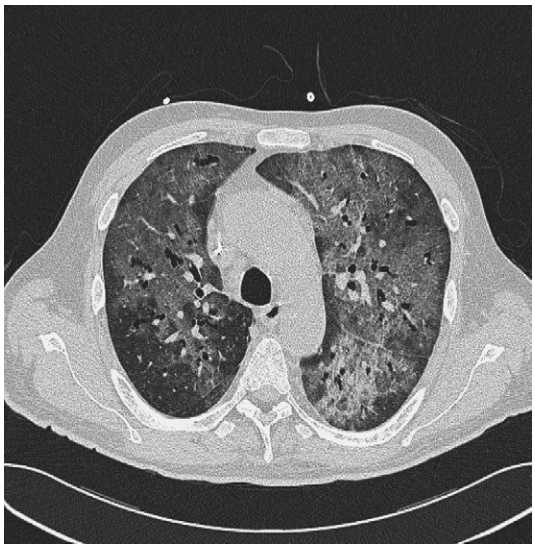
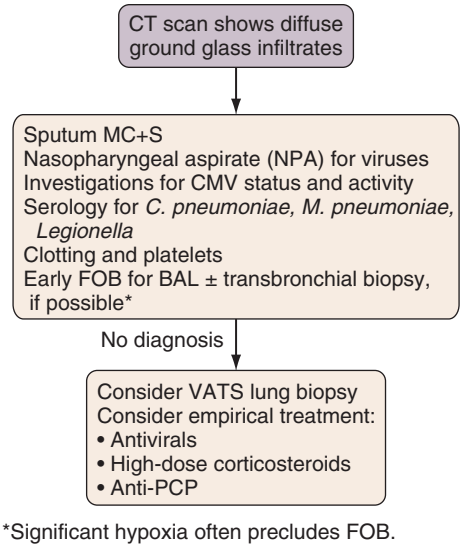


Figure 28-3 Computed tomography (CT) scan of thorax showing widespread bilateral ground glass infiltration in a hematopoietic stem cell transplant recipient. The differential diagnosis for this imaging appearance is broad in scope, including cytomegalovirus pneumonia, *Pneumocystis* pneumonia, drug reactions, and idiopathic pneumonia syndrome, and early invasive investigation typically is required even though with such widespread lung disease the patient is likely to have significant hypoxia.

INVESTIGATION OF DIFFUSE GROUND GLASS INFILTRATION

The differential diagnosis for ground glass infiltrates and centrilobular nodules (Figures 28-3 and 28-4) is wide in scope and includes CMV infection, viral pneumonias, PCP, extensive bacterial infection, and noninfective causes such as acute



*Significant hypoxia often precludes FOB.

Figure 28-4 Investigation of diffuse ground glass infiltrates in the immunocompromised patient. *BAL*, bronchoalveolar lavage; *CMV*, cytomegalovirus; *FOB*, fiberoptic bronchoscopy; *MC+S*, microbial culture and sensitivity [testing]; *PCP*, *Pneumocystis* pneumonia; *VATS*, video-assisted thoracoscopic surgery.

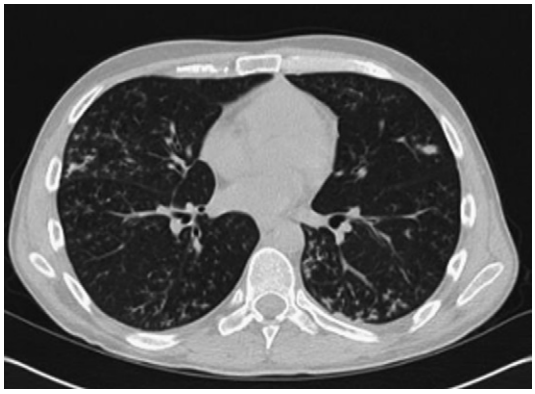


Figure 28-5 Computed tomography (CT) scan showing widespread bilateral "tree-in-bud" changes in a hematopoietic stem cell transplant recipient. This appearance is caused by marked small airway inflammation secondary to respiratory virus infection, bacterial bronchitis (e.g., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Pseudomonas aeruginosa*, or *Haemophilus influenzae* infection), and, when more focal, *Aspergillus* tracheobronchitis or mycobacterial infection.

respiratory distress syndrome (ARDS), drug toxicity, and IPS associated with HSCT (see Chapter 77). As a consequence, unless nasopharyngeal aspirate studies identify a respiratory viral infection, early FOB with BAL and, if possible, transbronchial biopsy should be attempted. Often, however, these patients are markedly hypoxic, increasing the risk associated with the procedure. Negative results on FOB do not exclude infective causes, and a decision then needs to be taken about empirical treatment versus VATS lung biopsy. CT-guided biopsy for investigation of diffuse lung disease carries a high risk of complications coupled with low diagnostic yield and therefore is not appropriate in this setting.

INVESTIGATION OF TREE-IN-BUD CHANGES

Tree-in-bud changes (Figures 28-5 and 28-6) suggest small airway pathology, which in immunocompromised patients is

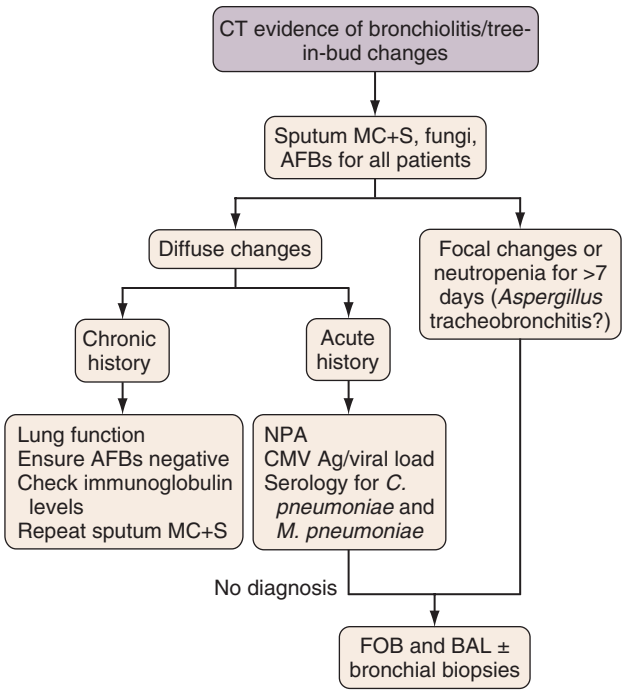
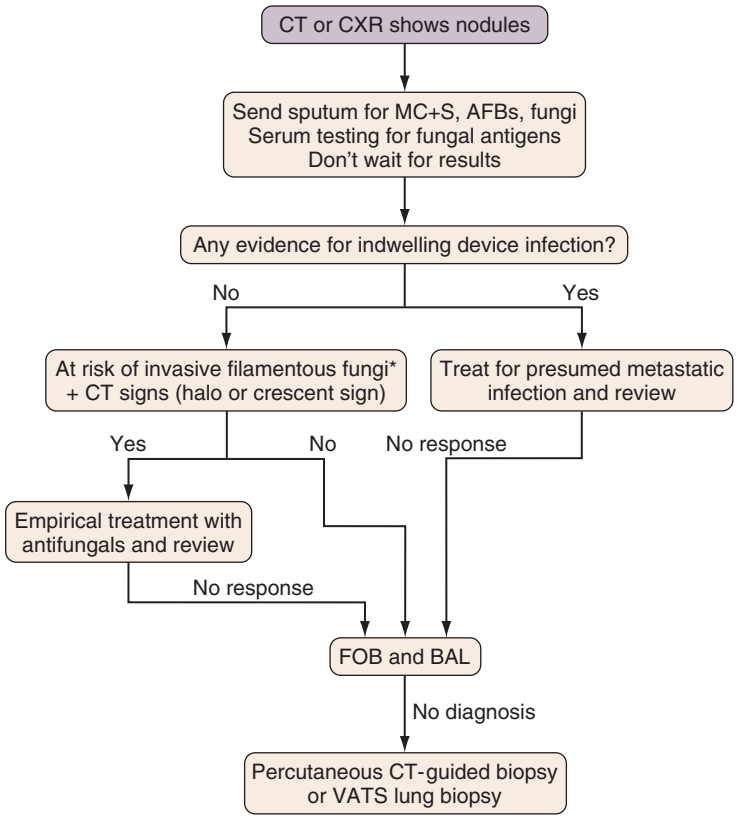


Figure 28-6 Investigation of "tree-in-bud" pattern associated with bronchiolitis in the immunocompromised patient. *AFBs*, acid-fast bacilli; *BAL*, bronchoalveolar lavage; *CMV*, cytomegalovirus; *CT*, computed tomography; *FOB*, fiberoptic bronchoscopy; *MC+S*, microbial culture and sensitivity [testing].

likely to be caused by respiratory virus infection, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, or, especially if the changes are focal and associated with nodular changes, *Aspergillus* tracheobronchitis. Subacute or chronic changes also could reflect bacterial infection in bronchiectasis or nontuberculous mycobacteria infection. If results of nasopharyngeal aspirate studies are negative, then early FOB for BAL and bronchial biopsy of macroscopically inflamed bronchial mucosa should be performed. *Aspergillus* tracheobronchitis usually is obvious at FOB and is readily confirmed by culture and cytologic examination of bronchial washings and by bronchial biopsy. Infections due to respiratory viruses, *C. pneumoniae*, and *M. pneumoniae* often are difficult to diagnose but usually are either self-limiting illnesses or readily controlled with macrolide therapy.

INVESTIGATION OF PULMONARY NODULES

Considerations in the differential diagnosis for pulmonary nodules include infection with *Aspergillus* (or other invasive filamentous fungi), *Nocardia*, or mycobacteria (**Figure 28-7**). *Aspergillus* and *Nocardia* tend to cause a small number of nodules, whereas mycobacteria also can cause large numbers of small nodules. In addition, blood-borne spread of bacteria or *Candida* from infected indwelling devices can cause a variable number (often numerous) of pulmonary nodules. Serum testing for fungal antigens (galactomannan or β-D-glucan) should be performed. Nodules caused by pyogenic bacterial and viral pneumonia tend to be associated with other radiographic changes findings such as ground glass infiltrates or consolidation. The



*Neutropenia >7 days, high-dose steroids, GVHD, previous episode invasive aspergillosis. Even with halo or crescent signs present on the CT scan there should be a low threshold for performing BAL to identify the fungal species.

Figure 28-7 Investigation of pulmonary nodules in the immunocompromised patient. *AFBs*, acid-fast bacilli; *BAL*, bronchoalveolar lavage; *CMV*, cytomegalovirus; *CT*, computed tomography; *FOB*, fiberoptic bronchoscopy; *GVHD*, graft-versus-host disease; *MC+S*, microbial culture and sensitivity [testing]; *VATS*, video-assisted thoracoscopic surgery.

other major causes of nodules are underlying malignant disease and lymphoproliferative disorders secondary to prolonged immunosuppression. In the absence of CT signs suggestive of invasive filamentous fungal infection (the halo and crescent signs), nodules in patients with line infections or a positive blood culture may be treated empirically as for metastatic infection. For a majority of other patients with lung nodules, FOB with BAL is necessary, although for patients at high risk for infection with invasive filamentous fungi, if CT changes suggestive of *Aspergillus* infection are present, then empirical antifungal therapy is a reasonable alternative strategy, especially if the result of fungal antigen testing is positive. If FOB findings are unhelpful, the patient should progress to percutaneous CT-guided or VATS lung biopsy, because infections due to fungi, *Nocardia*, or mycobacteria are accompanied by specific histopathologic changes, and biopsy frequently is diagnostic.

BRONCHOSCOPY

Although many immunocompromised patients with pneumonia are hypoxic and have low platelet counts and/or abnormal clotting, FOB generally is safe and has a diagnostic yield of 30 to 50%. Exclusion of active infection is necessary to make a diagnosis of IPS after HSCT, so even a negative result can be useful. In our own experience, peroral FOB can be performed without significant bleeding in patients with a platelet count of 10,000/mL. BAL should be performed in patients with marked hypoxia or severe tachypnea only after careful consideration of risk versus benefit, because the procedure commonly reduces PaO_2 by 20 mm Hg and may precipitate the need for intubation and mechanical ventilation. Transbronchial biopsy improves the diagnostic yield of FOB by perhaps 5% to 10% but often is not possible, because the patient needs to be able to tolerate the potential complication of a pneumothorax and have a platelet count above 50,000/mL.

SPECIFIC CLINICAL ENTITIES

BACTERIAL PNEUMONIA

General Considerations

Pneumonia due to bacterial pathogens is the most common lung infection in the immunocompromised patient, causing about 40% to 50% of infective episodes. The main risk factor is neutropenia, but cell-mediated immune defects and functional defects in phagocyte responses due to cytotoxic or immunosuppressive therapy also will markedly increase the risk for development of pneumonia. Antibody deficiencies associated with lymphoproliferative disorders, myeloma, and HSCT predispose affected patients to development of pneumonia with encapsulated organisms such as *S. pneumoniae* and *Haemophilus influenzae.* Many cases of bacterial pneumonia are nosocomial infections in patients who have been hospitalized for long periods and who previously have been treated with antibiotics so that the normal oropharyngeal flora has been replaced mainly by gram-negative bacteria. As a consequence, the range of potential organisms causing bacterial pneumonia is very different from that seen in community-acquired pneumonia, with a high frequency of resistant organisms such as *P. aeruginosa* and MRSA (see Table 28-1).

Clinical Features and Diagnosis

Bacterial pneumonia often manifests with a clinical picture similar to that seen in immunocompetent patients, with new-onset fever, cough, chest and radiologic signs of lobar consolidation, and a rapid rise in the level of inflammatory markers such as CRP. However, a more insidious or diffuse presentation that is more difficult to differentiate from viral or fungal infection is not uncommon. CT scans showing dense focal consolidation with a lobar distribution are helpful in differentiating bacterial from fungal or viral pneumonia (**Figure 28-8**), and blood cultures will be positive in about 20% of cases. Antigen testing of the urine may identify *Legionella pneumophila* or *S. pneumoniae* infections. Patients with an atypical clinical presentation or those who do not respond to first- or second-line antibiotics should have FOB and BAL, which has a reasonably high diagnostic yield for bacterial pneumonia. Protected specimen brush procedures probably add little information over and above that obtained with directed BAL. Histologic examination is unlikely to reveal specific features, and lung biopsy is mainly used to exclude other causes of lung infiltrates.

Management

Oxygen therapy to maintain a normal PaO_2 is essential and may require continuous positive airway pressure (CPAP) support. Intubation may be necessary if the patient's underlying disease

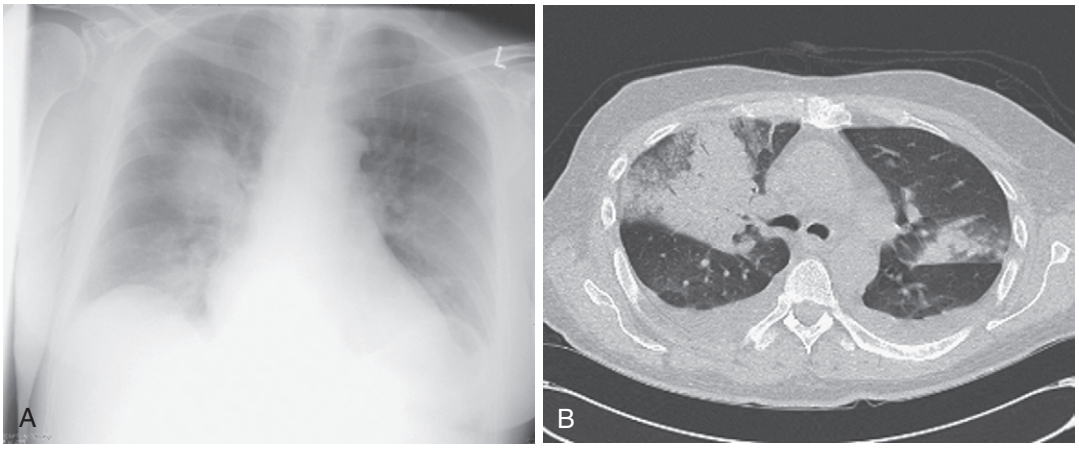


Figure 28-8 **A,** Chest radiograph showing a mass-like consolidation in the right middle lung zone in a patient with acute myeloid leukemia recently treated with chemotherapy and presenting with a high temperature but no respiratory symptoms after 9 days of neutropenia. **B,** Computed tomography (CT) scan of thorax in the same patient, showing that the shadowing is due to dense consolidation in the right upper lobe, with a smaller area of consolidation in the left upper lobe. The blood cultures grew *Escherichia coli*, and the patient improved rapidly on appropriate antibiotics, suggesting that the consolidation was a hospital-acquired pneumonia due to *E. coli*.

does not preclude mechanical ventilation but is associated with a poor prognosis in immunocompromised patients (up to a 95% mortality rate). Initial antibiotic therapy should be effective against the local pattern of hospital-acquired infections and will therefore probably include extended-range beta-lactams, aminoglycosides, or ciprofloxacin. Lack of response within 72 to 96 hours should prompt a switch to another broad-spectrum parenteral antibiotic (e.g., a carbapenem) in case the causative pathogen is resistant to first-line agents. Treatment for infections due to MRSA or other resistant gram-positive organisms also should be considered. Carbapenems and extended-range beta-lactams usually have good efficacy against anaerobic organisms.

Prevention

Antibacterial prophylaxis with a fluoroquinolone (e.g., levofloxacin) often is used during the neutropenic phase after HSCT. Prolonged antibiotic prophylaxis with penicillin V against encapsulated organisms is necessary for patients rendered functionally asplenic by their disease or therapy. Antibiotic prophylaxis also may be indicated in patients with chronic graft-versus-host disease, immunoglobulin deficiencies, and bronchiectasis. Vaccination against *S. pneumoniae* is recommended for all hematopoietic stem cell transplant recipients, and the conjugated vaccine probably should be used because of its stronger immunogenicity. Concern has emerged about the risk of whooping cough in recipients of hematopoietic stem cell transplants, who perhaps should receive vaccination against *Bordetella pertussis* and prophylaxis with azithromycin if exposed to an infected case.

MYCOBACTERIAL INFECTIONS

Mycobacterial infections usually are associated with defects in cell-mediated immunity and tend to develop subacutely. The risk for *Mycobacterium tuberculosis* infection is strongly dependent on the ethnic background and country of origin of the patient. Tuberculosis should be considered in at-risk patients with a cell-mediated immune defect or patchy or nodular lung shadowing, particularly those with a high-risk ethnic background. Nontuberculous mycobacterial infections (e.g., *Mycobacterium kansasii* or *Mycobacterium avium* complex [MAC]) are infrequent complications in immunocompromised patients. Exclusion of the diagnosis by negative culture takes too long to be clinically useful in patients with progressive disease. Therefore, with significant clinical suspicion of mycobacterial infection, invasive investigations are necessary to obtain material for a rapid diagnosis by identification of acid-fast bacilli, specific histopathologic changes, or possibly polymerase chain reaction (PCR) assay for samples obtained from sterile sites. Treatment is with the standard chemotherapy regimens.

NOCARDIAL INFECTIONS

Nocardia are gram-positive aerobic organisms found in soil and stagnant water. They grow relatively slowly as branching filaments. Immunocompromised patients should avoid gardening or occupations that result in exposure to soil and plants. Infection occurs through inhalation, so patients who wish to continue gardening may minimize exposure by wearing protective clothing such as an N-95 mask and gloves. The organisms most commonly causing human infection belong to the *Nocardia asteroides* complex, but other *Nocardia* spp. also can cause disease. Around 2% of lung infections in immunocompromised patients are due to *Nocardia*, and like mycobacterial infections, nocardial infections tend to affect patients with defects in cell-mediated immunity. In hematopoietic stem cell transplant recipients, the median time to onset is approximately 200 days after transplantation. Risk factors for disease also include corticosteroid use, active graft-versus-host disease, and concomitant opportunistic infections, especially with CMV.

Nocardia infection can manifest as a relatively acute pneumonia or as a more indolent disease similar to infection with *Mycobacteria* or *Aspergillus*. Radiologic changes include patches of consolidation, large nodules, often with cavitation, and pleural involvement in up to a third of cases. Hematogenous spread to other organs such as the brain, joints, and soft tissues occurs in up to 50% of patients. Microscopy or histologic examination can make the diagnosis rapidly through identification of characteristic beaded, branching, gram-positive and weakly acid-fast filaments. Respiratory and occasionally blood cultures can be positive but require prolonged aerobic culture. Most *Nocardia* strains are sensitive to co-trimoxazole as well as carbapenems, amikacin, third-generation cephalosporins, tetracyclines, and co-amoxiclav, but treatment needs to be very prolonged, lasting up to 12 months in immunocompromised patients. Mortality is high, reportedly up to 70%.

CYTOMEGALOVIRUS INFECTION

General Considerations

CMV infection is one of the most important complications in patients with defects in cell-mediated immunity such as transplant recipients and patients receiving potent immunosuppressive drugs such as fludarabine or alemtuzumab. CMV is the largest member of the Herpesviridae family of human double-stranded DNA viruses. It has a 230-kb genome that encodes over 200 products, which are expressed during replication in three overlapping phases over 24 hours termed immediate-early, early, and late.

Primary CMV infection is common in the general population, occurring mainly in children or young adults, but usually is asymptomatic or causes only mild disease. Previous infection is identified by serologic studies and leads to asymptomatic latent infection that can be reactivated in immunocompromised persons. Reactivation can be initiated by the cytokine tumor necrosis factor and stress catecholamines, so the virus often will be detected in transplant recipients 3 to 4 weeks after an infective episode involving another pathogen. Around 60% of immunocompromised patients with negative results on serologic testing for CMV who then receive transplants or blood products containing leukocytes from CMV-positive donors will develop CMV infection, which tends to be more severe than disease due to CMV reactivation. CMV-negative immunocompromised patients also can rarely develop primary infection after exposure to someone with active CMV infection.

Clinical Features and Diagnosis

The potential effects of CMV reactivation in immunocompromised patients are varied and include (1) clinically asymptomatic infection, which is common even in immunocompromised patients; (2) a CMV syndrome, defined as fever, a 50% fall in the leukocyte count, and a 2.5-fold increase in transaminases; (3) organ-specific infection, including the liver, central nervous system (CNS), gastrointestinal system, and lungs, often associated with more severe involvement of the transplanted organ; (4) accentuated rejection-related damage to the target organ (e.g., bronchiolitis obliterans in lung transplant recipients);

(5) impaired host immunity with increased incidence of opportunistic infections including pneumonia due to *Aspergillus, Pneumocystis jirovecii*, gram-negative bacteria, and *Nocardia*; and (6) increased incidence of EBV-associated lymphoproliferative disease.

CMV pneumonitis commonly manifests with insidious onset of fever, malaise, cough, and dyspnea with hypoxia. The chest radiograph may be normal in appearance or show nonspecific diffuse bilateral infiltrates. CT scan is more sensitive at identifying pulmonary infiltrates and classically shows bibasal symmetric ground glass opacities, septal line thickening, and multiple small centrilobular nodules (**Figure 28-9**). More asymmetric changes, consolidation, and effusions are not uncommon, however. The main considerations in the differential diagnosis are IPS, drug-induced pneumonitis, and, in patients not receiving effective prophylaxis, PCP. Serologic determination of either IgG or IgM has no place in the diagnosis of CMV disease, because these antibodies merely reflect previous exposure. However, CMV reactivation is nowadays readily detected by identifying significant viremia through either measuring the level of pp65 antigenemia or CMV DNA using PCR assay in the blood. CMV viremia usually is detectable 2 to 5 days before any clinical manifestations. Unfortunately, CMV viremia is not always present in patients with CMV pneumonitis; conversely, evidence of reactivation does not necessarily mean that new lung infiltrates are due to CMV pneumonitis. The chance that CMV infection is responsible for new lung infiltrates is proportional in part to the level of CMV in the blood, especially if the viral load increased rapidly. Definitive confirmation that CMV is causing pneumonia requires identification of CMV in the respiratory tract by FOB for BAL and preferably a transbronchial biopsy, or possibly a VATS lung biopsy. The presence of "owl's eye" intranuclear inclusions on cytologic examination is pathognomonic for CMV infection and although this modality is rapid, it is a relatively insensitive test. CMV can be cultured from respiratory samples using fibroblast cell culture to look for the distinctive cytopathogenic effect, but this takes at least a week and therefore is of little clinical benefit. The main diagnostic techniques for CMV pneumonitis are the relatively sensitive rapid tests for CMV antigens using BAL samples directly, or indirectly by probing cell cultures inoculated with the samples after 24 to 48 hours incubation (the shell vial or early antigen detection assays). Quantitative PCR assay on BAL fluid has been used to improve the predictive value for the diagnosis of CMV pneumonitis but requires further investigation. Despite this range of diagnostic techniques, a well-validated standard for identifying CMV pneumonitis is lacking, except for VATS biopsy.

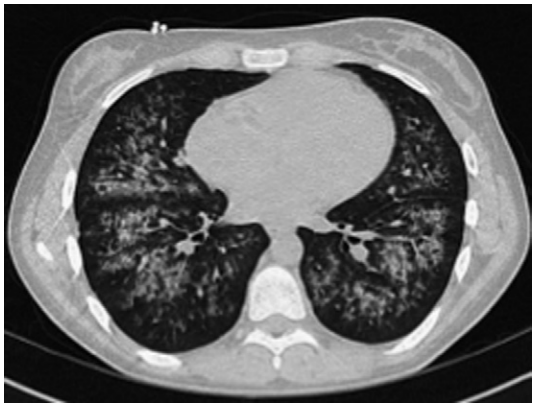


Figure 28-9 Computed tomography (CT) scan of thorax showing changes due to cytomegalovirus pneumonitis in a patient who had undergone hematopoietic stem cell transplantation for lymphoma 3 months previously.

Treatment

The currently available antiviral agents for treatment of CMV infection and disease are acyclovir, valacyclovir, ganciclovir, valganciclovir, foscarnet, and cidofovir (**Table 28-4**). A regimen based on the purine analogue ganciclovir is the preferred treatment; this agent, once phosphorylated within infected cells, competitively inhibits viral DNA polymerase. Ganciclovir has significant marrow-depressant effects and may be too toxic for use in hematopoietic stem cell transplant recipients or in patients with existing pancytopenia. Oral absorption is poor, but oral therapy with the valine ester valganciclovir has excellent bioavailability. The second-line agent foscarnet also inhibits the activity of viral DNA polymerase (by binding to the pyrophosphate-binding site). Foscarnet frequently causes significant renal toxicity. Alternatively, cidofovir has a broad activity against DNA viruses including CMV, acting as a competitive inhibitor of viral DNA polymerases. Cidofovir causes both myelosuppression and renal toxicity, and patients should be prehydrated and given probeniced before initiation of treatment. Patients with CMV disease also are frequently given hyperimmune intravenous immunoglobulin (IVIG) as passive vaccination therapy. Very few studies have compared these drugs for efficacy in CMV pneumonia. Treatment lasts from 14 to 21 days and should be guided by blood tests measuring the level of CMV viremia. Patients at risk for such infection often are given antiviral prophylaxis such as with valganciclovir. The mortality rate for established CMV pneumonia is up to 50% in hematopoietic stem cell transplant recipients but is less in other types of immunocompromised patients. Detection of CMV viremia frequently leads to preemptive therapy before symptomatic CMV infection develops, increasing the numbers of patients requiring treatment but improving overall outcome.

LUNG INFECTIONS DUE TO OTHER HERPESVIRUSES

Herpes simplex virus (HSV) and varicella-zoster virus (VZV) are rare causes of lung infection in immunocompromised patients, with a presentation similar to that for CMV pneumonia, but patients also may have the characteristic skin involvement. Microbiologic diagnosis relies on isolation of the virus from skin lesions or BAL fluid, and treatment is with high-dose acyclovir. Human herpesvirus type 6 (HHV6) may be an important pathogen causing infection after HSCT. Patients with HHV6 viremia have more CMV reactivation and unexplained fever and rash compared with patients without HHV6 viremia, and high-level HHV6 viremia (up to 25,000 copies/mL) has been associated with culture-negative pneumonitis.

INFECTIONS WITH RESPIRATORY VIRUSES

General Considerations

Lower respiratory tract infections with respiratory viruses are relatively common in immunocompromised patients. The common relevant viruses are respiratory syncytial virus (RSV), parainfluenza virus (PIV) (90% serotype III), influenza A virus, adenovirus, human metapneumovirus, coronavirus, and possibly rhinovirus. Infection is acquired by inhalation of infected respiratory droplets from other infected patients or mildly affected immunocompetent contacts. Consequently, immunocompromised patients should avoid contact with social

Table 28-4 Treatment Options for Viral Lung Infections

Treatment	Dose	Mode of Action	Viruses	Role/General Comments
Ganciclovir	2.5-5 mg/kg IV 2-3×/day	Inhibitor of viral DNA polymerase	CMV, HSV, HHV6	First-line agent; myelosuppressive; good efficacy
Valganciclovir	900 mg PO 1-2×/day	Prodrug of ganciclovir	CMV, HSV, HHV6	Better oral availability than ganciclovir
Foscarnet	60 mg/kg IV 3×/day	Inhibitor of viral DNA polymerase	CMV	Second-line agent; good efficacy; nephrotoxic
Acyclovir	10-15 mg/kg IV 3×/day	Inhibitor of viral DNA polymerase	HSV, VZV, HHV-6	Toxicity relatively uncommon
Cidofovir	1-5 mg/kg IV once weekly	Inhibitor of viral DNA polymerase	Adenovirus Possibly CMV	Third-line agent for CMV infection; efficacy against adenovirus unclear; nephrotoxic
Ribavarin	0.8 mg/kg inhaled	Nucleoside analogue	RSV, PIV, influenza virus, adenovirus, human metapneumovirus	Questionable benefit; nebulizer requires a scavenger tent because of potential toxicity; given over 12 to 18 hours
IVIG	E.g., 500 mg once daily	Passive vaccination	CMV, RSV	Combination treatment with antiviral agent
Palivizumab	15 mg/kg IV	Humanized anti-RSV monoclonal antibody	RSV	Efficacy unclear; used in combination with ribavarin
Amantidine	100 mg PO 2×/day	M2 inhibitor	Influenza A virus	Efficacy unclear; lowers incidence of progression to pneumonia?
Zanamivir	10 mg inhaled 2×/day	Neuraminidase inhibitor	Influenza virus	Probably reasonable efficacy
Oseltamivir	75 mg PO 2×/day	Neuraminidase inhibitor	Influenza virus	Probably reasonable efficacy

CMV, cytomegalovirus; *HHV-6*, human herpesvirus-6; *HSV*, herpes simplex virus; *PIV*, parainfluenza virus; *RSV*, respiratory syncytial virus; *VZV*, varicella-zoster virus.

contacts or members of the hospital staff clearly suffering from upper respiratory tract infections. Nosocomial epidemics of respiratory viruses readily occur, so infected patients should be effectively isolated. Respiratory viral infections are associated with defects in cell-mediated immunity and generally are a late complication after HSCT.

Clinical Features and Diagnosis

Respiratory virus lung infections often cause a bronchiolitis, manifesting with cough, fever, wheeze, and inspiratory squeaks. They frequently are preceded by a few days of coryzal symptoms. The chest radiograph may be normal in appearance, but a CT scan will show evidence of small airway involvement, with widespread tree-in-bud changes (**Figure 28-10**). The main considerations in the differential diagnosis in this clinical scenario are *Chlamydia* or *Mycoplasma* infection, extensive bacterial bronchitis (usually associated with bronchiectasis), and possibly *Aspergillus* tracheobronchitis. With more severe disease associated with significant pneumonitis, CT evidence will include small, poorly defined centrilobular nodules and usually bilateral patchy areas of peribronchial ground glass opacity and consolidation. The differential diagnosis in such cases is much broader in scope, including bacterial pneumonia, CMV pneumonitis, PCP, and noninfective causes of pneumonitis. In many patients, the diagnosis of respiratory viral infection can be rapidly confirmed by noninvasive testing using nasopharyngeal aspirate samples for either immunofluorescence for viral antigens or PCR assay for viral nucleic acids. A negative result on nasopharyngeal aspirate studies should lead to FOB, because these tests are more sensitive with BAL fluid than with nasopharyngeal aspirate samples. Respiratory viral infections in immunocompromised patients are often very prolonged but not too severe, with symptoms and positive results on nasopharyngeal aspirate studies persisting for several weeks.

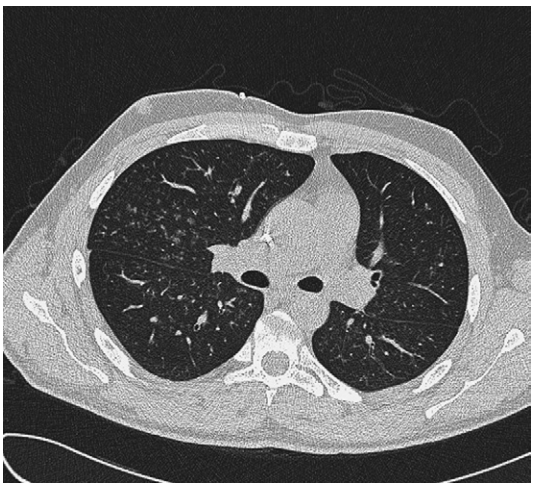


Figure 28-10 Computed tomography (CT) scan showing "tree-in-bud" changes (most obvious in the right upper lobe) due to PIV serotype 3 bronchiolitis in a patient with relapsed acute myeloid leukemia who had completed chemotherapy 25 days previously and presented with coryzal symptoms, cough, and a mild fever. *PIV*, parainfluenza virus.

Treatment and Special Considerations with Specific Viruses

With the exception of influenza, treatment options for respiratory viruses are limited and depend on the underlying virus (see Table 28-4). In the absence of pneumonia, the mortality associated with respiratory virus infection in immunocompromised

patients is relatively low, and patients can be given supportive therapy only. By contrast, pneumonia due to respiratory viruses after HSCT is associated with significant mortality (up to 40%). Secondary infections are common, and patients frequently need concurrent treatment with antibiotics.

Influenza Viruses Infection after HSCT with influenza viruses is perhaps surprisingly less common than infection with RSV and PIV. First-line therapy is with neuraminidase inhibitors (zanamivir or oseltamivir), which do seem to be effective at limiting disease severity and duration. An alternative agent for treatment of influenza virus infection is amantidine, but its efficacy is not clear. Transplant recipients (and their family members or household contacts) should receive lifelong seasonal influenza vaccination with the trivalent inactivated vaccine. If an outbreak occurs with a nonvaccine influenza strain, chemoprophylaxis with zanamivir or oseltamivir should be considered.

Parainfluenza Virus Although infection with PIV probably is among the most common causes of respiratory viral infection after HSCT, currently data on effective treatments are scarce. Ribavarin and IVIG may have activity against PIV infection but have not yet been shown to be beneficial in clinical practice. No useful vaccine is generally available as yet.

Respiratory Syncytial Virus Hematopoietic stem cell transplant recipients, particularly those who are pre-engraftment and lymphopenic or those who have preexisting obstructive airway disease, are at highest risk for severe RSV pneumonia. Therapies for RSV infection include systemic or aerosolized ribavirin, passive immunization with high-RSV-titer immunoglobulin, and monoclonal antibody directed at the RSV F antigen (palivizumab). No randomized trial has been completed to test the efficacy of these strategies, and efficacy data are limited. Some centers provide monthly palivizumab prophylaxis for hematopoietic stem cell transplant recipients during the RSV season (November to April in the Northern Hemisphere), particularly for pediatric recipients. Preemptive aerosolized ribavirin may be effective in those transplant recipients with lymphopenia and preexisting impaired lung function who develop RSV upper respiratory tract infection before the emergence of evidence that the infection has spread to the lungs.

Human Metapneumovirus Human metapneumovirus (hMPV) is a relatively recently identified RNA paramyxovirus related to RSV. It has been increasingly associated with lower respiratory tract infection and pneumonia in hematopoietic stem cell transplant recipients, with mortality rates of up to 50%. IVIG and ribavirin have in vitro activity against hMPV, but no recommendations on treatment are currently available owing to lack of data.

Adenovirus Adenovirus infections can occur in patients with impaired cell-mediated immunity due to reactivation or de novo acquisition. Many different adenovirus serotypes exist, so pretransplant serology is not helpful. In HSCT, the risk of adenovirus infection is increased for allograft recipients, after T cell depletion or treatment with antithymocyte globulin (alemtuzumab), and for patients with graft-versus-host disease receiving systemic steroids. Clearance of adenovirus has been shown to be associated with recovery of adenovirus-specific T cell immunity. Few antiviral agents have in vivo activity against adenoviruses, and no randomized, placebo-controlled study of antiviral drug therapy for adenoviral infection has been performed. The available data suggest that cidofovir or ribavirin may have some efficacy.

Respiratory Viruses and Lung Allograft Syndromes

Respiratory viral infection early after hematopoietic cell transplantation can be a predictor for the development of alloimmune lung syndromes such as progressive airways obstruction due to bronchiolitis obliterans, perhaps as they sensitize the respiratory epithelium for lung involvement by graft-versus-host disease. Clinically, patients will present with rapidly progressive airway obstruction in the context of active respiratory viral infection and will require aggressive immunosuppression to prevent progression to respiratory failure.

INVASIVE ASPERGILLOSIS

General Considerations

Invasive infections with *Aspergillus* constitute a common and important cause of lung infection in immunodeficient patients. *Aspergillus* organisms are saprophytic filamentous fungi that are found ubiquitously in the environment. They propagate by dispersal of airborne spores, which are 2 to 3 μm in diameter and can therefore reach the distal airway. Exposure to airborne spores is essentially continuous, but this rarely causes a clinical problem unless the host's immune response is impaired. In a patient with impaired macrophage or neutrophil function, however, the spores can germinate and form a colony of branching multicellular hyphae that gradually expands and penetrates through host tissue, causing invasive pulmonary aspergillosis (IPA). The usual site of infection is the respiratory tract, including the sinuses, but blood-borne spread to internal organs (especially the CNS), bone, and skin is common. The most frequently isolated species causing infection are *A. fumigatus* (66% of cases), *Aspergillus flavus* (14%), *Aspergillus niger* (7%), and *Aspergillus terreus* (4%).

Clinical Features

IPA is mainly a disease that affects patients with hematologic malignancies receiving chemotherapy, persons with aplastic anemia, or transplant recipients in the early phase after HSCT. Significant persistent neutropenia is the strongest risk factor, with the incidence proportional to the depth and duration of neutropenia, so that more than 50% of patients with neutropenia lasting for over 4 weeks will develop IPA. Patients at high risk also include those receiving high-dose systemic corticosteroid therapy and/or have graft-versus-host disease (causing IPA in the late phase after HSCT), lung and liver transplant recipients, and patients with inherited disorders of phagocyte function such as chronic granulomatous disease (CGD), in which mutations in genes encoding the NADPH oxidase system impair the phagocyte oxidative burst. Various genetic polymorphisms affecting Toll-like receptors (TLRs) and cytokines seem to modify the risk of invasive aspergillosis for patients in the above risk groups.

The speed of development of IPA is proportional to the level of immunosuppression, but the disease usually evolves relatively slowly over days and weeks. Fever may be the only symptom of IPA, although cough, pleuritic chest pain, and hemoptysis are common. Chest radiographs show expanding patches of irregular consolidation (often infarct shaped) or nodules that can cavitate. CT scans are very helpful, because they will define the nodular nature of infiltrates, may show specific signs associated with IPA, and can identify the lung as

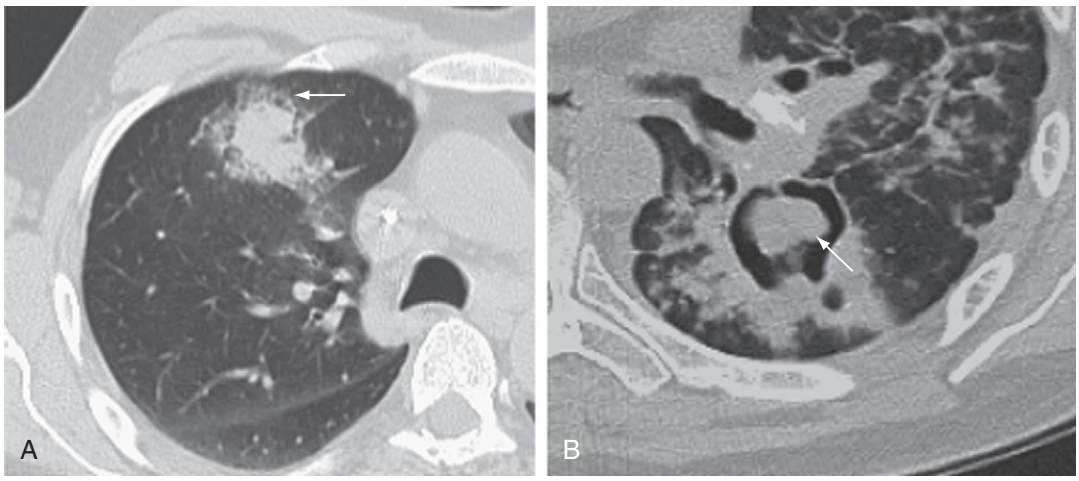


Figure 28-11 **A,** Computed tomography (CT) scan showing a nodule surrounded by an area of lower attenuation ground glass infiltration (the halo sign, indicated by the *white arrow*) suggestive of invasive aspergillosis. **B,** CT scan showing an area of invasive aspergillosis that has cavitated. Within the cavity, a mycetoma (*white arrow*) is evident.

the source of infection in patients with pyrexia and a normal chest radiograph. Specific CT appearances for IPA include the *halo sign*, an area of lower attenuation shadowing around a nodule or patch of consolidation reported in 50% of cases of IPA and usually occurring in the first week of infection (**Figure 28-11**); the *air crescent sign*, a partial cavity formed by infarcted necrotic lung, which is a very specific but later-onset sign occurring around the third week of infection; and an *intrapulmonary cavity containing a fungal ball*, especially associated with recovery of the patient's neutrophil count (see Figure 28-11). The halo sign may be detected in other infections, with neoplasms (adenocarcinoma, bronchoalveolar carcinoma, Kaposi sarcoma, and metastases), and in vasculitis. *Aspergillus* has a predilection for growing into blood vessels, and patients with IPA may suffer fatal massive hemorrhage. Other manifestations of invasive *Aspergillus* infections affecting the lung include *Aspergillus* tracheobronchitis, chronic necrotizing pulmonary aspergillosis (CNPA), and chronic cavitary pulmonary aspergillosis (CCPA).

With *Aspergillus* tracheobronchitis, infection is restricted to the tracheobronchial tree and manifests with a severe unremitting cough and pyrexia. CT scans may show focal areas of bronchial wall thickening and tree-in-bud small airway disease (**Figure 28-12**). FOB usually is diagnostic, with a distinctive macroscopic appearance of patchy, highly inflamed mucosa with necrotic white slough. *Aspergillus* can be found in cultures and/or cytology of bronchial washings, and there may be evidence of fungal invasion of the respiratory mucosa in bronchial biopsy specimens.

The more indolent forms of invasive aspergillosis such as CCPA or CNPA are increasing in incidence and are associated with milder degrees of immunosuppression, including steroid and cytotoxic therapies, chronic lung disease or cystic fibrosis. Affected patients present with a long history of cough and marked systemic symptoms of malaise, fatigue, and weight loss. On chest radiographs, CNPA manifests as an indolent patch of consolidation with or without cavitation that progresses over weeks or months (**Figure 28-13**), whereas CCPA manifests with an expanding upper lobe dry cavity with a thickened and irregular wall. There may be associated pleural thickening. *Aspergillus* infection also can cause a progressive upper lobe fibrosis.

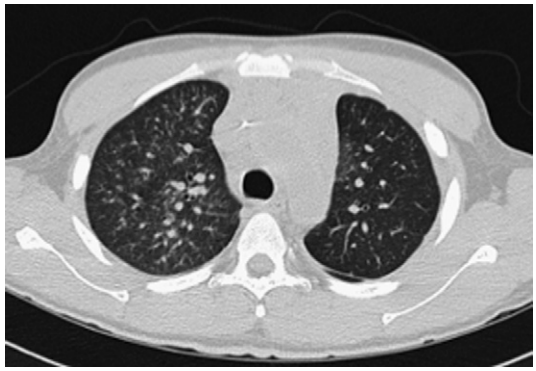


Figure 28-12 Computed tomography (CT) scan of thorax in a patient with acute lymphocytic leukemia treated with chemotherapy who presented with persistent cough and fever. The scan shows asymmetric "tree-in-bud" and nodular changes mainly affecting the right upper lobe, which were caused by *Aspergillus* tracheobronchitis.

Microbiologic Diagnosis

Investigations that can be helpful in making the diagnosis of IPA are described in **Table 28-5**. In high-risk patients with a compatible clinical syndrome and CT findings highly suggestive of IPA (halo and crescent signs), the diagnosis can be made clinically and may not require confirmation by invasive investigations. However, some *Aspergillus* species (e.g., *A. terreus*) are resistant to amphotericin B, and a clinical presentation similar to that in IPA can be caused by rarer filamentous fungi with drug sensitivities that differ from those demonstrated for *Aspergillus*. Hence, microbiologic confirmation is reassuring, because it ensures that appropriate treatment is given. A microbiologic diagnosis of IPA can be made by culture, cytologic, or histologic appearances in BAL or lung biopsy specimens, or by the detection of fungal cell wall antigen (galactomannan or β-D-glucan) or DNA (by PCR assay) in blood or BAL fluid. Isolation of *Aspergillus* from BAL in a high-risk immunodeficient patient is highly predictive of IPA but is relatively insensitive, identifying only 50% of cases of IPA. Culture from sputum is even less sensitive, and blood cultures are only rarely positive. Percutaneous CT-guided or VATS biopsy is highly sensitive, because

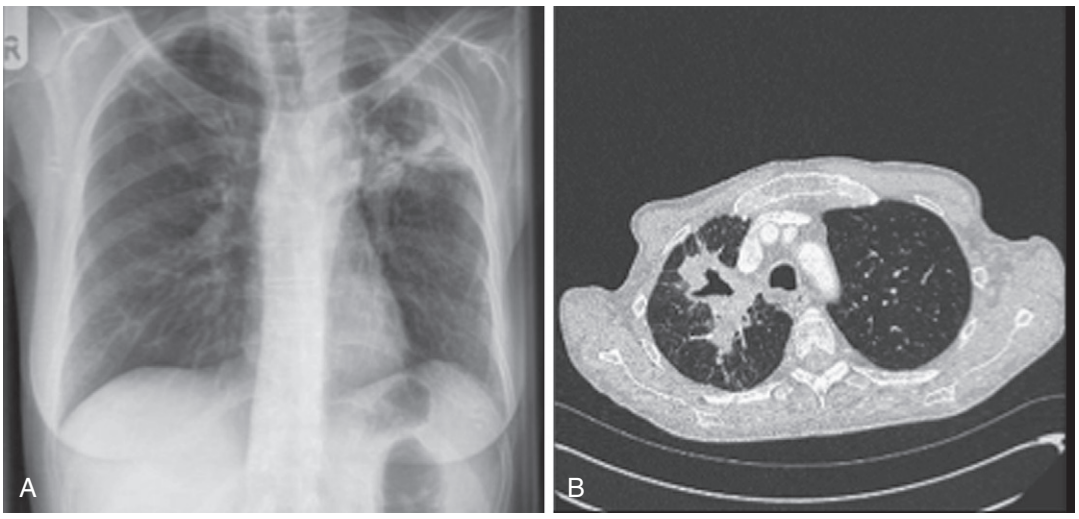


Figure 28-13 Slowly invasive aspergillosis in patients without severe immunosuppression. **A,** Chest radiograph showing a large irregular cavity in the left upper lobe with marked pleural thickening on a background of chronic obstructive pulmonary disease; the diagnosis was chronic cavitary pulmonary aspergillosis (CCPA), confirmed by surgical resection. **B,** Computed tomography (CT) scan showing a thick-walled dry cavity due to chronic necrotizing pulmonary aspergillosis (CNPA) in a patient with long-standing rheumatoid arthritis that was treated with a variety of immunosuppressive therapies. The diagnosis was confirmed by histologic identification of *Aspergillus* hyphae invading lung tissue in a biopsy sample obtained at video-assisted thoracoscopic surgery.

Table 28-5 Types and Roles of Diagnostic Tests for Invasive Aspergillosis

Test	Sample	Time Needed	Method	Role and General Comments
Culture	Sputum, BAL fluid, CSF, biopsy specimen	2-4 days	Culture on fungal media	Low sensitivity (50% for BAL) and does not necessarily improve invasive disease (can be colonizing the respiratory tract)
Cytologic examination	BAL fluid, biopsy specimen	6 hours	Microscopy for fungal elements	May not distinguish between fungal species
Histologic examination	Biopsy specimen	24-48 hours	Visualization of dichotomous branching septate hyphae	Fungal stains necessary; may not distinguish between fungal species
Antigen testing	Serum, BAL fluid	6 hours	Galactomannan detection	Cell wall antigen for *Aspergillus* and *Penicillium* spp.; sensitive; false positives occur
Antigen testing	Serum, BAL fluid	6 hours	β-D-Glucan detection	Cell wall antigen for *Candida*, *Aspergillus*, *Penicillium*, and *Pneumocystis* spp.; sensitive; false positives occur
PCR assay	Blood, BAL fluid	24 hours	Amplification of target DNA	Role not yet established, probably highly sensitive
CT appearance	—	Instant	Identification of halo or crescent sign, intracavitary mycetomas	Specific for invasive filamentous fungal infection but does not identify fungal species

BAL, bronchoalveolar lavage; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *PCR*, polymerase chain reaction.

histopathologic examination of the sample can readily identify fungal hyphae infiltrating through lung tissue if fungal stains are used. Hence, strong consideration should be given to biopsy of lung nodules not responding to conventional antibacterial antibiotics, especially if BAL was nondiagnostic. To decrease mortality by allowing rapid identification of cases of IPA before the fungal load is high, several noninvasive tests have been developed. These include detection of galactomannan or β-D-glucan cell wall antigen in the blood (or BAL fluid if FOB has been performed), or PCR assay for *Aspergillus* DNA from the blood or BAL fluid. These tests are highly sensitive and when used as surveillance in high-risk patients could lead to preemptive antifungal therapy before clinically apparent disease has developed, leading to an improved mortality. However, detection of fungal DNA in a single sample of peripheral blood is a poor indicator of early invasive fungal infection, and galactomannan antigen is not specific for *Aspergillus* spp., frequently giving false-positive results (especially in patients treated with piperacillin-tazobactam or in young children). Despite these caveats, a negative galactomannan assay result makes active IPA infection unlikely. Serologic tests for antibodies to *Aspergillus* usually yield negative results in immunocompromised patients with IPA.

Diagnosing chronic forms of IPA in less immunocompromised patients often is difficult owing to lack of sensitivity of culture and the lack of data on the predictive values for antigen testing. CT-guided or VATS biopsy frequently is necessary to exclude malignancy and to confirm fungal invasion of lung tissue. *Aspergillus* IgG levels usually are raised in patients with CCPA, but not necessarily so in those with CNPA.

Treatment

The treatment options for invasive aspergillosis have been considerably improved by the introduction of new azoles, voriconazole and more recently posaconazole, and a new class of antifungal agents, the echinocandins, the first example of which is caspofungin. Doses, modes of action, and common toxicities for the different treatment options are given in Table 28-6. Voriconazole may be more effective than amphotericin B for treating IPA, but which drug is used depends on the patient's tolerance for that agent and any preexisting medical conditions (e.g., amphotericin B should be avoided in patients with renal problems, and azoles in patients with liver disease). Itraconazole is less efficacious and should be reserved for oral treatment in patients recovering from IPA after induction treatment with amphotericin B, caspofungin, or voriconazole or for the long-term treatment required for chronic forms of invasive aspergillosis. Drug levels probably should be monitored for patients receiving itraconazole, voriconazole, and posaconazole, at least for patients on prolonged therapy. The role of combination therapy remains unclear, but this strategy is potentially attractive in view of different mechanisms of action for the three effective classes of drugs. Urgent surgical resection should be considered in patients with major hemoptysis, because fatal bleeding is not uncommon. Elective resection can be used as primary therapy for single lesions due to IPA, especially those containing an intracavitary mycetoma that might lead to reactivation of IPA during subsequent immunosuppression. Treatment of IPA for several weeks often is necessary, followed by prophylactic therapy in cases with persisting radiologic changes. Treatment of CNPA and CCPA will need to be continued for months if not years (and even lifelong). Owing to a combination of uncontrolled infection and the underlying disease, the mortality rate for IPA is around 50%, and with chronic forms of aspergillosis, the infection rate remains as high as 33%. Azoles can be used for prophylaxis in at-risk groups, including hematopoietic stem cell transplant recipients. Fluconazole is not effective at preventing mold infections such as IPA, and despite its efficacy against *Aspergillus*, voriconazole seems to offer no clinical benefit over prophylaxis with fluconazole. However, prophylaxis with the newer extended-spectrum triazole posaconazole reduced the incidence of invasive aspergillosis in patients with prolonged neutropenia, from 7% to 1%. Acquired resistance of *A. fumigatus* to posaconazole has emerged during the course of therapy, which may potentially limit its use for prophylaxis.

OTHER FUNGAL INFECTIONS

Infections Due to Non-*Aspergillus* Filamentous Fungi

Although *Aspergillus* spp. dominate infections due to molds, other filamentous fungi can cause invasive pulmonary infections in immunocompromised patients, including *Fusarium*, *Zygomycetes*, *Scedosporium*, and *Penicillium*. These infections often are clinically similar to invasive aspergillosis but have a different spectrum of susceptibilities to antifungal agents. Hence, non-*Aspergillus* filamentous fungal infection needs to be considered in patients with a clinical diagnosis of IPA who are not responding to antifungal therapy. Diagnosis is made by culture from respiratory samples or lung biopsy, and mortality is very high. Galactomannan and β-D-glucan cell wall antigen test results are negative in patients infected with zygomycetes. Treatment is with surgical débridement combined with amphotericin and, for infections due to *Fusarium* and *Scedosporium* but not zygomycetes, voriconazole or posaconazole.

Infections Due to *Candida* Spp.

Infection with *Candida* rarely manifests as a pneumonia, but candidemia may lead to metastatic lung infection that causes

Table 28-6 Treatment Options for Invasive Aspergillosis

Treatment	Dose	Mode of Action	Role and General Comments	Toxicity
Amphotericin B	1-1.5 mg/kg IV once daily	Binds to ergosterol in the fungal cell membrane	Effective; cheap; withdrawn in a third of patients due to toxicity	Fever and chills; phlebitis; hypokalemia, hypomagnesemia; uremia; bronchospasm; gastrointestinal disturbance; muscle pain
Lipid formulations of amphotericin B	1-5 mg/kg per day IV	As above	Expensive; much improved toxicity profile	As above (much lower incidence)
Itraconazole	200 mg once daily or 2-3×/day IV or PO	Inhibits ergosterol biosynthesis	Poor efficacy in acute IPA; poor absorbance (check levels)	Gastrointestinal disturbance; elevated hepatic transaminases; fluid retention; neuropathy
Voriconazole	6 mg/kg 2× on day 1; then 4 mg/kg IV once daily 200 mg PO 2×/day	Inhibits ergosterol biosynthesis	Effective; expensive; good absorption	Elevated hepatic transaminases; visual and CNS disturbances
Posaconazole	200 mg 3×/day PO (no intravenous formulation)	Inhibits ergosterol biosynthesis	Effective; expensive; good absorption	Elevated hepatic transaminases; paresthesia; tremor; visual disturbances Availability maximized with fatty food
Caspofungin	70 mg loading dose; 50 mg IV once daily	Inhibits fungal cell wall synthesis	Expensive; effective	Generally well tolerated; flushing; gastrointestinal disturbance
Surgery	—	—	For life-threatening hemoptysis or removal of single lesions	Pleural dissemination of *Aspergillus* as well as the usual postoperative complications

CNS, central nervous system; *IPA*, invasive pulmonary aspergillosis.

pyrexia and is associated with radiologic evidence of lung nodules that often are peripheral in location and sometimes very large. Neutropenic patients with mucositis or indwelling lines are at risk for invasive candidemia, which usually is caused by dissemination of endogenous colonizing *Candida* spp. The frequent use of fluconazole for prophylaxis has led to increasing isolation of non-*albicans* species such as *Candida glabrata* and *Candida parapsilosis*. Treatment is with caspofungin, amphotericin, voriconazole, or posaconazole.

Infections Due to *Cryptococcus* and Endemic Fungi

Cryptococcus neoformans infections are acquired by inhalation of the fungal spores. Although respiratory infection often is asymptomatic, cryptococcal disease can cause multifocal consolidation and severe pneumonia in patients with defects in cell-mediated immunity and carries a mortality rate of 30%. The diagnosis is made by microscopic identification or culture of *C. neoformans* from respiratory tract samples. Treatment is with intravenous amphotericin B in combination with flucytosine, followed by oral fluconazole. Reactivation of latent infection with endemic fungi such as *Histoplasma* and *Coccidioides* should be considered in patients with defects in cell-mediated immunity presenting with multifocal lung shadowing who have lived in relevant geographic areas, especially if there is evidence of extrapulmonary involvement. Diagnosis generally requires identification of the fungus in tissues samples.

Pneumocystis jirovecii Infection

In addition to its close association with HIV infection, PCP is an important type of pneumonia in non–HIV-infected immunocompromised patients with defects in cell-mediated immunity or who are receiving systemic corticosteroid therapy equivalent to greater than 20 mg daily of prednisolone. The clinical presentation generally is insidious in onset, with cough and progressive dyspnea developing over weeks, but can be more fulminant. Impaired gas transfer and hypoxia on exertion with progression to respiratory failure are common. The chest radiograph usually shows bilateral infiltrates but may be normal in appearance. Generally the CT scan will show ground glass infiltrates, which classically mainly affect the upper lobes and spare the lung peripheries (**Figure 28-14**). On rare occasions, however, even the CT scan may show only minimal abnormalities. The diagnosis is made by recognition of the clinical picture in an at-risk patient and should be confirmed by cytologic identification of the characteristic *P. jirovecii* cysts in BAL fluid. Diagnosis can be improved using immunohistochemistry assay for *Pneumocystis* antigens, and perhaps by PCR analysis, although the latter will have a significant false-positive rate as a consequence of colonization in the absence of disease.

First-line treatment is with high-dose co-trimoxazole and adjuvant steroids given according to the protocols used for PCP in HIV-infected patients. Myelosuppression due to co-trimoxazole means that many patients with hematologic disorders have to switch to second-line therapy with clindamycin and primaquine. In non-HIV immunocompromised patients, PCP is associated with intubation and mortality rates of around 30% each. PCP prophylaxis usually is prescribed for several months after allograft HSCT or organ transplantation, and occasionally longer in patients who continue to receive immunosuppressive drugs. Patients recovering from PCP should continue on chemoprophylaxis until their immunosuppression is resolved, although there are no clear parameters for defining this endpoint. Consensus is lacking on the requirement for PCP prophylaxis after autograft HSCT and for severe non–transplantation-related immunosuppression. Cotrimoxazole prophylaxis given either daily or three times per week is very effective (greater than 90% efficacy) and provides some protection against other pathogens, including *Toxoplasma*, *Nocardia*, and bacteria.

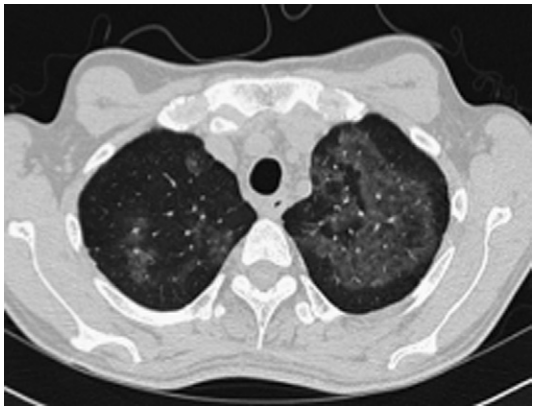


Figure 28-14 Computed tomography (CT) scan showing an upper lobe ground glass infiltrate with peripheral sparing. This pattern is highly suggestive of *Pneumocystis* pneumonia in patients with a defect in cell-mediated immunity.

CONTROVERSIES AND PITFALLS

- Exactly when bronchoscopy should be used for diagnosing respiratory infections in immunocompromised patients remains controversial, with no clear consensus on early versus late bronchoscopy. The approach described in this chapter based on the type of lung shadowing aims to target bronchoscopy to the patients for whom it may be most helpful.
- CMV pneumonitis is an especially difficult diagnosis to confirm; the specific diagnostic tests often are inconclusive, and the clinician is left with presumptive evidence of involvement of CMV consisting of the combination of a pneumonitis with blood test results indicating reactivation of the virus.
- A major pitfall to avoid is failure to consider noninfective causes of respiratory problems in the non-HIV-infected immunocompromised patient; pulmonary edema, alveolar hemorrhage, ARDS, drug-related or idiopathic pneumonitis, and rapidly progressive airway obstruction due to lung graft-versus-host disease (often precipitated by respiratory viral infections) often need to be included in the differential diagnosis.
- Although most infective causes of lung problems in the non–HIV-infected immunocompromised patient generally have fairly characteristic presentations and affect selected risk groups, considerable overlap between clinical presentations for illnesses due to specific infectious agents is typical. This is especially true for the more severely immunosuppressed patient, in whom the usual clinical presentations become less characteristic.
- Finally, the clinician needs to remember that non–HIV-infected immunocompromised patients often have two simultaneous pathologic conditions (e.g., a bacterial pneumonia complicated by ARDS, or a respiratory viral infection with lung graft-versus-host disease).

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