Abstract

The respiratory tract is a common site of infection in cancer patients and is associated with substantial morbidity and mortality in this population. Cancer, chemotherapy, and radiation can all cause noninfectious pulmonary infiltrates and respiratory symptoms that can masquerade as a respiratory tract infection. Cancer patients are at a particular risk for infection by a wide variety of different viruses, fungi, and bacteria that can be difficult to treat. Although noninvasive diagnostics have significantly improved recently, patients with severe pneumonia and those not responding to usual therapy should be candidates for aggressive diagnostic testing and tissue sampling. Initial therapy should be carefully chosen and individually tailored to account for the individual patient’s underlying risk factors for multi-drug-resistant pathogens, viral pathogens, or fungi. Once diagnostic testing returns, therapy should be altered to appropriately narrow the spectrum of coverage.

Keywords

Pneumonia · Cancer · Stem cell transplant · Lower respiratory tract infections

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1 Introduction

Respiratory tract infections are a common cause of illness among patients with cancer and are a substantial source of morbidity and mortality. Data regarding the incidence and epidemiology of respiratory tract infections in cancer patients are limited. In 2006, cancer was identified as the second leading cause of death in the United States (nearly 560,000 deaths), while influenza and pneumonia were listed at number 8 (comprising over 56,000 deaths) [1]. Mortality in the national vital statistics reports is listed as due to a single cause, while a substantial amount of mortality is due to the combination of cancer and pneumonia. Additionally, the fourth leading cause of death is chronic lower respiratory diseases (e.g., chronic obstructive pulmonary disease), which overlaps with lung cancer and pneumonia. Of documented infections in patients with febrile neutropenia, 15–30 % are eventually documented to be pneumonia [2]. Thus, although a detailed understanding of the morbidity and mortality associated with pneumonia in patients with malignancy is limited, the burden is substantial.

Respiratory tract infections are often divided into upper and lower respiratory tract infections. Upper respiratory tract infections primarily involve the nose, pharynx, and other adjacent structures. Lower respiratory tract infections are often defined as having evidence of infection, respiratory symptoms or physical examination findings suggesting lower respiratory tract disease, and abnormal chest imaging. Lower respiratory tract infections include bronchitis, bronchiolitis (e.g., in young children), and pneumonia.

A detailed discussion of upper respiratory tract infections is beyond the scope of this book chapter. Included within upper respiratory tract infections are pharyngitis, rhinitis, otitis media, and sinusitis. The majority of upper respiratory infections are due to viral etiologies [3]. Although pharyngitis may be due to viral etiologies (e.g., herpes simplex virus, cytomegalovirus, or Epstein Barr virus),
chemotherapy- or radiation-induced mucositis and bacterial etiologies (e.g., *Streptococcus pyogenes* most commonly) may also occur. Rarely perioral infections that involve the floor of the mandible can rapidly dissect through the tissue planes of the neck to cause Ludwig’s angina. In this disease process, a “bull neck” develops with potential airway narrowing and respiratory compromise, and risk of progression into the mediastinum. Lemierre’s syndrome can also develop due to spread of infection from the perioral space into the soft tissues of the neck causing a septic thrombophlebitis of the jugular vein and septic emboli to the lungs. *Fusobacterium*, an oral anaerobe, is most commonly responsible. These infections are uncommon, but potentially life threatening.

Otitis media and sinusitis can occur in patients with underlying malignancies. In healthy patients infections are most commonly due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [4]. In patients with more chronic disease, *Staphylococcus aureus*, enteric gram-negative bacteria, and anaerobes can also occur. In the setting of neutropenia or chronic graft versus host disease (GVHD), the possibility of invasive fungal sinusitis should be entertained and aggressively evaluated for if the patient develops symptoms potentially consistent with sinusitis. Rapid development of ocular findings, cranial nerve palsies, or mental status changes in the setting of sinusitis should prompt emergent sinus imaging and evaluation by an otolaryngologist for possible surgical debridement and biopsy. Failure to respond to usual empiric antibiotic therapy should also prompt additional imaging and possibly more invasive strategies to identify a pathogen and to evaluate for complications.

Lower respiratory tract infections classically include bronchitis, bronchiolitis, pneumonitis, and pneumonia. These terms are poorly defined, substantial overlap exists, and differentiation between these entities in an individual patient may be difficult. This chapter will refer to lower tract respiratory disease as pneumonia unless otherwise specified. Most epidemiological studies and clinical trials of pneumonia have required patients to have evidence of acute illness (e.g., fever, leukocytosis, or severe leukopenia), evidence of acute respiratory symptoms (e.g., cough, dyspnea, tachypnea, abnormal breath sounds), and abnormal imaging of the chest suggesting pulmonary abnormality (e.g., lobar consolidation) [5–8]. Unfortunately, many clinical trials of pneumonia have excluded most or all patients with underlying malignancies, and guidelines do not adequately address the issues in this patient population [9–14].

### 2 Differential Diagnosis of Pneumonia

The differential diagnosis of pulmonary infiltrates is broad and is outlined in Table 1. Considerations include cardiac, pulmonary, malignant, inflammatory, and infectious processes. Notably, cardiac or pulmonary toxicity from comorbid medical conditions (e.g., rheumatoid arthritis) or medications (e.g., amiodarone) can occur in the setting of cancer management. Cardiotoxic chemotherapeutic
Table 1  Common causes of respiratory symptoms or disease in cancer patients

| Infectious                                                                 |
|---------------------------------------------------------------------------|
| Lower respiratory tract illness (e.g., pneumonia)                         |
| Septic emboli from bacteremia                                             |
| Sepsis                                                                    |
| Aspiration pneumonia                                                      |
| Aspiration pneumonitis                                                    |
| Post-obstructive pneumonia (particularly in setting of an obstructing malignancy) |

| Cardiac                                                                    |
|---------------------------------------------------------------------------|
| Acute myocardial infarction (AMI)                                         |
| Congestive heart failure (CHF) with pulmonary edema                       |
| Chronic                                                                   |
| Acute e.g., due to AMI or acute valvular insufficiency                     |
| Cardiac toxicity from prior therapy, including                            |
| Cyclophosphamide                                                          |
| Mitoxantrone                                                              |
| Anthracyclines                                                            |
| Paclitaxel and docetaxel                                                  |
| Trastuzumab                                                               |
| Mediastinal or total body irradiation                                     |

| Pulmonary                                                                 |
|---------------------------------------------------------------------------|
| Noncardiogenic pulmonary edema                                            |
| Volume overload                                                           |
| Capillary leak (e.g., sepsis)                                             |
| Pulmonary embolism (particularly with infarction)                         |
| Fat embolism                                                              |
| Transfusion-related lung injury                                           |
| Alveolar hemorrhage                                                       |
| Idiopathic eosinophilic pneumonia                                        |
| ARDS                                                                       |
| Preexisting pulmonary disease (e.g., COPD, bronchiectasis)                |
| Preexisting medical disease (e.g., rheumatoid arthritis)                  |
| Medication related (e.g., amiodarone)                                     |

(continued)
agents such as cyclophosphamide, anthracyclines, mitoxantrone, paclitaxel, docetaxel, and trastuzumab or mediastinal radiation should always be considered as a potential cause of cardiovascular dysfunction, which may present with primarily respiratory symptoms [15, 16]. Similarly, interstitial pneumonitis may result from treatment with bleomycin, cyclophosphamide, gemcitabine, cytarabine, fluorouracil, procarbazine, gefitinib, rituximab, and many other agents [15, 17, 18]. In addition, inhibitors of the mammalian target of rapamycin (mTOR), such as sirolimus, everolimus, and temsirolimus, can cause a progressive noninfectious pneumonitis [19, 20].

Other complications of cancer treatment such as volume overload, acute lung injury after blood transfusion, pulmonary embolism, and diffuse alveolar hemorrhage should also be considered. Primary lung cancer or metastatic disease can

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**Table 1** (continued)

| Oncological                          |
|-------------------------------------|
| Metastatic malignancy               |
| Primary lung malignancy             |
| Leukemic infiltrates                |

**Treatment-Related Pulmonary Toxicity**

| Radiation-induced pneumonitis and fibrosis |
|-------------------------------------------|
| Medication related, including             |
| Bleomycin                                 |
| Busulfan                                  |
| Chlorambucil                              |
| Cyclophosphamide                          |
| Gefitinib                                 |
| Methotrexate                              |
| Nitrosoureas                              |
| Procarbazine                              |
| Rituximab                                 |
| Taxanes                                   |
| mTor inhibitor-associated pneumonitis     |
| Others                                    |

Cryptogenic organizing pneumonia (COP) (bronchiolitis obliterans organizing pneumonia, BOOP)

**After stem cell or bone marrow transplantation**

| Idiopathic pneumonia syndrome (idiopathic interstitial pneumonitis) |
| Graft versus host disease (GVHD)                                    |
also result in pulmonary opacities. Sometimes, malignancies, particularly primary lung cancer, can obstruct or impede air flow into or out of the lung, resulting in a post-obstructive pneumonia or a lung abscess. Radiation pneumonitis, particularly if associated with fever and an elevation in white blood cell count [21], is often difficult to distinguish from an infectious pneumonitis [22]. The infiltrates with radiation pneumonitis can have a perivascular haziness which can progress to patchy alveolar filling infiltrates [21]. In addition, multiple disease processes can simultaneously occur in the lungs, and this possibility should be entertained.

Indwelling catheter infections must also be considered in patients with symptoms of infection and pulmonary infiltrates on chest imaging. Indwelling catheters dramatically increase the risk of bloodstream infections and endocarditis. Bacteremia or right-sided endocarditis can result in embolic pulmonary infiltrates (typically peripheral) and respiratory distress. Bacteremia and sepsis can also result in capillary leak with associated diffuse patchy infiltrates or acute respiratory distress syndrome (ARDS).

3 Epidemiological Risk Factors for Pneumonia

Certain epidemiological risk factors exist for pneumonia, and ascertainment of such factors in an individual patient can be helpful in expanding or altering the differential diagnosis. A history of cigarette smoking has been identified as the strongest epidemiological risk factor for invasive pneumococcal disease in immunocompetent, nonelderly adults [23]. The season of the year should be considered as many respiratory viral infections occur predominantly in the winter and spring (e.g., influenza, respiratory syncytial virus (RSV), and human metapneumovirus). Children, particularly those in daycare, may transmit respiratory viruses such as RSV and influenza which are risk factors for invasive pneumococcal disease [23]. Sick contacts also may be a source for less commonly observed infections such as tuberculosis or measles. A history of exposure to tuberculosis is important since it may remain in a latent state for years before reactivating with increasing age or immune depletion. It is very important to consider that approximately 60% of tuberculosis cases diagnosed in the United States occur in individuals who were born outside the United States [24]. Geographic factors are also helpful in considering endemic fungi such as histoplasmosis (the Mississippi and Ohio River valleys) and coccidioidomycosis (desert southwest, particularly the San Joaquin valley) which are more frequently observed in cancer patients. Although blastomycosis is frequently mistaken for lung cancer or a metastatic malignancy, symptomatic disease is uncommon in those with cancer but may occur more frequently in those with defects in cell-mediated immunity [25]. Exposure to certain pets such as parakeets or parrots (a cause of psittacosis) or other animals such as birthing livestock (resulting in risk of infection with Coxiella burnetti or Q-fever) can suggest other uncommon causes of pneumonia. Ongoing construction at a medical center without appropriate
protective measures or exposure to aerosolized soil can result in an increased risk of *Aspergillus* pneumonia [26]. These and other nosocomial risk factors for *Aspergillus* and also for *Legionella* infections are outlined elsewhere in this volume (Chapter Infection Control and Prevention Considerations).

Recent history of a preceding or current viral illness should be obtained. It has been known that coinfections or mixed infections can be identified in community-acquired pneumonia (CAP) [12, 27]. Improved diagnostic testing, particularly the recent application of PCR testing for respiratory viral pathogens, has resulted in a greater appreciation for the interaction that can occur between bacterial and viral pathogens. In previously healthy children and adults who are admitted with pneumonia, 5–30% have both viruses and bacteria identified using molecular techniques [10, 28–33]. Additionally, viruses (e.g., influenza, RSV, and human metapneumovirus) have an important role in predisposing patients to invasive bacterial pneumonia. In a case-controlled study, prior influenza infection, 1–4 weeks before, predisposed children to subsequent severe pneumococcal pneumonia requiring hospitalization with an odds ratio of 12.4 [34]. Influenza infection is also a risk factor for severe *S. aureus* pneumonia (particularly methicillin-resistant *S. aureus* or MRSA) [35, 36]. A recent review of autopsies of patients who died during the 1918 influenza pandemic suggested that much of the mortality was actually due to bacterial superinfection [37]. Others have also identified *S. pneumoniae* more frequently in nasopharyngeal secretions in those with severe novel 2009 H1N1 disease than in those with mild cases [38]. Additional pediatric data suggest that invasive pneumococcal disease correlates with a preceding RSV infection (up to 4 weeks later) and with a preceding human metapneumovirus or influenza infection (up to 2 weeks later) [38]. It should be noted that pneumococcal vaccination of children has been associated with a decrease in lower respiratory tract infections caused by influenza, parainfluenza, RSV, and human metapneumovirus [39, 40]. Thus, although data are lacking specifically in the cancer patient population, recent data suggest that viruses may predispose to subsequent bacterial infection and that bacteria and viruses are commonly coidentified in pneumonia.

Additional baseline epidemiological risk factors related to the underlying malignancy should be assessed. For example, a lung cancer patient with underlying chronic obstructive pulmonary disease (COPD) with multiple prior COPD exacerbations is at risk for different pulmonary pathogens than are hematological malignancy patients. In addition to the specific tumor, the stage of the malignancy can also be helpful in suggesting potential oncology-related risk factors. For example, a patient with known brain metastases is at a higher risk of aspiration pneumonia than a patient without metastatic disease. Other risk factors for aspiration include impaired swallowing (especially with head and neck cancer), altered mental status, and procedures requiring sedation [41, 42].

Several points bear particular emphasis. First, immune deficits can occur from the underlying hematological malignancy (e.g., multiple myeloma) which can result in a deficit in humoral immunity which increases the risk of encapsulated organisms *S. pneumoniae* and *H. influenzae*. Second, strategies used to diagnose or
treat the underlying malignancy can also increase the risk of pneumonia due to certain pathogens. For example, although uncommonly performed, splenectomy is strongly associated with an increased risk of infection with encapsulated organisms. Prolonged administration of steroids can increase the risk of invasive fungal pathogens and *Pneumocystis jiroveci* pneumonia (PCP). Administration of anti-lymphocyte antibodies can result in severe depletion of CD4 cells, placing patients at risk of cell-mediated infections and reactivation of latent infections. It is increasingly being recognized that delayed lymphocyte reconstitution (perhaps as a marker of delayed reconstitution of certain lymphocyte populations) can significantly impact recovery from certain viral infections such as adenovirus [43]. The depth and duration of neutropenia that occurs during chemotherapy directly increases the risk of bacterial and fungal infections—*Aspergillus* most notably. Finally, the impairment of mucosal defenses due to the cytotoxicity of chemotherapy can also increase the risk of invasive bacterial pathogens and impair mucous clearance from the respiratory tract, further increasing the risk of invasive respiratory tract infections.

### 4 Stem Cell Transplant Risk Factors

Engraftment, particularly CD4+ cell engraftment, is better with peripheral blood stem cell transplantation (SCT) than with bone marrow transplantation (BMT) with fewer fungal, bacterial, and viral infections occurring after transplantation [44]. Despite these improvements, pneumonia frequently complicates SCT. The two most important factors impacting the risk of infection after transplantation are the presence or absence of GVHD and the time from transplantation [45]. Classically, during the pre-engraftment period (usually less than 2–6 weeks), bacterial infections, *Candida, Aspergillus*, and HSV are among the most common pathogens [45]. After engraftment until about 100 days from SCT, the impact of deficient cell-mediated immunity results in an increased risk of CMV, PCP, and *Aspergillus* infections [45–48]. In the late phase (after about 100 days), reactivation of CMV and VZV, and infections with encapsulated bacteria (e.g., pneumococcus) are most common and the risk correlates with the severity of prior GVHD [45]. Additionally, development of invasive *Aspergillus* infections >6 months after transplantation has been associated with chronic GVHD and prior CMV disease [46]. Notably, the risk of serious illness from respiratory viruses remains elevated throughout transplantation [45].

There are also other important factors impacting the risk of infection after transplantation. Allogeneic SCT recipients are at a higher risk of infectious complications than are autologous SCT recipients [45]. It is uncommon for autologous SCT recipients to have infectious complications after 3 months, while allogeneic SCT recipients continue to have measurable humoral, cell-mediated, and reticuloendothelial system deficits [49, 50]. Receipt of HLA-mismatched or unrelated donor transplants are also independent risk factors for latent viral
reactivation and invasive fungal disease [45, 48]. The impact of T-cell depletion with a monoclonal anti-CD52 antibody (alemtuzumab) upon subsequent risk of reactivation of latent infections such as CMV and development of new infections should not be underestimated [46, 47, 51, 52]. Prior CMV is a major risk factor for subsequent invasive fungal disease [46, 53, 54]. Other important risk factors for invasive aspergillosis after engraftment include GVHD, receipt of corticosteroids, neutropenia, lymphopenia, and respiratory virus infections [45, 46]. While hospitalized, patients remain at risk of nosocomial acquisition of respiratory viruses such as influenza, parainfluenza, RSV, and adenovirus, which have been known to cause large outbreaks in transplant centers [55–58]. The seasonality of these viruses appears to closely approximate that of the healthy population [59].

5 Organisms Causing Pneumonia in Cancer Patients

Common and uncommon organisms responsible for pneumonia in cancer patients are outlined in Table 2. Cancer patients are a heterogeneous group of individuals who may have pathogens that may closely resemble the organisms observed in patients with CAP [14], hospital-acquired pneumonia (HAP) [13], or pneumonia in immunosuppressed patients [60]. For example, a prostate cancer patient on hormonal therapy or an outpatient with colon cancer on 5-fluorouracil with no prior bone marrow suppression is likely to have pathogens that mirror those of CAP. In contrast, a surgically complicated colon cancer patient requiring a prolonged stay in the surgical intensive care unit and mechanical ventilation will be predisposed to pathogens that are commonly observed in HAP. A SCT recipient who develops pneumonia while neutropenic can be infected by pathogens observed in immunosuppressed patients, but could have pathogens more like a patient with HAP if the pneumonia develops during hospitalization or even CAP if the patient is >1 year out from SCT with immune reconstitution with no underlying GVHD. As well, the organisms causing aspiration pneumonia should be considered in patients with cancer for whom either comorbid conditions or medication use places them at a heightened risk of aspiration (e.g., alterations in mental status, mucositis, narcotic, and benzodiazepine use). One recent study documented that 15% of cancer patients who underwent bronchoalveolar lavage (BAL) had multiple pathogens identified [2]. Thus, physicians caring for cancer patients with pneumonia should carefully consider potential pathogens.

Of particular importance is the consideration of prior microbiological isolates identified in a patient and prior anti-infective therapy. Adherence to trimethoprim–sulfamethoxazole (TMP-SMX) prophylaxis greatly decreases the risk of PCP. Other prophylactic regimens for PCP are generally not as effective and also lack the protection that TMP-SMX provides against some bacteria and *Nocardia* [45, 61]. Prior antibiotic administration with broad-spectrum agents places patients at risk of infection with a drug-resistant pathogen. For example, prior levofloxacin administration has been previously associated with acquisition of fluoroquinolone-
| Common viral pathogens | Common bacterial pathogens | Common fungal pathogens |
|------------------------|---------------------------|------------------------|
| Influenza              | *Streptococcus pneumoniae* | Molds                  |
| A (H3N2 endemic)       | *Haemophilus influenzae*  | *Aspergillus* spp.     |
| A (H1N1 endemic)       | *Moraxella catarrhalis*   | *Mucormycoses*         |
| B                      | *Staphylococcus aureus*   | *Alternaria*           |
| 2009 H1N1 (epidemic)   | Methicillin susceptible   | *Cladosporium*         |
| Respiratory syncytial virus | Methicillin resistant   | *Scedosporium*         |
| Human metapneumovirus  | *Streptococcus pyogenes*  | *Fusarium*             |
| Parainfluenza, types 1-3 | Other *Streptococcus* spp. | *Penicillium*         |
| Adenovirus             | Group B streptococci      | Yeasts                 |
| Rhinovirus             | Group G streptococci      | *Candida* spp. (almost always embolic) |
| Herpes simplex virus, types 1 and 2 | Viridans group streptococci | *Cryptococcus*         |
| Cytomegalovirus        | *Enterobacteriaceae*      | *Pneumocystis* jerovechi (PCP, PJP) |
| Varicella zoster virus | *Escherichia coli*        | *Dimorphic fungi*      |
| Ebstein-Barr virus (as a cause of PTLD) | *Klebsiella pneumoniae* | *Histoplasma* capsulatum |
| Human herpesvirus 6    | *Pseudomonas aeruginosa*  | *Coccidioides* immitis |
| Human coronaviruses (e.g., NL63, HKU-1) | *Acinetobacter baumannii* | *Uncommon other pathogens* |
|                       | *Mycoplasma pneumoniae*   | *Severe acute respiratory syndrome (SARS)* |
|                       | *Chlamydiophila pneumoniae* | Avian influenza      |
|                       | *Legionella* spp.         | *Rubeola* (measles)    |
| Oral anaerobes (especially with aspiration) |                    |                        |

(continued)
| Pathogen/Microbial Group                        | Common Cause                                                                 |
|-----------------------------------------------|------------------------------------------------------------------------------|
| **Prevotella spp.**                            | Hantavirus                                                                   |
| **Fusobacterium spp.**                         | Mycobacterium kansasii                                                       |
| **Polymicrobial**                              | Mycobacterium avium intracellulare (MAC)                                     |
| **Actinomyces**                                |                                                                              |
| **Common acid fast pathogens**                 | Blastomyces dermatidis                                                      |
| **Mycobacterium tuberculosis**                 | Strongyloides stercoralis                                                    |
| **Nocardia spp.**                              | Toxoplasma gondii                                                            |
| **Uncommon bacterial pathogens**               |                                                                              |
| *Neisseria meningitidis* (especially serogroup Y) |                                                                              |
| *Bordetella pertussis*                         |                                                                              |
| *Chlamydia psittaci*                           |                                                                              |
| *Coxiella burnetii* (Q-fever)                  |                                                                              |
| *Yersinia pestis*                              |                                                                              |
resistant *S. pneumoniae* infections [62, 63]. Prior administration of an antiviral such as acyclovir, ganciclovir, or oseltamivir may substantially decrease the risk of infection, but if infection occurs, it may be due to a drug-resistant viral pathogen [48, 64]. Multiple authors have documented that prior administration of voriconazole in SCT recipients is a risk factor for breakthrough fungal infections due to mucormycosis (*Rhizopus*) [65–67].

Herpes simplex virus (HSV) infections can occasionally involve the lung. Since HSV can reactivate in up to 70% of BMT recipients [68], it is recommended that acyclovir prophylaxis be administered to all SCT recipients until engraftment occurs and mucositis resolves [49]. It is important to consider HSV as a potential pathogen of the lungs, particularly in patients with perioral lesions or mucositis. Although HSV can be identified from bronchial fluid by PCR, it is not routinely tested for by most molecular laboratories. Viral culture, rapid shell vial, and DFA tests all can easily identify HSV. Treatment is with high-dose acyclovir. Resistance to acyclovir can occur through mutations in the thymidine kinase gene and rarely through mutations in the HSV DNA polymerase [48]. Alternatives include the nephrotoxic medications foscarnet and cidofovir, although occasionally resistance to these can develop [69, 70] (See Chapter Antimicrobial Agents, Drug Adverse Reactions and Interactions, and Cancer).

CMV, and particularly CMV pneumonitis, had previously been the most common cause of death in BMT recipients [71], but has declined with aggressive monitoring and treatment of CMV reactivations. Consistently identified risk factors for CMV disease include CMV seropositivity, GVHD, lymphopenia, and use of alemtuzumab [47, 72–74]. CMV establishes latency; thus, isolation of CMV by viral culture from peripheral sites (e.g., nasopharyngeal, urine, and stool) is poorly predictive in identifying patients who will develop subsequent invasive CMV disease, and some patients who developed disease before peripheral cultures had enough time to grow [75, 76]. Although CMV pp65 antigen testing of blood resulted in more rapid identification, it was limited by the need for large blood volumes and could not be used in neutropenic patients [43]. The advent of PCR testing of the blood has further improved the detection of CMV in neutropenic patients and has been associated with improved survival over viral culture [43]. After treatment of patients for CMV, the physician should remain aware that the risk of subsequent bacterial and fungal infections is substantially increased [53, 54, 77, 78].

The epidemic of 2009 novel H1N1 dramatically impacted hospital admissions during the spring and fall of 2009. It has the capacity to replicate within human lung tissue and can cause a diffuse viral pneumonitis that can be associated with severe hypoxemia, ARDS, and sometimes multisystem organ failure [79–81]. Very few cases of severe illness occurred in patients >60 years of age [81, 82], but underlying immunosuppression was present in about 15% of patients with 2009 H1N1 disease requiring hospitalization [82]. A retrospective single cancer-center study conducted on May–June 2009 noted that 2009 H1N1 occurred more commonly among patients with an underlying hematological malignancy than among those with solid tumors [83]. Over 90% of patients presented with cough and
fever [83]. Thirty-seven percentage of patients required hospitalization, and 27 % of those that were assessed with radiographs had lower respiratory tract disease [83]. Almost all of these patients received neuraminidase therapy, 86 % received this on clinical presentation, and none of these patients required mechanical ventilation or died due to 2009 H1N1 disease [83]. Early administration of oseltamivir to patients who have 2009 H1N1 influenza has been associated with better outcomes and lower risk of death [81, 82]. Thus, when influenza is occurring in the community, empiric therapy for influenza should be instituted in patients with compatible symptoms awaiting results of testing [81]. Additionally, therapy should be continued in patients with negative testing if severe or progressive disease exists until an alternative diagnosis is established due to PCR being falsely negative in ~ 10 % of specimens [81]. Notably, >1/3 of healthy patients will continue to shed 2009 H1N1 or seasonal influenza by PCR for >7 days after onset of illness; viral shedding may be even more prolonged in hospitalized patients or patients with underlying immunosuppression [81, 84–86]. It is uncertain whether detectable influenza genetic material represents viable replicating virus [84]. Delayed viral clearance has been associated with late initiation of oseltamivir [81, 84, 85] and has been associated with comorbidities and with prolonged hospital stays [85].

6 Imaging

Chest radiography (chest X-ray) is necessary for the routine evaluation of patients suspected of having pneumonia due to its superior sensitivity and specificity over that of physical examination [14]. It is recommended in cancer patients that are febrile, neutropenic, and have any respiratory signs or symptoms [87]. It can be useful in suggesting other potential etiologies (e.g., congestive heart failure) and pathogens. Interstitial or peribronchial infiltrates are classically associated with viral pathogens, while lobar or alveolar infiltrates are more frequently seen with bacterial pathogens; however, substantial overlap exists. About 70 % of children with documented bacterial pneumonia will have airspace disease [8]. In children with influenza that have pulmonary infiltrates, up to 50 % may have an alveolar component to their infiltrate [88]. With 2009 H1N1 influenza, radiographic findings commonly included diffuse mixed interstitial and alveolar infiltrates [81]. In patients with bacterial superinfection of 2009 H1N1, lobar and a multilobar distribution can occur [81]. Chest radiography can also help identify a complicated pneumonia—usually defined as necrotizing pneumonia, lung abscess, loculated pleural fluid, or empyema. Presence of an effusion suggests a bacterial process—particularly *S. pneumoniae*, *S. aureus*, or *S. pyogenes*. Lateral decubitus films are useful in determining whether an effusion associated with pneumonia is free-flowing or loculated (suggested by failure of the fluid to move to the dependent region of the chest with changes in position). Chest X-rays are particularly limited in the early detection of pneumonia in patients with cancer, particularly when
obtained in the supine position [89]. It is also well known that a delay in chest X-ray appearance of pneumonia can occur; thus, patients who have a high clinical suspicion of pneumonia should be treated presumptively for 24–48 h before repeating the chest X-ray [14].

High-resolution CT scanning has improved sensitivity and specificity for pneumonia over that of chest X-ray in patients without underlying cancer [90]. The sensitivity of chest X-ray in comparison with CT scan has been shown to be about 50 % [89]. In one study, the use of high-resolution CT scanning resulted in a median increase of 5 days in the time of detection of a pulmonary infiltrate over that of using chest X-rays alone [91]. Importantly, in those with a negative high-resolution CT scan, no individuals developed an inflammatory lung lesion within the next 5 days and <10 % developed an inflammatory lung lesion within the next 20 days [91]. CT angiography can help in the evaluation of pulmonary embolism which is also common in oncology patients while still proving substantial information about the lung parenchyma and mediastinal lymphadenopathy. Although classic findings on CT imaging include consolidation with bacterial disease, nodules with fungal disease, a perihilar ground glass opacity with PCP, and a mosaic pattern of ground glass opacities with viral disease, these findings are nonspecific and not diagnostic [89]. CT can be helpful in suggesting noninfectious etiologies (e.g., radiation pneumonitis, drug toxicity, malignancy) and in providing precise localization of the infiltrate for subsequent diagnostic procedures [89].

Certain characteristics are strongly associated with invasive Aspergillus in the setting of neutropenia. These findings include the presence of a halo sign, which is an area of hemorrhage around a nodular lesion, or the presence of an air-crescent sign [92, 93]. These findings are strongly suggestive of Aspergillus, but can also occur in infections with Pseudomonas aeruginosa, Nocardia, zygomycetes, Fusarium, and scedosporium [92, 94]. These classic findings are not the most sensitive findings observed with invasive pulmonary aspergillosis. In a large multicentered study of invasive Aspergillus, 95 % had at least one macronodule (defined as ≥1 cm), 61 % had a halo sign, 30 % had consolidation, 27 % had an infarct-shaped macronodule, 20 % had cavitation, and only 10 % had an air-crescent sign [94]. Interestingly, a good prognostic sign is the finding of a halo sign, which correlated with improved response to therapy and survival [94].

Other imaging tests may be appropriate depending on the clinical setting to exclude other diagnoses. For example, brain natriuretic peptides (BNP) or echocardiography may be beneficial in individual patients in excluding congestive heart failure. Transesophageal echocardiography is more sensitive than transthoracic echocardiography for endocarditis and should be used in adult patients in whom endocarditis is being strongly considered in the differential diagnosis [95].
7 Diagnostic Strategies

The gold standard for the diagnosis of pneumonia requires sampling of respiratory tract tissue and identifying pathogens by tissue culture or on histopathological examination. However, an invasive diagnostic strategy is usually unnecessary or not feasible due to its attendant risks in cancer patients (e.g., risk of infection and bleeding). It should be recognized that *S. pneumoniae* is considered the predominant pathogen in CAP; it is identified in about 2/3 of bacteremic pneumonia [3, 96]. A recent study using transthoracic lung aspiration has confirmed this finding [97]. Some evidence suggests that although *Mycoplasma pneumoniae* and *Chlamydiophila pneumoniae* are relatively common causes of pneumonia in outpatients, they are infrequently observed in patients with severe disease in whom *S. aureus*, *Legionella* species, and gram-negative bacilli are more frequently observed [3]. This may be even truer in patients with underlying cancer who require hospitalization for pneumonia.

In general, more aggressive diagnostic strategies are necessary in patients with cancer than in patients without cancer who present with a routine pneumonia. This is due to the higher likelihood of alternative diagnostic possibilities (e.g., metastatic malignancy). As well, unusual pathogens (e.g., PCP, tuberculosis) and multidrug-resistant pathogens occur with a higher frequency. A higher rate of clinical failure and mortality has been observed in patients with pneumonia that are not initiated on appropriate antimicrobial therapy [13, 14, 98–101]. In another study of 200 immunocompromised patients (140 of which had either hematological malignancy or SCT), mortality was associated with SCT (53 % vs. 33 %), requirement of mechanical ventilation (odds ratio [OR] of 28), an APACHE II score of $\geq 20$ (OR 5.5), and a delay of $\geq 5$ days in establishing a specific diagnosis (OR 3.4) [102].

7.1 Noninvasive Testing Modalities

Tables 3 and 4 outline routine and supplemental testing that may be of potential benefit in patients with underlying malignancies who present with pneumonia. Although blood cultures identify a pathogen in 5–14 % of patients with CAP [3, 14], these are particularly important in patients with underlying malignancies in whom other etiologies (e.g., central line infection with embolic lung lesions) must be considered. Sputum cultures, although not universally recommended [3], are likely to be of higher benefit in patients with underlying malignancies in whom common pathogens are less frequently observed. Obtaining sputum for culture prior to antibiotic administration increases the yield. In particular, they can be helpful in identifying pathogens that empiric coverage may not have adequately covered (e.g., MRSA, a drug-resistant gram-negative rod).

A number of tests for the presence of antigens have been developed for identifying fungal and bacterial pathogens. Several important caveats exist for antigen
| Assay                     | Sensitivity | Specificity | Time  | Cost | Expertise required | Pathogens commonly tested                                      | Important limitations                                                                 |
|-------------------------|-------------|-------------|-------|------|-------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Viral culture           | +++         | ++++        | –     | –    | +                 | HSV, CMV, VZV, influenza, RSV, parainfluenza                     | This will routinely miss human metapneumovirus and many rhinoviruses                     |
| Rapid shell vial        | +           | +++         | +     | +    | –                 | HSV, CMV, VZV, influenza, RSV, parainfluenza                     | This will routinely miss human metapneumovirus and many rhinoviruses                     |
| Rapid antigen           | –           | +++         | ++++  | +++  | +++++             | Influenza, RSV                                                   | This assay will only detect the virus for which antigen is specifically tested. Recent literature suggests less sensitive in adults as they are in children and poor sensitivity in detecting 2009 H1N1 influenza |
| DFA                     | ++          | +++         | ++++  | ++   | –                 | HSV, VZV                                                        | This assay will only detect the virus for which antigen is specifically tested          |
| ELISA/EIA               | +++         | ++++        | ++++  | +    | –                 | Any respiratory virus                                           | Rarely used                                                                             |
| CMV pp65 antigenemia    | ++          | +++         | ++++  | +    | –                 | CMV                                                             | Extensive supportive literature correlation with active disease. It is limited by requiring that the patient not be neutropenic |
| PCR/RT-PCR              | ++++        | ++ ±        | ++ ±  | –    | –                 | Testing for all viruses is possible                           | Each virus requires molecular amplification (if not specifically tested for, it will be missed). Correlation of a positive test with active disease may be lacking (nucleic acid may remain longer than infectious or actively replicating virus). This is the current gold standard test, but laboratory contamination is always a possibility |

*DFA* direct fluorescent antibody, *ELISA/EIA* enzyme-linked immunosorbent assay/enzyme immunoassay, *CMV* cytomegalovirus, *PCR/RT-PCR* polymerase chain reaction/reverse transcription–polymerase chain reaction, *HSV* herpes simplex virus, *VZV* varicella zoster virus, and *RSV* respiratory syncytial virus. Modified from Anderson EJ. Viral diagnostics and antiviral therapy in hematopoietic stem cell transplantation. Current pharmaceutical design 2008; 14:1997–2010. With permission from Bentham Science Publishers.
| Table 4  | Diagnostic tests for oncology patients with possible pneumonia |
|----------|---------------------------------------------------------------|
| **Initial laboratory testing** | **Additional baseline laboratory tests to consider** |
| CBC with manual differential | Nasal or nasopharyngeal specimen for extended viral testing for human metapneumovirus, adenovirus, rhinovirus, parainfluenzavirus |
| Comprehensive metabolic panel | Sputum fungal stain and culture |
| Blood cultures | Sputum AFB stain and mycobacterial culture |
| Minimum of 2, more if endocarditis is suspected | Urinary *Histoplasma* antigen |
| Urinalysis and urine culture | Urinary *Blastomyces* antigen |
| Chest XRAY (PA and lateral views) | Urinary *Coccidioides* antigen |
| Sputum culture for bacterial culture | Fungal serologies (lower yield than urinary antigens) |
| Useful specimen if >25 WBC/hpf and <10 epithelial cells/hpf observed | Serum cryptococcal antigen |
| Nasal or nasopharyngeal specimen for viral PCR testing (for influenza and RSV) | *Strongyloides* serology and stool examination for ova and parasites |
| *Streptococcus pneumoniae* urinary antigen | |
| *Legionella* urinary antigen (serogroup 1) | |
| *Aspergillus* galactomannan assay | |
| CMV pp65 or CMV PCR from blood\(^a\) | |
| If bronchoalveolar lavage or lung tissue is obtained | If pleural fluid is obtained |
| Gram stain and quantitative bacterial culture | pH\(^c\) |
| *Legionella* DFA and culture | LDH\(^c\) |
| KOH stain and fungal culture | Protein\(^c\) |
| AFB stain and mycobacterial culture | Glucose\(^c\) |
| Viral culture (rapid shell vial culture) or Extended viral PCR testing | Cell count with differential |
| PCP DFA assay | KOH stain and fungal culture |
| *Aspergillus* galactomannan assay | AFB stain and mycobacterial culture |
| 16S ribosomal RNA sequencing\(^b\) | *Legionella* DFA and culture |

(continued)
tests. First, all of the antigen tests have sensitivities that are <90 % and some much less than this. Thus, they should not be viewed as tests that can “rule out” the presence of a pathogen. Second, the antigen tests are most sensitive before or shortly after initiation of treatment with an agent that has activity against the specific pathogen. These tests generally become negative fairly quickly and in some cases (e.g., histoplasmosis) can be used to gauge response to therapy. Finally, these tests are more sensitive in the setting of disseminated disease than in pneumonia alone.

Urinary antigen assays for Legionella (70 % sensitivity, >90 % specificity for serogroup 1) and S. pneumoniae (60–90 % sensitivity with approaching 100 % specificity) should be obtained from patients who have failed outpatient antibiotic therapy, those with pleural effusions, and those requiring intensive care admission for pneumonia [3, 14]. It should be recognized that many other Legionella species can cause pneumonia but are not detected by the urinary antigen; to diagnose these species, culture or PCR of respiratory specimens is necessary. In patients at risk of endemic fungal disease, urinary antigen tests exist for histoplasmosis, blastomycosis, and coccidioidomycosis that have excellent sensitivities but some risk of cross-reaction with other fungal pathogens including other endemic fungi and Penicillium [103–107]. Response to therapy can be followed by obtaining serial specimens for some of these urinary antigen tests [103].

Serum antigen tests also exist but are limited to evaluation for certain invasive fungal pathogens. First, the cryptococcal latex antigen test is widely available and should be considered in patients with cell-mediated immunity deficits. An antigen test (Fungitell BG, Associates of Cape Cod, East Falmouth, Mass.) was developed to detect (1→3)-β-D-glucan which is a cell wall component of Aspergillus and most other fungi [108]. Thus, it is not specific for Aspergillus and has been found to be positive in patients with candidemia and with cryptococcosis, fusariosis, PCP, and histoplasmosis [109–112]. The sensitivity of this test for Aspergillus has ranged from 50 to 100 % with a specificity that ranges from 44 to 98 % [108, 111]. In clinical practice, the (1→3)-β-D-glucan assay was not found to be helpful in discriminating fungal from bacterial infections in the intensive care unit setting.
Even in healthy populations, a false-positive rate of 7–20% has been observed, which may be even higher in populations at risk for invasive fungal infections [108]. False positives have also been observed with certain medications, following hemodialysis, with use of IV tubing filters, with administration of albumin or immunoglobulin, and after exposure to gauze [108, 111]. Additionally, echinocandins interfere with (1→3)-β-D-glucan synthesis and administration of an echinocandin (e.g., caspofungin, micafungin, anidulafungin) may be associated with a falsely negative assay [110].

Another antigen test, the Platelia (BioRad Laboratories, Redmond, WA) Aspergillus enzyme immunoassay has a sensitivity of 79–96% and specificity of 74–99% for invasive aspergillosis when performed on blood specimens [108]. The best cutoff for the Aspergillus galactomannan test to optimize sensitivity while maintaining a high degree of specificity has been an area of intensive investigation. Obtaining the Aspergillus EIA twice weekly with ≥2 samples ≥0.5 to 1.0 can result in earlier diagnosis of invasive pulmonary aspergillosis [114, 115]. Unfortunately, false-negative and false-positive results can occur with the Aspergillus galactomannan test. Administration of piperacillin–tazobactam is associated with false-positive tests, which may be due to galactomannan being carried through the drug production processing stages from Penicillium [116, 117]. False-positive tests have also occurred after receipt of other Penicillium-derived antibiotics including amoxicillin and ticarcillin both with and without a beta-lactamase inhibitor [108]. Additionally, false-positive tests have occurred in patients infected with all of the endemic fungi, and with Fusarium, Rhodotorula, Trichophyton, Penicillium, Paecilomyces, and Alternaria species [108, 116, 118]. Plasmalyte (Baxter Healthcare Corporation), an electrolyte replacement solution containing sodium gluconate produced by Aspergillus flavus, has also been associated with false-positive Aspergillus galactomannan tests [108, 119]. Probably the most frequent cause of a false-negative Aspergillus galactomannan test is the administration of mold-active antifungal therapy. Marr et al. demonstrated that the sensitivity of the galactomannan test fell from 89 to 52% in patients receiving mold-active antifungal therapy [120]. False-negative results have also been noted in patients who have localized Aspergillus infections [108].

The diagnosis of invasive fungal infections is difficult in patients with cancer or SCT, resulting in the European Organization for Research and Treatment of Cancer and Mycoses Study Group setting guidelines for definitive, probable, and possible invasive fungal infections [121]. In part, this is due to the difficulty that exists in obtaining a tissue diagnosis which would prove invasive fungal disease. In general, host factors predisposing the patient to fungal infection (e.g., neutropenia, GVHD), clinical features of fungal infection (e.g., CT imaging showing a halo sign or an air-crescent sign, sinusitis), and mycological evidence of infection (e.g., positive antigen test, positive culture) all must be present to demonstrate a probable case of invasive fungal disease [121]. In clinical practice, many cases are possible cases and this should not dissuade the clinician from treating for invasive fungal disease since these guidelines were primarily written to help develop common research definitions [121].
In a retrospective study from M.D. Anderson, clinical characteristics and risk factors were able to separate pulmonary zygomycosis from invasive pulmonary aspergillosis. Risk factors for zygomycosis infection included voriconazole prophylaxis (OR 7.76), concomitant sinusitis (OR, 25.7), ≥10 pulmonary nodules (OR, 19.8) and pleural effusion (OR, 5.07) on initial CT scan [66]. The authors did not observe a difference on CT scan in other findings commonly associated with pulmonary mold infections such as masses, cavities, halo signs, or an air-crescent sign [66]. In another study from the same group, sinus involvement alone or in combination with pulmonary disease strongly suggested invasive zygomycosis in comparison with Aspergillus [67].

Commonly performed viral testing strategies are outlined in Table 3. In the past several years, there has been increasing realization of the poor sensitivity of most rapid antigen tests in identifying viral pathogens [29, 81] and an increased reliance upon the use of PCR [43, 59, 122, 123]. In the past, many “home-brew” PCR-based assays were used at various centers [43]. In many centers, PCR is available for testing for the most common respiratory pathogens (e.g., influenza and RSV) and for CMV. Some centers also have access to the FDA-approved XTAG Respiratory Viral Panel (Luminex Corp, Austin, TX) which has the ability to test for influenza A, B, RSV A and B, parainfluenza types 1–3, adenovirus, human metapneumovirus, and rhinovirus [43]. Real-time PCR provides more rapid results that are quantitative and can also detect multiple viruses simultaneously [43]. In a recent retrospective study of SCT recipients, quantitative PCR viral load of respiratory virus RNA from BAL specimens did not correlate with subsequent mechanical ventilation or death [124]. In contrast, 5/6 patients from the same study, who had viral RNA detected in serum specimens, died. In a multivariate analysis, detection of viral RNA in serum was associated with an adjusted relative risk of death within 30 days of 1.8 in comparison with those who were not viremic [124]. These results remain to be confirmed, but could provide useful prognostic information in the future. Several caveats to PCR testing for viral pathogens should be emphasized. PCR identification of a virus may indicate recent infection but not active disease. Data for this are lacking in cancer patients, but in healthy infants, prolonged shedding of RSV by real-time PCR has been observed (20–30 days after symptoms begin) [43, 125]. Although PCR is considered the gold standard for the diagnosis of 2009 H1N1, PCR specimens from both the upper and lower respiratory tracts have been falsely negative in about 10% of patients [81]. In addition, cross-contamination of samples can easily occur with PCR, resulting in false-positive tests. Thus, PCR results should always be viewed in the context of the clinical scenario of the patient and additional respiratory specimen types should be obtained in a patient in whom the clinical impression is discordant with the test results [81].

Finally, screening for tuberculosis can now be performed either with PPD skin test or through a new blood test called the interferon-gamma release assay (IGRA). In the test, the patient’s blood is mixed in vitro with tuberculosis-specific antigen that then results in the release of interferon gamma from any T cells that have previously been exposed to tuberculosis. The benefit of this test is that there is not
the potential for cross-reaction in patients who have previously been exposed to BCG vaccine (administered routinely in countries of the world in which tuberculosis is endemic). It should be recognized that a PPD is least sensitive for detecting prior tuberculosis disease when the patient is actively infected with tuberculosis. For example, in a study from Africa of TB and HIV-infected patients, the IGRA was 65 % sensitive, while the PPD was 31 % sensitive [126]. Both PPD and IGRA were least sensitive in those with CD4 counts < 200 [126]. Data regarding use of the IGRA are lacking in patients with active tuberculosis and cancer. Thus, neither a negative PPD nor a negative IGRA rules out the possibility of active tuberculosis. Instead, anyone suspected of having active pulmonary tuberculosis should immediately be placed in negative pressure isolation and undergo sputum evaluation for tuberculosis.

7.2 Invasive Diagnostic Testing

Obtaining an etiological diagnosis can also be helpful in avoiding prolonged broad-spectrum antibiotic administration, avoiding antibiotic toxicity, and decreasing the risk of bacterial superinfections (e.g., Clostridium difficile). Thus, an unusual clinical presentation, particularly severe pneumonia (e.g., necessitating ICU admission or intubation with mechanical ventilation), and failure to respond to initial empiric antimicrobial therapy within 48–72 h should all prompt aggressive diagnostic measures with attempts to obtain deep specimens or tissue early in the clinical course of pneumonia.

Several issues are frequently raised as objections to diagnostic procedures in this population. First, patients frequently have coagulopathies due to their underlying malignancy or chemotherapy. Second, concern may exist about risk of introducing infection in those who are immunosuppressed. Third, many patients are clinically unstable and at risk for needing more substantial respiratory support (either noninvasive mechanical ventilation or routine mechanical ventilation) after a procedure. Fourth, those in whom a diagnostic procedure is considered often have been pretreated with broad-spectrum empiric coverage. Thus, the yield from the procedure is often low. Finally, the procedures with the best yield are the most invasive and the most likely to result in complications.

Despite these frequent potential issues, obtaining a deep specimen or tissue can often be quite helpful. If all the cultures return negative, this can sometimes provide support for stopping empiric antibiotic escalation in a patient who is not doing well. It may also provide support for narrowing antibiotic administration (e.g., stopping empiric MRSA coverage or PCP coverage). It can also identify other noninfectious causes of fever and pulmonary infiltrates such as malignancy or pulmonary hemorrhage.

Unfortunately, no standard approach exists in the management of cancer patients needing a diagnostic procedure. A great deal of center-to-center variability exists in the way in which these patients are managed. Some centers have very
little experience with certain techniques, limiting their diagnostic options. The location of the patient’s infiltrate must also be considered. A peripheral, pleural-based nodule will not be very amenable to BAL but is likely to be easily reached by either an imaging-guided needle biopsy, or a video-assisted thorascopic (VAT) biopsy. In contrast, a perihilar or very medial lesion will be more amenable to BAL and less easily accessed by an imaging-guided needle biopsy or VATS.

Bronchoscopy with BAL is probably least invasive and can be combined with a protected sampling, but this does not increase yield [127]. Yield can approach 50% using BAL [127]. The combination of BAL with a transbronchial biopsy will improve the yield due to the tissue that is available for pathological review but requires a specially trained bronchoscopist and is associated with a higher risk of bleeding and pneumothorax [128]. BAL fluid can be tested for Aspergillus galactomannan where it has 91% sensitivity and 88% specificity when a cutoff of ≥1.0 was used [129]. It should be noted that like all antigen tests, its sensitivity may be impacted by effective treatment (patients receiving antimold therapy) [129].

In one study of open thoracotomies in patients with malignancies, a specific diagnosis was reached in 62% of those that underwent biopsies with a change in management made in 57% of patients after the procedure [130]. Infections, inflammatory disease (primarily cryptogenic organizing pneumonia), and malignancy had a similar contribution to those in which a specific diagnosis was reached [130]. Yield was better in those with a focal infiltrate, who were not on a ventilator, and who were not neutropenic [130]. Complications were seen in 13% of individuals [130]. An additional benefit to this approach is opportunity to directly visualize the lesion, send larger pieces for pathology, and drain any coexistent effusion for diagnostic and therapeutic purposes. A recent study of patients with a history of hematological malignancy that were found to have lung lesions that subsequently underwent CT-guided needle biopsy had a 60% diagnostic yield [131]. Since this study included a number of patients without evidence of infection, the yield of CT-guided needle biopsy may be lower in the setting of infectious pulmonary infiltrates.

In patients with severe pneumonia who require intubation, aspiration from the endotracheal tube shortly after intubation can provide important information in which it does not require patient cooperation and bypasses the upper airway-colonizing agents [14]. A regular bronchoscopy can be considered, or a technique available at some institutions is nonbronchoscopic BAL which appears to have a higher yield with less contamination than endotracheal aspiration [132, 133]. Such a specimen should be sent for all of the same studies that are routinely sent with bronchoscopy including viral testing, Legionella testing, PCP DFA, fungal testing, and cytology (see Table 4).

Pleural effusion has been associated with early nonresponsiveness to antimicrobial therapy and with ultimate clinical failure [100, 101]. Thus, the current CAP guideline recommendations are to perform a thoracentesis in all individuals in whom a pleural effusion is >5 cm in size on imaging [14]. In cancer patients, a thoracentesis can provide both diagnostic benefits by potentially identifying
pathogens and alternative diagnoses (e.g., metastasis) and therapeutic benefit by improving the lung–chest wall interaction. Risks include bleeding and pneumothorax.

Careful examination of the skin should be performed to identify any new or changing skin lesions. The skin can provide important information about some systemic infections. Infections due to Cryptococcus, Nocardia, Aspergillus, Pseudomonas, Fusarium, and mycobacteria can all spread to the skin from a pulmonary source. A skin biopsy which is minimally invasive can sometimes provide diagnostic information that would be difficult to obtain from the lungs.

Other sites that can sometimes also be helpful are the eyes and the sinuses. Endophthalmitis or retinal lesions can be suggestive of fungal disease. In addition to usual bacterial pathogens, both Aspergillus and mucormycosis can cause sinus disease. It should be noted, however, that sinusitis is much more strongly associated with zygomycosis infection than is Aspergillus [66].

8 Need for Hospital Admission

The approach to management of lower respiratory tract infections includes the decision whether hospitalization is necessary in an individual patient. Several severity scores have been developed for deciding which individuals with CAP should be admitted. The most common severity scores are the CURB-65 and the PORT score/pneumonia severity index (PSI). The CURB-65 scale does not take into account any underlying comorbidities, but instead gives a single point for each factor noted in clinical assessment: Confusion, elevated Urea Nitrogen, Respiratory rate (>30 breaths/min), low Blood pressure, and age >65 years. The points for each of these factors are then added together and are validated with 30-day mortality data. For patients with a score of 0, mortality is 0.7 %, 1 = 2.1 %, 2 = 9.2 %, 3 = 14.5 %, 4 = 40 %, and 5 = 57 % [3, 14]. Thus, patients with scores of 0–1 are often treated as outpatients, 2 is recommended to be admitted to the general medical wards, and ≥3 should be admitted to the intensive care unit [14]. It is important to realize that CURB-65 does not take into account patients with underlying malignancy in which mortality would be expected to be even higher. The PORT score or PSI is more complicated and requires addition of additional variables, but does take into account underlying renal disease, liver disease, and malignancy [14, 134]. Again, higher scores correlate with higher mortality. Forms for calculating both CURB-65 and the PSI are widely available both on the Internet and also as applications for PDAs. It is recommended that scoring systems should contribute to and not supersede clinical judgment [3]. Both severity scoring systems underestimate the mortality in patients with underlying malignancy and severity scoring system is validated neither in HAP/VAP nor in patients with neutropenia nor those who are severely immunocompromised.
### Treatment

Appropriate empiric antimicrobial coverage is crucial to optimizing outcomes in patients with cancer and pneumonia. Prior recent antibiotic administration should be taken into account when choosing an empiric antibiotic regimen for pneumonia. Patients receiving fluoroquinolone prophylaxis should not be treated empirically with a fluoroquinolone if they become ill [87]. In addition, prior colonization with multi-drug-resistant pathogens should be taken into account in empiric coverage. For example, prior colonization with MRSA should prompt empiric coverage with an agent known to be active this pathogen (e.g., vancomycin, linezolid). It should be noted that daptomycin is not effective in the treatment of pneumonia which may be due to binding of the drug by surfactant in the lungs [135]. Additionally, recent drug-resistant microbiological isolates (e.g., carbapenem-resistant *Acinetobacter baumannii* or carbapenem-resistant *Klebsiella pneumoniae*) identified from a patient should prompt the physician to modify empiric antibiotics to include drugs that will include the drug-resistant pathogen(s).

In those patients that have had minimal antimicrobial exposure and health care contact, empiric coverage with a regimen to cover CAP in a patient being admitted may be appropriate (e.g., respiratory fluoroquinolone or an intravenous β-lactam plus a macrolide) [14]. Outpatient therapy options would be the same choice of a respiratory fluoroquinolone or of an oral β-lactam plus a macrolide [14]. In those who meet criteria for HCAP, HAP, or VAP, risk factors for drug resistance usually exist. Empiric coverage with an antipseudomonal β-lactam or carbapenem plus either an antipseudomonal fluoroquinolone or an aminoglycoside plus an agent active against MRSA (vancomycin or linezolid) is warranted [13]. In the setting of neutropenic fever, empiric coverage will usually appear fairly similar to that of the HAP/VAP guidelines although coverage with an agent active against atypical organisms is important for those being admitted from home (e.g., levofloxacin or a macrolide). Empiric coverage for aspiration may also be necessary or for influenza, depending on the time of year. In the setting of MDR pathogens such as carbapenem-resistant *A. baumannii* or carbapenem-resistant *K. pneumoniae*, consultation with a local infectious disease specialist is encouraged to help make recommendations based on the local antibiotic sensitivity patterns.

As previously discussed, failure to respond to empiric therapy should lead to a reconsideration of the diagnosis and more aggressive invasive diagnostic testing. When possible, it is important to narrow the antibiotic coverage to avoid placing the patient at risk for colonization with new MDR pathogens or infection with *C. difficile*. In those in whom a reduction in immunosuppression can be achieved, this should be considered when appropriate. Administration of chemotherapy may need to be delayed until the acute infection resolves.

In the treatment of CMV pneumonitis, induction doses of IV ganciclovir are recommended. Some use the combination of high-titer CMV-IVIG with ganciclovir since an improvement was noted in comparison with historical controls in outcomes [43].
In cancer patients with influenza (who are usually immunosuppressed), duration of administration should be 10 days instead of 5 [81]. In patients with pneumonia or progressive disease, a higher dose (150 mg given twice daily) should be considered [81]. Additionally, patients should be monitored for viral clearance and the development of oseltamivir resistance should be considered if the time to viral clearance is delayed [81]. Intravenous formulations of zanamivir and peramivir exist for patients with severe disease [81]. Development of oseltamivir resistance in 2009 H1N1 has been associated with immunosuppression, failed post-exposure oseltamivir prophylaxis, and prolonged administration of oseltamivir [81, 136]. Currently, almost all 2009 H1N1 disease that has accumulated oseltamivir resistance has remained susceptible to zanamivir which is more active than is peramivir against these oseltamivir-resistant isolates [81]. Notably, in the 2008–2009 season, almost all seasonal H3N2 disease was resistant to the adamantanes (amantadine and rimantadine). It is certain that the resistance in 2009 H1N1 and seasonal influenza will continue to change, and current recommendations should be reviewed prior to each influenza season (see www.cdc.gov/flu/).

Classically, empiric administration of antimold therapy has been recommended for patients with persistent neutropenic fever. This was driven by a number of older studies that suggested an increased mortality in patients in whom antifungal therapy was withheld [137]. Data demonstrating benefit with the early use of CT scan of the chest and the Aspergillus galactomannan test have resulted in some recent authors challenging the dogma of routine administration of mold-active antifungals to all patients with prolonged neutropenic fever [115, 137–140]. Limited data suggest that in those with a negative high-resolution CT scan, this strategy of withholding empiric antifungal therapy was not associated with an increased risk of invasive fungal infections or death [140]. This approach is not considered the current standard of practice as defined in the 2011 guidelines for the management of febrile neutropenia but is an interesting approach and an active area of research [87]. Empiric coverage with a mold-active agent such as liposomal amphotericin or an echinocandin is recommended [87]. Among those with neutropenia who actually have invasive fungal disease, a subset will get clinically worse usually as the neutropenia resolves and an acute inflammatory response occurs at the site of preexisting fungal infection. Usual therapy for fungal infections is otherwise outlined in Chapter Fungal Infections in Cancer Patients.

There is increasing recognition that prior treatment regimens for CAP of 7–14-day duration may not be necessary and may be associated with an increased risk of complications such as C. difficile [14, 141, 142]. Data for courses as short as 3 days with azithromycin or 5 days with a fluoroquinolone exist [6, 14, 141]. For ventilator-associated pneumonia randomized controlled trial data suggest that, for most pathogens, 8 days is sufficient, although patients with neutropenia, immunosuppressant, and long-term steroids were excluded from the trial [13, 143]. Notably, patients with nonfermenting gram-negative rods such as P. aeruginosa and A. baumannii had a higher risk of relapse with this approach [143]. Others
suggest that use of additional noninvasive tests such as procalcitonin, which is elevated in bacterial infections but not viral disease, may allow physicians to greatly shorten the duration of therapy for pneumonia [142]. Data for shortening the antimicrobial course are lacking in oncology patients. Guidelines recommend 7–14 days as appropriate for the infection or longer until the absolute neutrophil count is 500 cells and rising [87].

10 Outcomes

Evidence suggests 1-year mortality rates of 20–40 % in elderly patients without cancer admitted with CAP [144]. One would expect that the 1-year mortality rates would be higher in patients with underlying malignancy. As previously described, mortality is increased in patients with pneumonia that are not initiated on appropriate antimicrobial therapy [13, 14, 98, 99, 101]. In viral infections, delayed lymphocyte reconstitution and development of end-organ disease have been associated with worse outcomes [43, 51, 145–147]. In a prior study of severe CAP requiring ICU admission, being immunosuppressed (which included patients that had received radiation, chronic steroids, and those receiving cytotoxic therapy) was associated with a 2.25-fold increased risk of mortality on multivariate analysis [7]. Mortality has been 3.2-fold higher in those with cancer who develop VAP on multivariate analysis [98]. In a study of cancer patients who developed acute respiratory failure, almost 50 % died, and survival was associated with cardiogenic pulmonary edema and was very poor in anyone in whom mechanical ventilation was required [148]. Goals of care should be revisited in anyone not responding after the first 48–72 h of ICU care, particularly in the setting of progressive malignancy and need for mechanical ventilation since mortality is exceedingly high [148].

11 Conclusions

Respiratory tract infections occur commonly in cancer patients and contribute substantially to morbidity and mortality. Noninfectious infiltrates occur commonly in these patients and should be considered in the differential diagnosis. Recent molecular methods have improved our capacity to diagnose the pathogens responsible for pneumonia, but frequently empiric therapy is still necessary and should take into account the patient’s underlying risk factors for multi-drug-resistant pathogens, viruses, and fungi. Since many pathogens can cause disease in this population, in those not responding to empiric therapy, aggressive diagnostic testing and tissue sampling is necessary to help focus treatment modalities.
References

1. Heron M, Hoyert DL, Murphy SL, Xu J, Kochanek KD, Tejada-Vera B (2009) Deaths: final data for 2006. Natl Vital Stat Rep 57:1–134
2. Rolston KV, Bodey GP, Safdar A (2007) Polymicrobial infection in patients with cancer: an underappreciated and underreported entity. Clin Infect Dis 45:228–233 (An official publication of the Infectious Diseases Society of America)
3. File TM (2003) Community-acquired pneumonia. Lancet 362:1991–2001
4. Piccirillo JF (2004) Clinical practice. Acute bacterial sinusitis. New England J Med 351:902–910
5. McIntosh K (2002) Community-acquired pneumonia in children. New England J Med 346:429–437
6. Dunbar LM, Wunderink RG, Habib MP et al (2003) High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin Infect Dis 37:752–760 (An official publication of the infectious diseases society of America)
7. Bodi M, Rodriguez A, Sole-Violan J et al (2005) Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to infectious diseases society of America guidelines on survival. Clin Infect Dis 41:1709–1716 (An official publication of the Infectious Diseases Society of America)
8. Bradley JS, McCracken GH (2008) Unique considerations in the evaluation of antibacterials in clinical trials for pediatric community-acquired pneumonia. Clin Infect Dis 47(3):S241–S248 (An official publication of the Infectious Diseases Society of America)
9. Johansson N, Kalin M, Giske CG, Hedlund J (2008) Quantitative detection of Streptococcus pneumoniae from sputum samples with real-time quantitative polymerase chain reaction for etiologic diagnosis of community-acquired pneumonia. Diagn Microbiol Infect Dis 60:255–261
10. Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J (2010) Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis 50:202–209
11. Ruiz M, Ewig S, Marcos MA et al (1999) Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med 160:397–405
12. Lim WS, Macfarlane JT, Boswell TC et al (2001) Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 56:296–301
13. Niederman MS, Craven DE, Bonten MJ, Chastre J, Craig WA, Fagon JY, Wunderink RG (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 71:388–416
14. Mandell LA, Wunderink RG, Anzueto A et al (2007) Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44(Suppl 2):S27–S72
15. Yahalom J, Portlock CS (2008) Long-term cardiac and pulmonary complications of cancer therapy. Hematol Oncol Clin North Am 22:305–318
16. Katayama M, Imai Y, Hashimoto H et al (2009) Fulminant fatal cardiotoxicity following cyclophosphamide therapy. J Cardiol 54:330–334
17. Wagner SA, Mehta AC, Laber DA (2007) Rituximab-induced interstitial lung disease. Am J Hematol 82:916–919
18. Danzon S, Blackhall F, Hulse P, Ranson M (2005) Interstitial lung disease in lung cancer: separating disease progression from treatment effects. Drug Saf 28:103–113
19. Everolimus and pazopanib: two new drugs for renal cell cancer (2010). Med Lett Drugs Ther 52:33–34
20. Rodriguez-Pascual J, Cheng E, Maroto P, Duran I (2010) Emergent toxicities associated with the use of mTOR inhibitors in patients with advanced renal carcinoma. Anti-cancer Drugs 21:478–486
21. Crawford SW (1999) Noninfectious lung disease in the immunocompromised host. Respiration 66:385–395
22. Salinas FV, Winterbauer RH (1995) Radiation pneumonitis: a mimic of infectious pneumonitis. Semin Respir Infect 10:143–153
23. Nuorti JP, Butler JC, Farley MM et al (2000) Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. New Engl J Med 342:681–689
24. Centers for Disease Control and Prevention (CDC) (2010) Trends in tuberculosis–United States. MMWR Morbidity and mortality weekly report 2011; 60:333–337
25. Smith JA, Kauffman CA (2010) Blastomycosis. Proc Am Thorac Soc 7:173–180
26. Maschmeyer G, Haas A, Cornely OA (2007) Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. Drugs 67:1567–1601
27. Jokinen C, Heiskanen L, Juvonen H et al (2001) Microbial etiology of community-acquired pneumonia in the adult population of 4 municipalities in eastern Finland. Clin Infect Dis 32:1141–1154
28. Juven T, Mertsola J, Waris M et al (2000) Etiology of community-acquired pneumonia in 254 hospitalized children. Pediatr Infect Dis J 19:293–298
29. Centers for Disease Control and Prevention (CDC) (2009) Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus—United States. Mmwr 2009, 58:826–829
30. Michelow IC, Olsen K, Lozano J et al (2004) Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 113:701–707
31. de Roux A, Marcos MA, Garcia E et al (2004) Viral community-acquired pneumonia in nonimmunocompromised adults. Chest 125:1343–1351
32. Angeles Marcos M, Camps M, Pumarola T et al (2006) The role of viruses in the aetiology of community-acquired pneumonia in adults. Antivir Ther 11:351
33. Jennings LC, Anderson TP, Beynon KA et al (2008) Incidence and characteristics of viral community-acquired pneumonia in adults. Thorax 63:42–48
34. O'Brien KL, Walters MI, Sellman J et al (2000) Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. Clin Infect Dis 30:784–789
35. Centers for Disease Control and Prevention (CDC) (2007) Severe methicillin-resistant Staphylococcus aureus community-acquired pneumonia associated with influenza—Louisiana and Georgia, December 2006–January 2007. Mmwr 2007, 56:325–329
36. Hageman JC, Uyeki TM, Francis JS et al (2006) Severe community-acquired pneumonia due to Staphylococcus aureus, 2003–04 influenza season. Emerg Infect Dis 12:894–899
37. von Linstow ML, Eugen-Olsen J, Koch A, Winther TN, Westh H, Hogh B (2006) Excretion patterns of human metapneumovirus and respiratory syncytial virus among young children. Eur J Med Res 11:329–335
38. Palacios G, Hornig M, Cisterna D et al (2009) Streptococcus pneumoniae coinfection is correlated with the severity of H1N1 pandemic influenza. PLoS ONE 4:e8540
39. Madhi SA, Ludewick H, Kuwanda L et al (2006) Pneumococcal coinfection with human metapneumovirus. J Infect Dis 193:1236–1243
40. Madhi SA, Klugman KP (2004) A role for Streptococcus pneumoniae in virus-associated pneumonia. Nat Med 10:811–813
41. Petroianni A, Ceccarelli D, Conti V, Terzano C (2006) Aspiration pneumonia. Pathophysiological aspects, prevention and management: a review. Panminerva Med 48:231–239
42. Langerman A, Maccracken E, Kasza K, Haraf DJ, Vokes EE, Stenson KM (2007) Aspiration in chemoradiated patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 133:1289–1295
43. Anderson EJ (2008) Viral diagnostics and antiviral therapy in hematopoietic stem cell transplantation. Curr Pharm Des 14:1997–2010
44. Storek J, Dawson MA, Storer B et al (2001) Immune reconstitution after allogeneic marrow transplantation compared with blood stem cell transplantation. Blood 97:3380–3389
45. Tomblyn M, Chiller T, Einsele H et al. (2009) Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant 15:1143–1238
46. Marr KA, Carter RA, Boeckh M, Martin P, Corey L (2002) Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 100:4358–4366
47. Chakrabarti S, Mackinnon S, Chopra R et al (2002) High incidence of cytomegalovirus infection after nonmyeloablative stem cell transplantation: potential role of Campath-1H in delaying immune reconstitution. Blood 99:4357–4363
48. Anderson EJ, Ison MG (2008) Adenoviral Infections in transplant recipients. In: Scheld WM, Hammer SM, Hughes JM (eds) Emerging infections, vol 8. ASM Press, Washington, pp 75–91
49. Dykewicz CA (2001) Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 33:139–144
50. Lum LG (1987) The kinetics of immune reconstitution after human marrow transplantation. Blood 69:369–380
51. Chakrabarti S, Mautner V, Osman H et al (2002) Adenovirus infections following allogeneic stem cell transplantation: incidence and outcome in relation to graft manipulation, immunosuppression, and immune recovery. Blood 100:1619–1627
52. Lion T, Baumgartinger R, Watzinger F et al (2003) Molecular monitoring of adenovirus in peripheral blood after allogeneic bone marrow transplantation permits early diagnosis of disseminated disease. Blood 102:1114–1120
53. Grow WB, Moreb JS, Roque D et al (2002) Late onset of invasive Aspergillus infection in bone marrow transplant patients at a university hospital. Bone Marrow Transplant 29:15–19
54. Nichols WG, Corey L, Gooley T, Davis C, Boeckh M (2002) High risk of death due to bacterial and fungal infection among cytomegalovirus (CMV)-seronegative recipients of stem cell transplants from seropositive donors: evidence for indirect effects of primary CMV infection. J Infect Dis 185:273–282
55. Nichols WG, Erdman DD, Han A, Zukerman C, Corey L, Boeckh M (2004) Prolonged outbreak of human parainfluenza virus 3 infection in a stem cell transplant outpatient department: insights from molecular epidemiologic analysis. Biol Blood Marrow Transplant 10:58–64
56. Leruez-Ville M, Chardin-Ouachee M, Neven B et al (2006) Description of an adenovirus A31 outbreak in a paediatric haematology unit. Bone Marrow Transplant 38:23–28
57. Taylor GS, Vipond IB, Caul EO (2001) Molecular epidemiology of outbreak of respiratory syncytial virus within bone marrow transplantation unit. J Clin Microbiol 39:801–803
58. Harrington RD, Hooton TM, Hackman RC et al (1992) An outbreak of respiratory syncytial virus in a bone marrow transplant center. J Infect Dis 165:987–993
59. Ison MG (2007) Respiratory viral infections in transplant recipients. Antivir Ther 12:627–638
60. Ewig S, Welte T, Chastre J, Torres A (2010) Rethinking the concepts of community-acquired and health-care-associated pneumonia. Lancet Infect Dis 10:279–287
61. Green H, Paul M, Vidal L, Leibovici L (2007) Prophylaxis of Pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc 82:1052–1059
62. Davidson R, Cavalcanti R, Brunton JL et al (2002) Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. New Engl J Med 346:747–750
63. Low DE (2004) Quinolone resistance among pneumococci: therapeutic and diagnostic implications. Clin Infect Dis 38(4):S357–S362
64. Baz M, Abed Y, Papenburg J, Bouhy X, Hamelin ME, Boivin G (2009) Emergence of oseltamivir-resistant pandemic H1N1 virus during prophylaxis. New Engl J Med 361:2296–2297
65. Imhof A, Balajee SA, Fredricks DN, Englund JA, Marr KA (2004) Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. Clin Infect Dis 39:743–746
66. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP (2005) Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis 41:60–66
67. Kontoyiannis DP, Lionakis MS, Lewis RE et al (2005) Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis 191:1350–1360
68. Wade JC, Newton B, Flourney N, Meyers JD (1984) Oral acyclovir for prevention of herpes simplex virus reactivation after marrow transplantation. Ann Intern Med 100:823–828
69. Chakrabarti S, Pillay D, Ratcliffe D, Cane PA, Collingham KE, Milligan DW (2000) Resistance to antiviral drugs in herpes simplex virus infections among allogeneic stem cell transplant recipients: risk factors and prognostic significance. J Infect Dis 181:2055–2058
70. Frangoul H, Wills M, Crossno C, Engel M, Domm J (2007) Acyclovir-resistant herpes simplex virus pneumonia post-unrelated stem cell transplantation: a word of caution. Pediatr Transplant 11:942–944
71. Wingard JR, Chen DY, Burns WH et al (1988) Cytomegalovirus infection after autologous bone marrow transplantation with comparison to infection after allogeneic bone marrow transplantation. Blood 71:1432–1437
72. Einsele H, Ehninger G, Steidle M et al (1993) Lymphocytopenia as an unfavorable prognostic factor in patients with cytomegalovirus infection after bone marrow transplantation. Blood 82:1672–1678
73. Meyers JD, Flourney N, Thomas ED (1986) Risk factors for cytomegalovirus infection after human marrow transplantation. J Infect Dis 153:478–488
74. Castagnola E, Cappelli B, Erba D, Rabagliati A, Lanino E, Dini G (2004) Cytomegalovirus infection after bone marrow transplantation in children. Hum Immunol 65:416–422
75. Einsele H, Ehninger G, Hebart H et al (1995) Polymerase chain reaction monitoring reduces the incidence of cytomegalovirus disease and the duration and side effects of antiviral therapy after bone marrow transplantation. Blood 86:2815–2820
76. Goodrich JM, Mori M, Gleave CA et al (1991) Early treatment with ganciclovir to prevent cytomegalovirus disease after allogeneic bone marrow transplantation. New Engl J Med 325:1601–1607
77. Broers AE, van Der Holt R, van Esser JW et al (2000) Increased transplant-related morbidity and mortality in CMV-seropositive patients despite highly effective prevention of CMV disease after allogeneic T-cell-depleted stem cell transplantation. Blood 95:2240–2245
78. Craddock C, Szydlo RM, Dazzi F et al (2001) Cytomegalovirus seropositivity adversely influences outcome after T-depleted unrelated donor transplant in patients with chronic myeloid leukaemia: the case for tailored graft-versus-host disease prophylaxis. Br J Haematol 112:228–236
79. Zhang J, Zhang Z, Fan X et al (2009) Pandemic H1N1 influenza virus replicates in human lung tissues. J Infect Dis 201:1522–1526
80. Webb SA, Pettila V, Seppelt I et al (2009) Critical care services and 2009 H1N1 influenza in Australia and New Zealand. New Engl J Med 361:1925–1934
81. Bautista E, Chotpitayasunondh T, Gao Z et al (2010) Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. New Engl J Med 362:1708–1719
82. Jain S, Kamimoto L, Bramley AM et al (2009) Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. New Engl J Med 361:1935–1944
83. Redelman-Sidi G, Sepkowitz KA, Huang CK et al (2009) H1N1 influenza infection in cancer patients and hematopoietic stem cell transplant recipients. J Infect 60:257–263
84. Ling LM, Chow AL, Lye DC et al (2010) Effects of early oseltamivir therapy on viral shedding in 2009 pandemic influenza A (H1N1) virus infection. Clin Infect Dis 50:963–969
85. Lee N, Chan PK, Hui DS et al (2009) Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis 200:492–500
86. Leekha S, Zitterkopf NL, Espy MJ, Smith TF, Thompson RL, Sampathkumar P (2007) Duration of influenza A virus shedding in hospitalized patients and implications for infection control. Infect Control Hosp Epidemiol 28:1071–1076
87. Freifeld AG, Bow EJ, Sepkowitz KA et al (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis 52:e56–e93 (An official publication of the Infectious Diseases Society of America)
88. Lahti E, Peltola V, Virkki R, Ruuskanen O (2006) Influenza pneumonia. Pediatr Infect Dis J 25:160–164
89. Heussel CP, Kauczor HU, Ullmann AJ (2004) Pneumonia in neutropenic patients. Eur Radiol 14:256–271
90. Syrjala H, Broas M, Suramo I, Ojala A, Lahde S (1998) High-resolution computed tomography for the diagnosis of community-acquired pneumonia. Clin Infect Dis 27:358–363 (An official publication of the Infectious Diseases Society of America)
91. Heussel CP, Kauczor HU, Heussel GE et al (1999) Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. J Clin Oncol 17:796–805
92. Walsh TJ, Anaissie EJ, Denning DW et al (2008) Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 46:327–360 (An official publication of the Infectious Diseases Society of America)
93. Vento S, Cainelli F, Temesgen Z (2008) Lung infections after cancer chemotherapy. Lancet Oncol 9:982–992
94. Greene RE, Schlamm HT, Oestmann JW et al (2007) Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis 44:373–379 (An official publication of the Infectious Diseases Society of America)
95. Baddour LM, Wilson WR, Bayer AS et al (2005) Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 111:e394–e434
96. Fine MJ, Smith MA, Carson CA et al (1996) Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA 275:134–141
97. Ruiz-Gonzalez A, Falguera M, Nogues A, Rubio-Caballero M (1999) Is Streptococcus pneumoniae the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. Am J Med 106:385–390
98. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH (2002) Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 122:262–268
99. Kollef MH, Sherman G, Ward S, Fraser VJ (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 115:462–474
100. Roson B, Carratala J, Fernandez-Sabe N, Tubau F, Manresa F, Gudiol F (2004) Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. Arch Intern Med 164:502–508
101. Arancibia F, Ewig S, Martinez JA et al (2000) Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. Am J Respir Crit Care Med 162:154–160

102. Rano A, Agusti C, Benito N et al (2002) Prognostic factors of non-HIV immunocompromised patients with pulmonary infiltrates. Chest 122:253–261

103. Wheat LJ, Freifeld AG, Kleiman MB et al (2007) Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 45:807–825 (An official publication of the Infectious Diseases Society of America)

104. Mongkolrattanothai K, Peev M, Wheat LJ, Marcinak J (2006) Urine antigen detection of blastomycosis in pediatric patients. Pediatr Infect Dis J 25:1076–1078

105. Chapman SW, Dismukes WE, Proia LA et al (2008) Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis 46:1801–1812 (An official publication of the Infectious Diseases Society of America)

106. Durkin M, Connolly P, Kuberski T et al (2008) Diagnosis of coccidioidomycosis with use of the Coccidioides antigen enzyme immunoassay. Clin Infect Dis 47:e69–e73

107. Durkin M, Witt J, Lemonte A, Wheat B, Connolly P (2004) Antigen assay with the potential to aid in diagnosis of blastomycosis. J Clin Microbiol 30:367–377 (viii)

108. Wheat LJ (2009) Approach to the diagnosis of invasive aspergillosis and candidiasis. Clin Chest Med 30:367–377 (viii)

109. Egan L, Connolly P, Wheat LJ et al (2008) Histoplasmosis as a cause for a positive Fungitell (1→3)-beta-D-glucan test. Med Mycol 46:93–95

110. Persat F, Ranque S, Derouin F, Michel-Nguyen A, Picot S, Sulahian A (2008) Contribution of the (1→3)-beta-D-glucan assay for diagnosis of invasive fungal infections. J Clin Microbiol 46:1009–1013

111. Ostrosky-Zeichner L, Alexander BD, Kett DH et al (2005) Multicenter clinical evaluation of the (1→3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis 41:654–659

112. Tasaka S, Hasegawa N, Kobayashi S et al (2007) Serum indicators for the diagnosis of pneumocystis pneumonia. Chest 131:1173–1180

113. Digby J, Kalbfleisch J, Glenn A, Larsen A, Browder W, Williams D (2003) Serum glucan levels are not specific for presence of fungal infections in intensive care unit patients. Clin Diagn Lab Immunol 10:882–885

114. Maertens J, Theunissen K, Verbeken E et al (2004) Prospective clinical evaluation of lower cut-offs for galactomannan detection in adult neutropenic cancer patients and hematological stem cell transplant recipients. Br J Haematol 126:852–860

115. Busca A, Locatelli F, Barbui A et al (2006) Usefulness of sequential Aspergillus galactomannan antigen detection combined with early radiologic evaluation for diagnosis of invasive pulmonary aspergillosis in patients undergoing allogeneic stem cell transplantation. Transplant Proc 38:1610–1613

116. Viscoli C, Machetti M, Cappellano P et al (2004) False-positive galactomannan platelet Aspergillus test results for patients receiving piperacillin-tazobactam. Clin Infect Dis 38:913–916

117. Adam O, Auperin A, Wilquin F, Bourhis JH, Gachot B, Chachaty E (2004) Treatment with piperacillin-tazobactam and false-positive Aspergillus galactomannan antigen test results for patients with hematological malignancies. Clin Infect Dis 38:917–920

118. Wheat LJ, Hackett E, Durkin M et al (2007) Histoplasmosis-associated cross-reactivity in the BioRad Platelia Aspergillus enzyme immunoassay. Clin Vaccine Immunol 14:638–640

119. Racil Z, Kocmanova I, Lengerova M, Winterova J, Mayer J (2007) Intravenous PLASMA-LYTE as a major cause of false-positive results of platelia Aspergillus test for galactomannan detection in serum. J Clin Microbiol 45:3141–3142
120. Marr KA, Laverdiere M, Gugel A, Leisenring W (2005) Antifungal therapy decreases sensitivity of the *Aspergillus* galactomannan enzyme immunoassay. Clin Infect Dis 40:1762–1769
121. Ascioglu S, Rex JH, de Pauw B et al (2002) Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clinical Infect Dis 34:7–14 (An official publication of the Infectious Diseases Society of America)
122. Roghmann M, Ball K, Erdman D, Lovchik J, Anderson LJ, Edelman R (2003) Active surveillance for respiratory virus infections in adults who have undergone bone marrow and peripheral blood stem cell transplantation. Bone Marrow Transplant 32:1085–1088
123. Ison MG, Hayden FG (2002) Viral infections in immunocompromised patients: what’s new with respiratory viruses? Curr Opin Infect Dis 15:355–367
124. Campbell AP, Chien JW, Kuypers J et al (2010) Respiratory virus pneumonia after hematopoietic cell transplantation (HCT): associations between viral load in bronchoalveolar lavage samples, viral RNA detection in serum samples, and clinical outcomes of HCT. J Infect Dis 201:1404–1413
125. Gerna G, Campanini G, Rognoni V et al (2008) Correlation of viral load as determined by real-time RT-PCR and clinical characteristics of respiratory syncytial virus lower respiratory tract infections in early infancy. J Clin Virol 41:45–48
126. Kabeer BSA, Sikhamani R, Swaminathan S, Perumal V, Paramasivam P, Raja A (2009) Role of interferon gamma release assay in active TB diagnosis among HIV infected individuals. PloS one 4:e5718
127. Boersma WG, Erjavec Z, van der Werf TS, de Vries-Hosper HG, Gouw AS, Manson WL (2007) Bronchoscopic diagnosis of pulmonary infiltrates in granulocytopenic patients with hematologic malignancies: BAL versus PSB and PBAL. Respir Med 101:317–325
128. Ninane V (2001) Bronchoscopic invasive diagnostic techniques in the cancer patient. Curr Opin Oncol 13:236–241
129. Maertens J, Maertens V, Theunissen K et al (2009) Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. Clin Infect Dis 49:1688–1693 (An official publication of the Infectious Diseases Society of America)
130. White DA, Wong PW, Downey R (2000) The utility of open lung biopsy in patients with hematologic malignancies. Am J Respir Crit Care Med 161:723–729
131. Gupta S, Sultenfuss M, Romaguera JE et al (2010) CT-guided percutaneous lung biopsies in patients with haematologic malignancies and undiagnosed pulmonary lesions. Hematol Oncol 28:75–81
132. Arora SC, Mudaliar YM, Lee C, Mitchell D, Iredell J, Lazarus R (2002) Non-bronchoscopic bronchoalveolar lavage in the microbiological diagnosis of pneumonia in mechanically ventilated patients. Anaesth Intensive Care 30:11–20
133. Fujitani S, Cohen-Melamed MH, Tuttle RP, Delgado E, Taira Y, Darby JM (2009) Comparison of semi-quantitative endotracheal aspirates to quantitative non-bronchoscopic bronchoalveolar lavage in diagnosing ventilator-associated pneumonia. Respir Care 54:1453–1461
134. Fine MJ, Auble TE, Yealy DM et al (1997) A prediction rule to identify low-risk patients with community-acquired pneumonia. New Engl J Med 336:243–250
135. Pertel PE, Bernardo P, Fogarty C et al (2008) Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis 46:1142–1151 (An official publication of the Infectious Diseases Society of America)
136. Update on oseltamivir-resistant pandemic A (H1N1) 2009 influenza virus: January 2010. Wkly Epidemiol Rec 2009;85:37-40
137. Segal BH, Almyroudis NG, Battiwalla M et al (2007) Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. Clin Infect Dis 44:402–409 (An official publication of the Infectious Diseases Society of America)

138. Maertens J, Theunissen K, Verhoef G et al (2005) Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis 41:1242–1250

139. de Pauw BE (2005) Between over- and undertreatment of invasive fungal disease. Clin Infect Dis 41:1251–1253

140. Dignan FL, Evans SO, Ethell ME et al (2009) An early CT-diagnosis-based treatment strategy for invasive fungal infection in allogeneic transplant recipients using caspofungin first line: an effective strategy with low mortality. Bone Marrow Transplant 44:51–56

141. Scalera NM, File TM Jr (2007) How long should we treat community-acquired pneumonia? Current Opin Infect Dis 20:177–181

142. Wunderink RG (2006) A CAP on antibiotic duration. Am J Respir Crit Care Med 174:3–5

143. Chastre J, Wolff M, Fagon JY et al (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA J Am Med Assoc 290:2588–2598

144. Yende S, Angus DC, Ali IS et al (2007) Influence of comorbid conditions on long-term mortality after pneumonia in older people. J Am Geriatr Soc 55:518–525

145. Kampmann B, Cubitt D, Walls T et al (2005) Improved outcome for children with disseminated adenoviral infection following allogeneic stem cell transplantation. Br J Haematol 130:595–603

146. Chakrabarti S, Collingham KE, Fegan CD, Pillay D, Milligan DW (2000) Adenovirus infections following haematopoietic cell transplantation: is there a role for adoptive immunotherapy? Bone Marrow Transplant 26:305–307

147. Heemskerk B, Lankester AC, van Vreeswijk T et al (2005) Immune reconstitution and clearance of human adenovirus viremia in pediatric stem-cell recipients. J Infect Dis 191:520–530

148. Azoulay E, Thiery G, Chevret S et al (2004) The prognosis of acute respiratory failure in critically ill cancer patients. Medicine (Baltimore) 83:360–370