Respiratory Infections

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Abstract

The respiratory tract is a common site of infection in cancer patients and is associated with substantial moribidity 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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Contents

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 (particulary 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)

Table 1 (continued)

Oncological
Metatstatic malignancy
Primary lung malignancy
Leukemic infiltrates
Treatment-Related Pulmonary Toxicity
Radiation-induced pneumonitis and fibrosis
Medication related, including
Bleomycin
Busulfan
Chorambucil
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)

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

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 antilymphocyte 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-

Table 2 Respiratory tract pathogens of importance in cancer patients

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*	
	Mycoplasma pneumoniae	***Uncommon other pathogens***
	Chlamydiophila pneumoniae	Severe acute respiratory syndrome (SARS)
	Legionella spp.	Avian influenza
	Oral anaerobes (especially with aspiration)	Rubeola (measles)

(continued)

Table 2 (continued)

	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 burnetti (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 $\sim$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 >20 (OR 5.5), and a delay of >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

Table 3 Assays used in viral detection

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 immnoassay, *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 naspopharyngeal 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	Cell count with differential
Extended viral PCR testing	Gram stain with quantitative bacterial culture
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)

Table 4 (continued)

Cytology ± histology depending on specimen	PCP DFA assay
	16S ribosomal RNA sequencing[b]
	Cytology (+Histology if tissue obtained)
	Aspergillus galactomannan assay

[a]Send in stem cell transplant recipients
[b]Limited availability, primarily a research tool
[c]Determine whether pleural fluid is transudate or exudate
CBC complete blood count, *PA* posteroanterior, *hpf* high-power field, *PCR* polymerase chain reaction; *RSV* respiratory syncytial virus, *DFA* direct fluorescent antibody, *KOH* potassium hydroxide, *AFB* acid fast bacilli, *PCP Pneumocystis jerovechi*, and *RNA* ribonucleic acid

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 coccidiodiomycosis 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 cyptococcosis, 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

[113]. 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 thoracoscopic (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 $\geq$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. Endopthalmitis 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: *C*onfusion, elevated *U*rea Nitrogen, *R*espiratory rate ($\geq$30 breaths/min), low *B*lood 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 $\geq$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.

9 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** 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. baumanni* 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.

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