S.7.C.2 Upper and lower respiratory tract infection

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Introduction

Respiratory tract infection, whether acquired in the community or in the hospital, continues to be a major cause of morbidity and mortality when its course requires intensive care support [1–4]. Infections of the respiratory tract may involve either the upper central airways (trachea, major bronchi), commonly termed tracheobronchitis, or the more distal respiratory tract commonly termed "pneumonia". Pneumonia is defined by the presence of parenchymal inflammation due to overwhelming invasion of the normally sterile lower airways by one or more respiratory pathogens. It is important to categorize pneumonia based on where the infecting organisms were acquired. Community-acquired pneumonia represents only lower respiratory tract infection which was contracted outside the hospital setting, or was incubating at the time of hospitalization. Nosocomial pneumonia is defined as the onset of compatible clinical signs and symptoms with radiographic findings after a minimum of 48 hours of hospitalization, either in an ICU environment or in the general wards. Infection of the respiratory tract is the second most frequent nosocomial-acquired infection and has the highest associated case-fatality rate for all nosocomial infections [5, 6]. Ventilator-associated pneumonia is a distinct subset of nosocomial pneumonia which occurs exclusively in ICU patients on mechanical ventilators and for which clinical outcome is significantly worse than the general population with hospital-acquired pneumonia [3, 7, 8]. There has been a great deal of important clinical investigation in recent years which has provided more insight into the pathophysiology, diagnostic methodology and prevention of pneumonia. However, there still remains much controversy on this subject, such that the diversity of clinical practices between different institutions is still a wide one. Our discussion will focus on three distinct patient categories which, due to their unique characteristics, should be approached in a separate manner; community-acquired pneumonia, nosocomial pneumonia, including ventilator-associated pneumonia, and respiratory tract infections in the immunocompromised host.

Pulmonary host defenses and normal colonizing flora

The lower respiratory tract is maintained sterile by a complex hierarchy of native host defenses [9, 10]. The likelihood of developing pneumonia is a function of the virulence and inoculum of microorganism(s), and the status of the pulmonary and systemic host defenses. Microorganisms may gain access to the lung parenchyma by one of four routes; 1) micro- or gross aspiration of secretions from the mouth, naso- or oropharynx [11, 12], 2) inhalation and alveolar deposition of aerosolized organisms or infectious particles, 3) hematogenous spread from a non-pulmonary focus of infection or intestinal translocation, and 4) direct

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invasion from a contiguous site such as the pleural or subdiaphragmatic space.

Impairment of these protective mechanisms may present as an acute or chronic pneumonic processes, with either a specific or diverse spectrum of pathogens.

Inspired air is filtered of large airborne particulate matter (>2.0 mm) by passive entrapment by mucous membrane secretions and actively transported by the mucociliary clearance mechanism [13]. The latter consists of upwardly beating cilia which project from the luminal surface of columnar epithelial cells, between the proximal trachea and terminal bronchioles. Squamous metaplasia due to chronic airway insults, particularly tobacco smoke, and loss of the cilia is one contributor to upper and lower respiratory tract infection in this population. The protective airway reflexes maintain the integrity of the respiratory tract from the digestive tract, and an intact cough mechanism is critical for the rapid transport of particulate matter or endogenous secretions of pulmonary origin [14]. The latter requires both an intact afferent sensing mechanism and efferent respiratory forces generated by strong contraction of the respiratory muscles, with narrowing of the glottic aperture, to produce the high intrathoracic pressure and air velocity required. Pneumonia may develop in patients with a depressed level of consciousness due to a variety of conditions including drug overdose, seizures, metabolic encephalopathies, and cerebrovascular accident. Compromise of the protective airway reflexes and a diminished cough reflex are the dominant predisposing factors for the development of pneumonia in these conditions, and may occur either in the community or nosocomial settings.

The humoral immune system is an important local and systemic pulmonary host defense against several important respiratory pathogens. Local production of secretory IgA provides a nonspecific neutralizing antibody effect against a wide variety of potential respiratory pathogens. The systemic humoral immune system, consisting of specific antigen-directed antibody production by B-lymphocytes present in the lymphatic system and spleen, are a critically important defense against several polysaccharide encapsulated bacteria, including *Streptococcus pneumoniae* and *Hemophilus influenzae*. The alveolar macrophages provide a last line of defense, by interacting with and engulfing viable microorganisms, which have penetrated the more proximal pulmonary defenses. These cells also initiate the proximal cytokine cascade with the elaboration of interleukin – 1 and tumor necrosis factor. These, in turn, promote the synthesis of interleukin-8, which is a potent chemoattractant for monocytes and neutrophils [15, 16]. Alveolar macrophage function may be compromised by a variety of conditions which are quite prevalent in the critically ill patient, such as corticosteroids and other cell-mediated immunosuppressants, pulmonary edema, hyperoxia, uremia, acidosis and malnutrition.

Upper respiratory infections

In the ICU setting, upper respiratory infection most often manifests as tracheobronchitis, usually due to acute exacerbations of chronic bronchitis in patients with a history of obstructive lung disease, or in patients who have been on prolonged mechanical ventilation. The etiology of tracheobronchitis may be infectious (bacteria, viruses) or non-infectious. These episodes may be severe enough to warrant hospitalization and ICU admission due to respiratory failure, or they may occur in ICU patients after other major interventions, such as in the postoperative setting. The clinical manifestations are protean but generally include one or more of the following; an increased frequency and severity of cough, increased sputum production with purulent characteristics, dyspnea, chest discomfort, hemoptysis and wheezing. Systemic symptoms are not a major part of the tracheobronchitis syndrome. Low grade fever may be present. However, any signs of sepsis should prompt the clinician to consider a more serious diagnosis such as pneumonia, or a significant extra-pulmonary site of infection. The chest radiograph should not reveal any evidence of progressive air space disease (alveolar infiltrates, air-bronchograms, or consolidation). The sputum Gram's stain demonstrates numerous polymorphonuclear cells but stainable bacteria may or may not be present. The microbial etiology is closely related to the clinical setting. Thus, community-acquired bacteria (*H. influenzae*, *S. pneumoniae*, and *Branhamella catarrhalis*) and viruses (adenovirus, influenza, rhinovirus, coronavirus) are most frequently implicated in patients admitted to the ICU with primary exacerbations of chronic bronchitis or asthma. In patients with febrile tracheobronchitis in the setting of prolonged mechanical ventilation, the microbial etiology is usually enteric gram-negative, or the aerobic gram-negative bacilli (*Pseudomonas spp. Acinetobacter spp.*) [17]. The benefits of antimicrobial therapy for tracheobronchitis are marginal. In patients who are admitted to the ICU from the community, the choice of therapy should be based on the predominant bacterial morphology on the sputum Gram's stain. Thus, the appearance of pleomorphic gram-negative coccobacilli should be presumptively treated for *Hemophilus spp.*

(ampicillin, amoxicillin), while gram-negative diplococci merits coverage for *Branhamella spp.* with a beta-lactamase resistant agent or combination (ampicillin/sulbactam, amoxicillin/clavulanate, erythromycin, or tetracycline). Parenteral therapy is advisable in the critically ill patient, however, early conversion to oral administration is indicated in patients who demonstrate an early clinical response. Antimicrobial therapy for tracheobronchitis, which occurs after a period of mechanical ventilation, should be directed against the pathogen isolated in culture. Ciprofloxacin, due to its excellent penetration into respiratory secretions and excellent gram-negative coverage, has become the drug of choice for both empiric and definitive therapy of ICU tracheobronchitis. The use of aminoglycosides for tracheobronchitis should be avoided, due to their poor efficacy and nephrotoxicity. In general a 10 to 14-day course of antimicrobial therapy is adequate. Recent studies have shown that followup Gram's stain of the sputum was a better predictor of outcome than the culture; in patients with chronic bronchitis who had a clinical recovery, sputum cultures still grew the pathogen in 50% of cases but only 5.4% had a persistently positive Gram's stain [18]. However, it is not established whether such data, obtained from a population with chronic bronchitis, is applicable to acute episodes of bronchitis related to mechanical ventilation in the ICU setting.

Severe community-acquired pneumonia

Pneumonia due to community-acquired pathogens may require intensive care support in patients with a fulminant course, culminating in respiratory failure or shock or, in patients with serious underlying conditions such as chronic obstructive lung disease, diabetes, immunosuppression, alcoholism, or asplenia. Severe community-acquired pneumonia may require ICU admission in 18% to 36% of cases and has a mortality rate of 47% to 76% [19–22]. The spectrum of community-acquired pathogens and their relationship to specific underlying conditions is shown in Table 1. Recent epidemiologic studies from several centers in the United States and Europe all show that *S.pneumoniae* is still the most common pathogen, with a range of 15–36% for all episodes of community-acquired pneumonia [23, 24]. The remaining distribution of etiologies varies considerably with *H. influenzae*, *Legionella spp.*, *Staphylococcus aureus*, gram-negative bacilli and anaerobes, comprising the majority of bacterial pathogens. Notably, the microbial

Table 1. Common etiologies of severe community-acquired pneumonia and related underlying conditions

Pathogen	Common underlying conditions
S. pneumoniae	humoral immune deficiency
	asplenia
	alcoholism
	cirrhosis
	chronic lung disease
H. influenzae	chronic lung disease
Legionella spp.	chronic lung disease
	corticosteroid therapy
S. aureus	post-influenza
	diabetes
	hemodialysis
	iv drug abuse
anaerobes	gross aspiration
	poor dentition
	encephalopathy
Klebsiella spp.	institutionalization
	elderly
	alcoholism

etiology of community-acquired respiratory tract infection is not determined in approximately 50% of cases [24]. Improved diagnostic methods, however, have demonstrated a significant incidence of community-acquired pneumonia due to *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and certain viruses. Cases which require hospitalization and ICU care are predominantly of bacterial origin [25]. Over the past several decades, the spectrum of community-acquired pathogens has also become more diverse, due to the higher frequency of immunocompromised patients who are now admitted to the hospital from the community. Examples include infection due to *Mycobacterium tuberculosis*, atypical mycobacteria, fungi and *Pneumocystis carinii*, in patients with the acquired immunodeficiency syndrome (AIDS), and corticosteroid-treated conditions i.e. allograft recipients, autoimmune disorders, or chronic obstructive lung disease.

Another important trend has been the emergence of multi-drug resistant bacterial strains in the general community. Strains of *S. pneumoniae* with moderate penicillin resistance, defined as a minimum inhibitory, concentration (MIC) of 0.1–1.0 ug/ml or high-level penicillin resistance, MIC >1.0 ug/ml have been described in South Africa, Europe and the United States [26, 27]. Some of these strains also exhibit resistance to second- and third-generation cephalosporins, erythromycin, trimethoprim- sulfamethoxasole and tetracycline, which narrow the therapeutic, options to only vancomycin or chloramphenicol [28].

Methicillin-resistant *Staphylococcus aureus* (MRSA) may cause community-acquired Staph. in-

fections including pneumonia, however its occurrence has been primarily limited to intravenous drug abusers, hemodialysis patients and institutionalized populations [29, 30].

Clinical presentation and evaluation

The clinical symptoms and signs of community-acquired pneumonia are generally categorized as either "typical" or "atypical" syndromes. Typical presentations are more often characteristic of bacterial pneumonia and may include a rapid onset, productive cough, high-grade fever, rigors, and systemic signs of serious infection, i.e. delirium, hypotension. A leukocytosis and/or leftward shift of the differential count and consolidated radiographic pattern is common. Atypical presentations have a more gradual onset, a viral prodrome, nonproductive cough, lower grade fever and less systemic sequelae. Radiographic consolidation is present only rarely and there is often a low leukocyte count. The diagnostic value of "typical" and "atypical" clinical and radiographic presentations are still nonspecific, and thus poorly predictive of any specific respiratory pathogen [24].

Early epidemiologic studies suggested that *Legionella* pneumonia was more often accompanied by gastrointestinal (vomiting, diarrhea) and mental status changes, hyponatremia and elevated liver-associated enzymes, however, more recent evidence fails to support this association [31, 32].

The core diagnostic workup should include a sputum for Gram's stain and direct fluorescent antibody (DFA) stain, routine and *Legionella* culture, two sets of blood cultures, a complete blood count and differential, and a chest radiograph. An adequate sputum specimen is defined as having < 10 epithelial cells per low-power field and > 25 leukocytes per low-power field [33]. There are significant caveats for the interpretation of the sputum culture in community-acquired pneumonia. The sensitivity of the sputum culture in community-acquired pneumonia is very limited, as up to 50% of bacteremic pneumococcal pneumonia, and 34–47% of proven *H. influenzae* pneumonia, will have negative sputum cultures for these organisms [34–36]. If sputum production is inadequate, or an endotracheal aspirate is of poor quality, then fiberoptic bronchoscopy should be considered in patients for whom the differential diagnosis is wide, i.e. immunocompromised hosts, or for those who fail to respond to the chosen empiric antibiotic regimen [37, 38].

Adjunct studies may include urine for *Legionella* radioimmunoassay, pleural fluid for Gram's stain and culture, and acute serologic titers for *M. pneumoniae* and *C. pneumoniae*. Counterimmunoelectrophoresis and latex agglutination methods for the detection of polysaccharide antigens of *S. pneumoniae*, and other bacteria in serum, pleural fluid and urine have shown poor sensitivity in recent studies [39].

Treatment of severe community-acquired pneumonia

Patients who are sufficiently ill to require ICU admission for a diagnosis of community-acquired pneumonia require immediate parenteral antimicrobial therapy. Often, this is administered in the emergency room setting prior to examination of the patient by the ICU clinician. Until a definite microbial etiology is established, the antimicrobial regimen should cover *S. pneumoniae*, *H. influenzae*, *S. aureus*, and in most cases, *Legionella pneumophila*. Possible antimicrobial regimens include a second generation cephalosporin (cefuroxime), third generation cephalosporin (cefotaxime, ceftriaxone) or beta lactam /betalactamase inhibitor combination (ampicillin-sulbactam), combined with either high dose erythromycin (4 grams/day) or ciprofloxacin for *Legionella* coverage. A sputum Gram's stain which demonstrates abundant gram-negative bacilli in a high risk patient should direct coverage with either a third generation cephalosporin with antipseudomonal activity (ceftazidime, cefoperazone), ciprofloxacin, or an anti-pseudomonal penicillin (piperacillin, mezlocillin). Vancomycin should be reserved for patients at high risk for MRSA infection, or clinical suspicion for high level penicillin resistant *S. pneumoniae*. The empiric regimen may be modified in 24–48 hours based on the results of respiratory specimen and blood cultures, and other ancillary tests. These suggested antimicrobial regimens are summarized in Table 2.

Nosocomial pneumonia

Nosocomial pneumonia is best defined as pneumonia developing after 48 hours of hospitalization, and excludes those which are incubating at the time of admission [5]. The reported incidence ranges between 0.8 and 0.9% of medical and surgical inpatients [6, 40]. It is the second most common site of hospital-acquired infection after urinary tract infection, and accounts for 13% to 18% of nosocomial infection [5, 6, 7, 11]. The impact of nosocomial pneumonia is even more concentrated in the ICU population, where the incidence is up to 20-fold higher than the non-ICU

Table 2. Empiric parenteral antibiotic regimens for severe community-acquired pneumonia requiring ICU admission.

Clinical presentation and history	Probable pathogen(s)	Antimicrobials
Acute onset with unilobe or multilobe alveolar infiltrates	*S. pneumoniae, H. influenzae* *L. pneumophila*	Cefuroxime Cefotaxime Ampicillin-sulbactam + Erythromycin or Ciprofloxacin
High community prevalence of S. pneumoniae with high-level penicillin resistance	*S. pneumoniae*	Vancomycin
Gross aspiration	anaerobes	Clindamycin Metronidazole
Post-influenza, diabetes, hemodialysis, iv drug abuse	*S. aureus*	Nafcillin
Elderly, institutionalized, with gram-negative bacilli on Gram's stain	enteric gram-negatives *Pseudomonas*[a]	Ceftazidime Aztreonam Imipenem-cilastatin Ciprofloxacin + aminoglycoside[b]

[a] two antipseudomonal agents recommended
[b] aminoglycoside should not be used as monotherapy

inpatient population [8, 40]. When compared to other nosocomial infections, the case-fatality rates are the highest for nosocomial pneumonia, ranging from a crude mortality of 20–60% and attributable mortality as high as 33% [41–43]. Higher mortality rates are observed for those with documented bacteremia, immunocompromised patients, and patients with pneumonia due to more virulent organisms, such as *P. aeruginosa* and *Acinetobacter spp* [44, 45]. Markers of significant morbidity include prolonged ICU and hospital length of stay, increased duration of mechanical ventilation and inflated costs for intensive medical support.

Pathogenesis of nosocomial pneumonia

The most common sequence of events which leads to bacterial pneumonia, includes colonization of the oropharyngeal cavity and upper respiratory tract with hospital-acquired flora, microaspiration of upper respiratory secretions and invasion of the lung parenchyma with an inflammatory, but inadequate, host response. A shift in the composition of the oropharyngeal bacterial flora from a predominance of gram-positive bacteria to gram-negative bacilli, is commonly observed in critical illness. Johanson and colleagues demonstrated a 45% rate of oropharnygeal colonization in medical ICU patients by the first week of hospitalization [46]. Moreover, the risk of subsequent pneumonia was 23% in the colonized patients, compared to only 3.4% in non-colonized patients. The risk of gram-negative colonization has been shown to be a function of the degree of illness; 16% in moderately ill patients and 57% in critically ill patients [46]. The shift in colonizing flora is mediated by an increase in the surface affinity of the oropharyngeal and upper respiratory epithelium for gram-negative bacilli [47, 48]. The molecular basis for the changes in affinity are multifactorial, and include a decrease in cell-bound fibronectin and specialized attachments on the pili of certain gram-negative species [49, 50]. Oropharyngeal concentrations of bacterial flora as high as 10^8/ml have been shown in prior studies [51].

Recent evidence has shown an important association between bacterial colonization of the stomach with both oropharyngeal and tracheal colonization, and the development of pneumonia. The loss of the normal gastric acid barrier, due either to native conditions (age, achlorhydria, malnutrition) or iat-

rogenic intervention (antacids, H-2 blockers for stress ulceration prophylaxis), may result in bacterial overgrowth in the stomach [52–54]. This effect has been observed when the gastric pH is sustained at greater than 4.0 [54]. A meta-analysis of multiple studies examining the efficacy of stress-ulcer prophylaxis, demonstrated a significantly lower rate of pneumonia with sucralfate prophylaxis than regimens which raised gastric pH (antacids and/or H-2 blockers) [55]. This phenomenon has also been observed in patients receiving continuous enteral (gastric) feedings [56, 57].

The species of colonizing bacteria and their antibiotic resistance characteristics are, in turn, related to several other factors. Prior exposure to broad-spectrum antibiotics may favor superinfection with multi-resistant gram-negative bacilli [58]. Examples include induction of multi-resistant Enterobacter spp. after administration of third-generation cephalosporins, and *Acinetobacter spp.* or *Pseudomonas spp.* after broad spectrum antibiotic therapy [59, 60]. The scrupulousness of infection control practices in the ICU setting may also determine the composition of the colonizing respiratory flora. Poor handwashing compliance or improper use of gloves leads to cross-transmission of nosocomial pathogens including MRSA and gram-negative bacilli [58, 61]. Contaminated respiratory therapy devices or aerosol solutions have been implicated in outbreaks of gram- negative pneumonia by directly inoculating the lower respiratory tree [62].

Microaspiration of endogenous or nosocomial-acquired bacteria is the major route of inoculation which may progress to pneumonia [11, 63]. There are multiple native and iatrogenic interventions which may lead to microaspiration in the ICU patient. Altered levels of consciousness due either to metabolic or structural CNS disease or sedative administration are associated with higher rates of pneumonia. Esophageal intubation with nasogastric or nasoduodenal tubes may compromise the integrity of the lower esophageal sphincter and allow aspiration of gastric contents or feedings [41, 57]. Failure to adequately monitor the residual gastric volume of tube feedings may result in the aspiration of a large volume into the lower respiratory tract. Prolonged positioning of the patient in the supine position shown an association with pulmonary aspiration [64]. The endotracheal tube itself may contribute to the bacterial contamination of the lower respiratory tract due to several mechanisms. An artificial airway can impair the mucociliary and mechanical clearance of secretions and denude the mucosal epithelium leading to an increase in binding of microorganisms [11]. The inner surface of the tube may become coated with a bacterial-laden biofilm which may become a reservoir for pulmonary aspiration [65, 66]. Moreover, improper hygenic precautions during endotracheal suctioning may directly inoculate the lung with exogenous bacteria. The inflatable cuff around the artificial airway creates a basin for the collection of pooled secretions above the cuff which easily migrate distally due to airway caliber changes during the respiratory cycle. Thus, it is not an unexpected finding that the incidence of ventilator-associated pneumonia is directly correlated with the duration of endotracheal intubation [60].

Microbial etiologies of nosocomial pneumonia

In the immunocompetent patient population, nosocomial pneumonia is predominantly of bacterial origin, while fungi and viruses are rarely implicated. The bacterial etiologies of nosocomial pneumonia in the ICU setting is significantly influenced by the composition of oropharyngeal colonization of the host, environmental hazards, and the endemic prevalence pattern of bacteria in an individual unit. Gram-negative bacilli account for more than 60% of nosocomial pneumonia [6, 67]. The most prevalent gram-negative respiratory pathogens are the enteric facultative gram-negative bacilli (*Klebsiella spp.*, *Enterobacter spp. E. coli*, *Serratia marcescens*, *Proteus spp.*, and other less common species), and the aerobic gram-negative bacilli (*Pseudomonas spp.*, *Acinetobacter spp.*, *Stenotrophomonas maltophilia*). Recent investigations, which have utilized quantitative culture methods, have shown a high incidence of polymicrobial pneumonia in patients on mechanical ventilation [68, 69]. Another investigation by Bartlett and colleagues demonstrated a polymicrobial pneumonia incidence of 54% in nonventilated patients [70]. Other gram-negative organisms which may cause pneumonia, particularly in the early hospitalization period, include *H. influenzae* and *B. catarrhalis*. Nosocomial *Legionella* pneumonia may occur either sporadically or in epidemic fashion, and has been traced to the contamination of the hospital hot water source [71, 72]. *Staph. aureus* is the dominant gram-positive etiology, accounting for up to 20–25% of nosocomial pneumonia [73]. The frequency of methicillin-susceptible and -resistant strains of *S. aureus* is highly dependent upon prior antibiotic exposure, the endemic ICU pattern of resistance and infection control practices [73, 74]. Other gram-positive pathogens include *S. pneumoniae*, *Corynebacteria*

spp., and enterococci. Anaerobic flora is probably a less important class of pathogens in ventilated patients, however, it is difficult to quantify their importance as many centers do not perform anaerobic cultures of endotracheal aspirates or bronchoscopic obtained specimens.

Clinical presentation

The classic symptoms and signs which may indicate a nosocomial pneumonia include fever, purulent secretions, leukocytosis and/or a leftward shift, a potential respiratory pathogen in the sputum and progressive infiltrate on the chest radiograph. However the reality is that these markers are individually and collectively lacking in sensitivity and specificity for the presence of bacterial pneumonia in the ICU population. This poor relationship has been demonstrated by several groups which have reported a pneumonia diagnostic accuracy of less than 40% for several common clinical parameters using postmortem lung histology to confirm the presence of pneumonia [75–77]. Andrews and colleagues demonstrated that such common variables as fever, leukocytosis or leukopenia, pathogens in the sputum and asymmetric infiltrates all lacked predictive power for the presence of pneumonia [76]. Moreover, a favorable clinical response to antibiotic therapy was also a poorly associated with histologic findings of pneumonia. Conversely, in patients with diffuse infiltrates, Bell and colleagues reported a 62% rate of histologically proven pneumonia in 26 patients for whom it was not suspected based on antemortem clinical criteria [77]. Though some have suggested that the presence of focal infiltrates is predictive of pneumonia, one study demonstrated an 80% rate of resolution of infiltrates with the application of chest physiotherapy alone [78].

The underlying reasons for the poor correlation of clinical and radiographic variables include the high prevalence of other causes of fever and/or leukocytosis which may be infectious or noninfectious and of extrapulmonary origin. Common pulmonary processes in ICU patients which affect the chest film include atelectasis, pulmonary edema, adult respiratory distress syndrome, pulmonary infarcts or hemorrhage, and pulmonary effusions.

Thus, the use of a clinical diagnostic approach has both a variably poor sensitivity and specificity particularly in the mechanically ventilated ICU patient with a complex clinical and radiographic picture. This may result in either antibiotic overuse or the administration of incorrect antibiotics in patients with noninfectious pulmonary processes or occult extrapulmonary infections.

Microbiologic diagnosis of nosocomial pneumonia

The lack of reliable clinical and radiographic diagnostic signs of nosocomial pneumonia elevates the importance of the microbiologic techniques, both to establish the presence and specific microbial etiologies of pneumonia.

Blood cultures may provide a precise etiologic diagnosis in the clinical setting where there is a high confidence level that an extrapulmonary infection is absent. Their major limitations are the time delay for positivity (24–48 hours) and their low sensitivity. Bacteremia secondary to nosocomial pneumonia is documented in only 8% to 20% of patients though up to 27% of patients with pneumonia and ARDS may have bacteremia [45, 60, 79]. Moreover, bacteremic pneumonia has been shown to be a poor prognostic marker in one series [45]. Overinterpretation of a positive blood culture should be avoided, as up to 50% of patients with pneumonia and positive blood cultures, may have an extrapulmonary source of infection [60]. Microbiologic examination of respiratory specimens obtained as expectorated sputum, and nasotracheal or endotracheal suctioning has poor specificity for the presence of pneumonia and its microbial etiology [45, 70, 80–83]. Colonization of the upper airways with one, or multiple, potential pathogens is a common antecedent process in both intubated and non-intubated hospitalized patients [46]. Nevertheless, there may be a limited amount of diagnostic information from such specimens which may be helpful to the clinician. The dominant bacterial morphology present on a Gram's stain of the endotracheal aspirate may better the direct the empiric antibiotic choices. Qualitative cultures of sputum and endotracheal aspirates have good negative predictive value. In a study by Salata and colleagues, a negative Gram's stain of an endotracheal aspirate more often demonstrated that pneumonia was absent, even in the setting of fever and a radiographic infiltrate [81]. Moreover, since the actual lower respiratory pathogen(s) is usually present in the colonizing upper respiratory flora, the absence of a specific pathogenic bacterial species reduces the probability that it is a causative pathogen. Finally, the isolation of certain obligatory pathogens such as *Mycobacterium tuberculosis* or *Legionella spp.* is always indicative of respiratory infection with these

organisms. Recent investigations, which have attempted to discriminate, colonizing from pathogenic flora based on quantitative methods, have had mixed results [84].

The use of flexible fiberoptic bronchoscopy to obtain lower respiratory secretions has become quite commonplace for the diagnosis of pneumonia in the ICU setting. However, contamination of the bronchoscope suction channel during passage of the scope through the upper airways has been shown to occur in 100% of nonventilated patients [85]. Though still controversial, use of either the ''wedged'' bronchoalveolar lavage (BAL), or protected specimen brushing (PSB), coupled with quantitative microbiologic culture techniques, may provide both enhanced sensitivity and specificity for the diagnosis of ventilator-associated pneumonia. PSB involves bronchoscopic visualization of the proximal ostia of the radiographically involved bronchopulmonary segment, and passage of a wire brush protected in a telescoped cannula and a distal occluding carbowax plug [86]. The end of the brush is cut and placed in a one-ml vial of trypticase soy broth for transport to the microbiology laboratory and quantitative processing of the broth. In a remarkable study, Chastre and colleagues performed postmortem PSB coupled with a wedge lung biopsy immediately after death in 26 ventilated patients [87]. Six patients with histologically proven pneumonia all had PSB cultures with $>10^3$ colony forming units (cfu) /ml with no false negative results. However, false positive rates were present in 7 of 12 patients (58%) who were receiving antibiotics at the time of death, and in 23% of patients not receiving antibiotics. Overall, there was a 73% positive predictive value using 10^3 cfu/ml as the diagnostic threshold. In a subsequent larger trial by the same investigator group, PSB demonstrated a positive predictive value greater than 75% in 45 patients with $>10^3$ cfu/ml, and a negative predictive value of 100% in 102 patients with $< 10^3$ cfu/ml [69]. A recent meta-analysis of 15 studies which used the PSB technique in ventilated patients, showed a 91% sensitivity and a 95% specificity [88]. The principal limitations of PSB include false-positive and false-negative results in antibiotic-treated patients, bleeding and pneumothorax, and those risks attributable for all types of bronchoscopy. An alternative diagnostic method in ventilated patients is quantitative BAL. Bronchoalveolar lavage is performed by wedging the bronchoscope tip in a distal airway segment, followed by the instillation of 200–250 ml of preservative-free saline, followed then by the application of suction to capture the specimen for microbiologic stains and quantitative cultures. [89]. Compared to PSB, which samples a small proximal segment of lung surface, BAL samples a much larger distal surface ($>10^6$ alveoli) [90]. Gram's staining of the cytocentrifuged sediment can identify the dominant type of bacteria, and screen for contamination ($>1\%$ squamous epithelial cells), and markers of pathogenic flora ($>2\%$ alveolar) cells with intracellular organisms [91, 92].

A meta-analysis of multiple studies using quantitative BAL for the diagnosis of ventilator-associated pneumonia, showed a sensitivity range of 86% to 100% and a specificity of 100% [88]. The principal drawback of quantitative BAL is contamination of the specimen by upper airway bacteria in up to 30% of specimens [90, 93]. This problem can be minimized by not performing suction maneuvers in the upper airways and discarding the first sample of aspirated lavage return. A recently described modification, termed ''protected BAL'', reduced the level of BAL contamination with the use of a balloon-tipped catheter [94].

There are several important caveats when interpreting the quantitative culture results of respiratory specimens. It is not uncommon that such data are often confounded by the recent or ongoing use of antibiotics, which may result in both false negative and false positive cultures [93, 95]. Nevertheless, investigation has shown that quantitative methods still retain accuracy if they are employed within 12 hours of the starting antibiotics. Also, performing quantitative methods in patients who deteriorate on empiric therapy, or recrudesce symptoms after an initial response, has been shown to demonstrate antibiotic-resistant pathogens which can redirect the choice of antibiotics [96, 97]. In addition, the use of a precise diagnostic threshold ($>10^3$ cfu/ml for PSB and $>10^4$ cfu/ml for BAL), in the patient with incipient pneumonia, may ignore the fact that the bacterial inoculum may rise continuously to above the diagnostic threshold in several days [98].

Treatment of nosocomial pneumonia

The administration of antibiotic therapy in seriously ill patients with nosocomial pneumonia has shown only a variable effect on clinical outcome. In the ICU setting, the development of pneumonia is a valid marker of illness-severity, with attributable mortality often a function of the underlying disease process(es). Thus, some studies which have examined the association of antimicrobial therapy and outcome have demonstrated a decrease in attributable mortality and morbidity

(length of stay, duration of mechanical ventilation), while other studies have failed to show a positive effect [3, 41]. Moreover, the inappropriate use or selection of antibiotics can result in increased rates of resistance, superinfection, toxicity and cost [42, 99]. Antibiotic therapy may be defined as either "empiric" or "definitive", based on the quality of available information at the time of starting antibiotics. Treatment which is begun prior to the microbiologic confirmation of pneumonia is empiric. Empiric therapy is mandatory in patients with a rapid clinical deterioration as manifested by hypotension, poor oxygenation, and other changes in organ function consistent with sepsis (oliguria, altered mental status, lactic acidosis), or those patients deemed to be at high risk for rapid deterioration. Table 3 illustrates some of the important epidemiologic, clinical, and radiographic data elements which influence the selection of empiric antimicrobial therapy.

Definitive therapy may include either the initial selection of antibiotics based on confirmatory evidence of pneumonia, or modification of the empiric regimen after culture results are known by the clinician.

Table 3. Factors to evaluate in selective empiric antibiotic therapy for nosocomial pneumonia

Duration of hospitalization
Underlying diseases
immune deficiency states
diabetes
cystic fibrosis
corticosteroid therapy
Radiographic pattern
alveolar vs. interstitial
focal vs. diffuse
cavitary changes
Specimen stains - Gram's stain, KOH, acid-fast, silver
Documented colonizing flora
– species and resistance patterns
ICU pattern of antimicrobial resistance
Recent institutional outbreaks
Recent or current antibiotic therapy
Allergy history
Toxicity
Cost

Several important general considerations include the route of administration, ability to penetrate respiratory secretions and lung tissue, and the need for synergistic bactericidal activity. Since gastrointestinal function is commonly disturbed in critical illness, initial antibiotic therapy should be administered parenterally in the ICU patient, to ensure therapeutic serum and tissue levels. The ability of an antibiotic to penetrate respiratory secretions and lung parenchyma may contribute to their efficacy in pneumonia [100]. Thus, aminoglycosides, which poorly penetrate lung tissue, may only achieve sub-inhibitory concentrations and result in clinical failure, particularly if used as a single agent in gram-negative pneumonia [101]. In a retrospective study of gram-negative pneumonia, Moore and colleagues showed better clinical outcomes in patients whose peak aminoglycosides were maintained in the high therapeutic range, than those with sub-therapeutic peaks [102]. Conversely, antibiotics which concentrate in bronchial secretions well above serum levels, such as the quinolones, may be of theoretically greater benefit than agents with poor lung penetration. However, clinical proof to support this concept is lacking. The need for bactericidal or synergistic activity for nosocomial pneumonia is not clearly established in the literature. Gram-negative pneumonia occurring in granulocytopenic patients, or pneumonia due to *P. aeruginosa*, may respond better to synergistic therapy, usually with the combination of a cell-wall active agent and an aminoglycoside.

Empiric therapy must have activity against the endemic gram-negative bacilli, including considerations for the prevalent antibiotic resistant pattern in the ICU and if known, the antibiotic-resistant pattern in the colonizing flora of the patient. When combined with information from the respiratory specimen Gram's stain, a reasonable empiric antibiotic(s) choice can be made. In general, empiric choice must possess significant activity against the nonpseudomonal facultative gram-negative bacilli including *Klebsiella spp.*, *Enterobacter spp.*, *Serratia spp.*, and *Proteus spp.* In most institutions, this can be accomplished with a second (cefuroxime) or third generation cephalosporin (ceftriaxone, cefotaxime), a beta-lactam/beta-lactamase inhibitor combination (ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam), a monobactam agent (aztreonam), or a fluoroquinolone (ciprofloxacin). Suspected or documented infection due to *P.aeruginosa* or *Acinetobacter spp.* requires coverage with either an anti-pseudomonal penicillin (piperacillin, mezlocillin, azlocillin), anti-pseudomonal third generation cephalosporin (ceftazidime, cefoperazone), imipenem-cilastatin, com-

bined with an aminoglycoside agent. Another approach is the use of two different beta-lactam agents or a beta-lactam agent with ciprofloxacin. Such regimens may offer additive or possibly synergistic coverage and reduced toxicity. A study by Hilf and colleagues demonstrated improved outcome of bacteremic *Pseudomonas* infection when two active anti-pseudomonal agents were used, regardless of whether they had synergistic activity [103]. However, combining a strong beta-lactamase inducer (ceftazidime, cefoxitin) with a beta-lactamase susceptible agent (piperacillin) may result in the early development of resistance to both agents [59]. If MRSA is a major concern, then vancomycin needs to be part of the empiric regimen. Empiric combination therapy may offer advantages, such as broader coverage, decreased emergence of resistance and synergistic or additive activity. However, some have advocated a monotherapeutic antibiotic approach to avoid some of the drawbacks of combination therapy, which potentially include increased rates of resistance, superinfection, toxicity and cost. The development of single agents, with broad spectrum coverage for hospital-acquired pathogens, has facilitated the use of monotherapy. Several studies have compared initial monotherapy to combination therapy in nosocomial pneumonia, and shown equivalent efficacy in patients without critical illness or *Pseudomonas* infection [104]. Various single agents which have shown efficacy include aztreonam, ceftazidime, ciprofloxacin, and imipenem-cilastatin. Recently, a large multicenter trial of critically ill patients with nosocomial pneumonia compared imipenem-cilastatin to ciprofloxacin [105]. Equivalent efficacy was seen for non-pseudomonal pneumonia. However, *Pseudomonas* pneumonia was associated with a significant rate of clinical and bacteriologic failure in both groups. Ciprofloxacin however, was superior for the treatment of pneumonia due to *Enterobacter spp.* Thus, combination therapy with pseudomonal activity is a prudent empiric choice in critically ill patients, but may be tailored to monotherapy after the results of respiratory cultures are available. Suggested antimicrobial regimens for nosocomial pneumonia are summarized in Table 4.

The optimal duration of antibiotic therapy has not been prospectively established from any clinical trials. Treatment duration should be tailored to the individual patient, according to the initial severity of illness, rapidity of response, and, to a certain extent, the pathogen(s) causing pneumonia. Several pathogens with a propensity for relapse include *Pseudomonas aeruginosa*, *Acinetobacter spp*, and *Legionella* [106]. Therapy for such cases is usually recommended for at least 21 days or more, depending on the host response.

Table 4. Suggested empiric parenteral regimens for nosocomial pneumonia.

Clinical presentation	Possible pathogens	Antimicrobials
Early hospital period No prior antibiotics	enteric gram-negative *H. influenzae* *S. pneumoniae* MSSA	Monotherapy[a] cefuroxime cefotaxime ampicillin-sulbactam ticarcillin-clavulante
Mechanical ventilation Prior antibiotics Severe disease	enteric gram-negative *P. aeruginosa* *Acinetobacter spp.* MRSA cefoperazone	Anti-pseudomonal agent piperacillin mezlocillin ceftazidime aztreonam imipenem-cilastatin ciprofloxacin + aminoglycoside ± vancomycin
Corticosteroids Chronic lung disease	*L. pneumophila*	erythromycin ciprofloxacin

[a] single agent may be sufficient
MSSA = methicillin-susceptible *S. aureus*
MRSA = methicillin-resistant *S.aureus*

Eradication of the inciting pathogen should not be used as the sole criteria to determine the length of therapy, since even appropriate therapy, with a favorable clinical response, may not be accompanied by pathogen eradication in patients with artificial airways. Conversion to oral therapy may be permissible in rapidly responding patients with intact gut function. The oral fluoroquinolones may be the strongest agent in this regard, as they achieve very high levels in bronchopulmonary secretions with oral administration [107].

After the initiation of antibiotic therapy, it is important to evaluate the patient's clinical response to ensure the accuracy of the diagnosis and efficacy of the chosen antibiotic therapy.

Common parameters to measure the response include fever pattern, sputum volume and purulence, leukocytosis and/or leftward shift, oxygen requirements, and hemodynamic stability, including pressor dependence. There are no prospective studies which measure the rate at which clinical improvement should occur. A minimum period of 48 to 72 hours of therapy should be administered prior to objectively evaluating the response to the antibiotic therapy. If rapid clinical deterioration should ensue, or definitive microbiologic results become available, the empiric regimen should be modified accordingly. Patients who do not exhibit a favorable clinical response or deteriorate after an initial response, need prompt evaluation. The common etiologies for a nonresponding ICU patient with pneumonia are summarized in Table 5.

Table 5. Common reasons for an absent or delayed clinical response to antibiotic therapy.

Inappropriate antibiotics
Superinfection
Development of resistance
Empyema
Repetitive aspiration
– nasogastric feedings
– encephalopathy
Poor drainage
– bronchus obstruction
– atelectasis
– inspissated secretions
Parenchymal lung abscess
Adult respiratory distress syndrome
Extrapulmonary infection
Non-infectious pulmonary conditions

Prevention of nosocomial pneumonia

Several prophylactic strategies have been employed to decrease the frequency of pneumonia in the mechanically ventilated ICU patient. Primarily, these efforts have focused on preventing the contamination of the ventilator circuitry, minimizing the risks for pulmonary aspiration and decreasing oropharyngeal and tracheobronchial colonization with potential pathogens. Unfortunately, many such practices have not been shown to be beneficial in rigorous clinical trials. Recently, investigators have shown that abolishing circuitry changes resulted in no increased risk for ventilator-associated pneumonia, when compared to changes every 48 hours [108]. This observation may be due to the accidental inoculation of the tracheobronchial tree, due to improper technique when making circuitry changes. Formation of condensate may be avoided with the use of a heat and moisture exchanger, which recycles exhaled moisture. However, care must be taken to ensure that adequate humidification occurs, to avoid the inspissation of secretions [109]. Bacterial adhesion to the artificial airway may be a permanent reservoir for inoculation of the lungs [65, 66]. Clinical investigations are ongoing to develop biomaterials for airways which impede the development of a bacterial biofilm. An innovative subglottic suction apparatus, incorporated with the endotracheal tube, has shown a reduction in the incidence of early pneumonia following intubation [110].

The use of selective digestive decontamination (SDD) to reduce the incidence of gram-negative and fungal pneumonia remains a controversial practice. SDD involves the use of 2 nonabsorbed agents with gram-negative activity (usually colistin and gentamicin) coupled with a nonabsorbed polyene antifungal (mycostatin or amphotericin B). This combination is applied both as a topical paste to the oral mucosa, and in liquid form for enteral administration. Some SDD protocols also use a systemic parenteral antibiotic. Studies which analyzed the use of SDD have shown a variable decrease in the rates of gram-negative pneumonia, but generally no change in overall mortality [111]. Though there may be select "high-risk" populations that may benefit from SBD prophylaxis, its use has not become widely accepted

due to concerns regarding the selection for both gram-positive cocci (*enterococci* and *staphylococci*) and multiresistant gram-negative bacilli, expense and side effects, including diarrhea and poor palatability. Another approach has been the aerosolized administration of either gentamicin or a combination of polymyxin B and an aminoglycoside. Unfortunately, these studies have shown no effect on mortality, and some have described the emergence of antibiotic-resistant gram negative pneumonia and increased mortality [112–114].

Pneumonia in the immunocompromised host

Immunocompromised patients are commonly admitted to the ICU with life-threatening infections of the upper and lower respiratory tract. There are several important general features pertaining to respiratory infection in these patients; 1) the spectrum of pathogens is more diverse than nonimmunocompromised patients, and may include less common bacterial pathogens, fungi, viruses, protozoa and parasitic infections; 2) the clinical and radiographic presentation of pneumonia may be altered significantly, due to the poor inflammatory response of the host to the invading pathogen; 3) the pneumonic process may be part of a general disseminated infection involving several viscera; and 4) any significant delay in administering appropriate therapy is poorly tolerated in the immunocompromised patient. A comprehensive review of respiratory infection in the immunocompromised host is beyond the scope of this chapter. Thus, our discussion is limited to a succinct review of the spectrum, diagnosis and therapy of respiratory infection in patients with granulocytopenia, solid organ recipients, and AIDS.

Spectrum of respiratory pathogens in the immmuncompromised host

Granulocytopenia

The majority of patients with granulocytopenia, either due to hematologic malignancies or solid tumors, who have received myelosuppressive chemotherapy and/or autologous or syngeneic bone marrow transplantation. Patients with absolute neutrophil counts less than 500/mm^3 and/or prolonged neutropenia, have the highest risk for the development of bacterial or fungal pneumonia [115–117]. The differential diagnosis of fever and progressive pulmonary infiltrates should include non-infectious processes seen in the granulocytopenic patient. These include pulmonary toxicity due to chemotherapeutic agents, i.e. bleomycin, cyclophosphamide, methotrexate and other cytotoxic agents, pulmonary hemorrhage or infarction, tumor emboli, and leukoagglutinin reactions.

Community-acquired bacteria (*S. pneumoniae*, *H. influenzae*, *S. aureus*) or nosocomial-acquired bacteria (gram-negative enteric bacilli, *Pseudomonas spp.*, *Acinetobacter spp.*, *S. aureus*) are the most frequent pathogens. Fungal pathogens such as *Aspergillus spp.*, *Mucor spp.*, *Pseudoallescheria boydii*, *Fusaria* and other filamentous fungi are usually seen in patients with protracted granulocytopenia and are associated with an extremely high rate of mortality [118].

Solid organ recipients

The immunosuppressive regimen for the major categories of solid organ recipients includes corticosteroids and either cyclosporine A or FK–506. Polyclonal or monoclonal anti-lymphocyte globulin may be used for refractory allograft rejection, and azathioprine for maintenance immunosuppression in some centers. The dominant host defect from such a combination of immunosuppressive agents is the impairment of cell-mediated defenses, which normally protect the host from both exogenous pathogens and dormant endogenous organisms (*cytomegalovirus*, *Herpes simplex virus*, endemic mycoses, *M. tuberculosis*) which can reactivate in the host. The interval from the time of transplant to the clinical presentation of respiratory infection is a major determinant of the specific type of respiratory pathogen [119–121]. Thus, nosocomial-acquired bacteria are the most prevalent respiratory pathogens within several weeks of the transplant. Fungal pneumonia particularly due to *Aspergillus spp.*, occurs at a higher frequency within several months of transplantation, a period when immunosuppression and the risk for nosocomial exposure is the highest. Respiratory tract infection due to *Coccidioides immitis*, *Histoplasma capsulatum* and *Blastomyces dermatitidis* may occur in recipients with either distant, or recent, residence in those respective geographic areas with a high endemic rate of infection.

Viral infection in the post-transplant period is dominated by the *Herpesvirus* family (*Herpes simplex virus*, *Cytomegalovirus*, *Varicella-zoster virus*, *Epstein-Barr virus*) [122]. *Herpes simplex virus* most frequently presents as an orolabial vesicular eruption

during the first post-transplant month. HSV infection of the tracheobronchial tree and or lower respiratory tract, may occur via contiguous spread of an orolabial infection or as an isolated pulmonary presentation.

CMV pneumonitis characteristically occurs after the first post-transplant month and within 3–6 post-transplant months [123]. Lung and heart-lung recipients are characteristically the most frequent and severely affected category of solid organ recipients [124]. Associated mortality rates have been reported as high as 64% even with anti-viral therapy [125]. *Pneumocystis carinii* pneumonitis was a significant pulmonary pathogen in solid organ recipients prior to the advent of chemoprophylaxis with oral trimethoprim/sulfamethoxasole, which has dramatically reduced the incidence of this life-threatening infection [126].

Finally, community-acquired respiratory pathogens may cause sporadic pneumonia in the late post-transplant period, however, their clinical presentation may be more severe than immunocompetent hosts.

Acquired immunodeficiency syndrome (AIDS)

The depletion of T-helper lymphocytes from HIV–1 infection leads to a profound loss of cell-mediated host defenses and susceptibility to a diverse range of respiratory pathogens. *P. carinii* remains the dominant cause of pneumonitis in AIDS patients who require intensive care support, though its overall incidence has been significantly reduced with the widespread use of primary prophylaxis [127, 128]. The stereotypical presentation includes progressive dyspnea, non-productive cough and fever culminating in hypoxemia. Diffuse interstitial infiltrates are the most common radiographic presentation, though alveolar infiltrates are seen in more advanced cases. Bacterial pneumonia with non-opportunistic pathogens has become a significant cause of respiratory infection in AIDS patients [129]. Other frequent respiratory pathogens include *Mycobacterium avium* complex, *M. tuberculosis*, *S. pneumoniae*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, CMV and *Toxoplasma gondii*. Due to the high incidence of *M. tuberculosis* in the AIDS population, it is prudent to place AIDS patients with a pneumonia of undefined etiology in respiratory isolation, until the microbial etiology is defined.

Diagnosis of pneumonia in the immunocompromised host

The wide diversity of pathogens and the urgency for appropriate anti-infective therapy necessitate both rapid and sensitive diagnostic techniques. Assessment of the dominant immunologic host defects, risk factors for exposure, rapidity of the clinical presentation, and radiographic evaluation can effectively help in focusing the differential diagnosis. Thus, a diffuse interstitial pneumonitis is more consistent with either a viral etiology or *P. carinii* in a host with a cell-mediated immunologic defect. Conversely, a focal upper lobe infiltrate with or without cavitary changes should be carefully evaluated for *M. tuberculosis*, especially in patients with a subacute or indolent presentation. Rapid clinical deterioration is more characteristic with bacterial etiologies i.e. gram-negative bacilli, *S. aureus*,and *Legionella*. A subacute presentation over several weeks may be seen with CMV, fungal pneumonia due to *Cryptococcus*, *Aspergillus spp*. A slow or insidious presentation is seen with some bacterial etiologies such as *Nocardia spp*.and *M. tuberculosis*. Interestingly, *P. carinii* has a more indolent progression in AIDS patients, in comparison to other immunocompromised hosts [130].

Conventional diagnostic methods for pneumonia in immunocompromised patients are unrevealing in the majority of cases. Singer and colleagues could only demonstrate a 10% diagnostic yield with the use of sputum and blood cultures and serologic methods in 80 immunocompromised patients with diffuse radiographic infiltrates [131]. Sputum production is characteristically minimal or absent, due in part to the poor inflammatory reaction in many immunocompromised hosts. If an adequate sputum specimen is available, isolation of specific pathogens may have excellent diagnostic value, and obviate the need for more invasive diagnostic intervention. In nonintubated patients, sputum-induction methods with high-flow nebulized saline may increase the sensitivity for the detection of *P. carinii* as high 95% of samples [132].

Invasive methods have been clearly shown to improve the diagnostic sensitivity for the etiology of respiratory tract infection in immunocompromised hosts. Due to its relatively low inherent risks and its excellent diagnostic sensitivity for some organisms, bronchoalveolar lavage has gained wide acceptance for the diagnostic evaluation of pulmonary infiltrates in the immunocompromised host [133]. A rapid diagnosis can be made with the use of special stains of the cytocentrifuged pellet. These should include stains for bacteria (Gram's stain, direct fluorescent antibody), fungi (potassium hydroxide wet mount or Calcoflour white), *M. tuberculosis* or atypical mycobacteria (Ziehl-Nieelsen or auramine/rhodamine), *P. carinii* (Giemsa or Grocott stain, toluidine blue-O stain), and studies for the presence of typical viral

inclusion bodies (Papinocolau stain). Stover and colleagues obtained an overall diagnostic yield of 66% in an immunosuppressed population of 97 patients with diffuse pulmonary infiltrates [134]. Similar diagnostic value has been shown in bone marrow and kidney transplant patients [135, 136]. BAL has demonstrated the greatest utility in the evaluation of the AIDS patient with diffuse infiltrates. Diagnostic sensitivity has been shown to exceed 90% in most series, and has obviated the need for transbronchial or open lung biopsy. BAL has also shown the greatest sensitivity for the detection of *M. tuberculosis* in a variety of immunosuppressed hosts [137, 138].

The necessity for more invasive techniques such as transthoracic needle biopsy, thoracoscopic biopsy, transbronchial biopsy, or open lung biopsy should be made on an individualized basis. The diagnostic yield of these invasive methods is higher in patients with single or multiple pulmonary nodules, masses where bronchoalveolar lavage was non-diagnostic. Open lung biopsy should also be considered when the patient has a significant coagulopathy or significant hypoxemia. Two large series of open lung biopsy in immunocompromised patients reported an acceptably low complication rate and no attributable mortality related to the surgery [139, 140]. The clinical impact of information obtained from an open lung biopsy has been reported to be as high as 50%, though other studies have failed to demonstrate a survival benefit even in those patients in whom a specific diagnosis was established by the open lung biopsy [141].

Treatment of respiratory infection in the immunocompromised host

Anti-infective therapy in the immunocompromised patient with a respiratory tract infection can be categorized as empiric, a therapeutic trial, or definitive therapy.

Due to the high potential for rapid clinical deterioration in immunocompromised hosts with untreated infection, empiric therapy directed at the most likely pathogen(s) is a critical part of management. The optimal empiric regimen should provide the highest probability that the most likely infecting pathogen(s) are covered. Diagnostic clues for the latter include type of immune defect(s), the duration and severity of immunosuppression, rapidity of the clinical deterioration, examination for extrapulmonary signs of disseminated infection, radiographic pattern, use or non-use of

Table 6. Anti-infective therapy for common opportunistic respiratory pathogens in the immunocompromised host.

Pathogen	Primary choice	Alternatives
Bacteria		
Legionella spp.	Erythromycin	Ciprofloxacin
Nocardia spp.	Sulfisoxazole	TMP/SMX
		Minocycline
		Amikacin
M. tuberculosis	INH/RIF/PZA + STM or ETH[a]	
M. avium-complex	CLA/ETH + CLO or RFB[b]	
Fungi		
Aspergillus spp.	ABLC[c]	Itraconazole
Cryptococcus	Amphotericin B + 5-FC[d]	Fluconazole
Candida spp.	Amphotericin B±5-FC[d]	Fluconazole
H. capsulatum	Amphotericin B	Itraconzazole
P. carinii	TMP/SMX	Pentamidine
		Dapsone
Atovaquone		
Viruses		
Herpes simplex	Acyclovir (15 mg/kg/day)	
Varicella-zoster	Acyclovir (30 mg/kg/day)	
Cytomegalovirus	Ganciclovir (10 mg/kg/day) ±hyperimmune CMV globulin	Foscarnet
Influenza A	Amantadine (100 mg bid)[e]	Rimantadine[e]

[a] INH = isoniazid; RIF = rifampin; PZA = pyrazinamide; ETH = ethambutol STM = streptomycin
[b] CLA = clarithromycin; ETH = ethambutol; CLO = clofazimine RFB = rifabutin
[c] ABLC = amphotericin B lipid complex
[d] 5-FC = 5-fluorocytosine
[e] must be administered within 48 hours of the onset of symptoms

chemoprophylaxis, knowledge of prior infections or exposure, and the viral serologic status of the patient, and allograft donor for organ recipients. Ideally, respiratory specimens should be obtained prior to beginning empiric treatment, however, treatment should not be delayed in a rapidly deteriorating patient. A therapeutic trial of anti-infective therapy may be indicated when an etiologic pathogen has not been isolated despite a thorough diagnostic workup. A common scenario is when there is clinical and radiographic suspicion of tuberculosis, however, the acid-fast stains of the respiratory specimens are negative. It may be reasonable to begin anti-tuberculous therapy in the 4–6 week incubation period for culture growth of *M. tuberculosis*.

Table 6 summarizes the primary and alternative therapies for many of the common opportunistic pathogens in the major categories of immunocompromised hosts discussed above. Dosing regimens should be tailored to the adequacy of the patients renal excretion and hepatic metabolism. The reader should consult a recent pharmaceutical guide for the suggested dosing regimen [142]. In addition to the appropriate anti-infective therapy, a judicious reduction in the immunosuppression should be undertaken if allograft rejection is not a concurrent clinical problem.

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