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Pneumonia and Empyema

Imad Y. Haddad and David N. Cornfield

Introduction

Pneumonia is defined as infection and inflammation of the lower respiratory tract in association with parenchymal radiographic opacity. This definition excludes bronchiolitis, tracheitis, neonatal pneumonia, and noninfectious causes of pneumonia and pneumonitis, and these are not discussed in this chapter.

In the pediatric intensive care unit (PICU), several pneumonia types may be encountered. First, a previously healthy child may be admitted to the PICU because of severe community-acquired pneumonia (CAP). The pneumonia is usually caused by organisms that are prevalent in the out-of-hospital environment. Second, patients with genetic or acquired immune deficiency commonly develop severe pneumonia with opportunistic infections that usually do not infect healthy children. These immunocompromised patients commonly have been given chemo-radiotherapy for cancer or are receiving immune-suppressive agents to prevent rejection episodes following solid organ and hematopoietic stem cell transplantation. Third, both previously healthy and immunocompromised patients may acquire nosocomial pneumonia during their hospital stay. Mechanically ventilated patients are at especially high risk to develop nosocomial ventilator-associated pneumonia (VAP). Finally, aspiration pneumonia caused by chronic inoculation of the lower respiratory tract with large amounts of less virulent bacteria in a susceptible host prone to aspiration is also observed in the PICU.

This classification of pneumonia types in the PICU is important because it has major implications on the causative microbial agent and, thus, the choice of initial empiric treatment that may be life saving. This chapter reviews respiratory host defenses that maintain sterility of the lower respiratory tract. In addition, the pathogenesis, classification, and treatment options for pneumonia and empyema in the PICU patient are briefly discussed.

Pulmonary Host Defense

In humans, the lung represents the largest epithelial surface of the body exposed to the external environment. This area is 40-fold larger than the skin. As a consequence, the upper airways and lower lung are continuously exposed to a variety of airborne particles and microbial agents. Despite this constant attack, sterility of the conducting airways, bronchioles, and alveoli is maintained by a complex pulmonary host defense system. Throughout the upper (nasopharynx) and lower (conducting airways and alveolar spaces) respiratory tracts, the innate and adaptive immune systems work synchronously to identify and eliminate foreign non-self particles, including microbes. In invertebrates, the innate system is the sole mechanism of host defense against pathogens, but in higher vertebrates it constitutes the first line of defense. The innate defenses are constitutive, rapid, and nonspecific. The innate system is based on pattern recognition of repetitive molecular patterns shared by microorganisms.

Major advances in innate immunity have focused on the discovery of a series of cell-surface receptors called *toll-like receptors* (TLRs), first described in *Drosophila*, but now at least 11 homologues have been discovered in humans [1] and 13 homologues in mice. Individual TLRs differ in their ligand specificities (Figure 17.1). The interaction between a TLR and a microbial component triggers adaptor proteins and signal molecules, leading to transcription factors activation, production of proinflammatory cytokines, and expression of host defense peptides [2]. Importantly, the innate system and TLR activation also induce co-stimulatory molecules that stimulate and drive the inducible and slower specific adaptive immune system such that antigen-presenting cells present antigen to T helper (Th) cells that differentiate along two pathways: the Th1 pathway, important in cell-mediated immunity, and Th2 pathway involved in humoral responses [3].

Mechanical defenses also play a major role in respiratory host defense. Aerodynamic filtration in the nose and nasopharynx prevents particles that are >10 μm from passing to the lower respiratory tract. Particles from 5 to 10 μm are filtered by impaction in the conducting airways. Material deposited along the airways is removed by the mucociliary system, which starts in the nasopharynx and ends in the terminal bronchioles. Ciliary beating occurs in a precise and well-orchestrated fashion, propelling mucus and deposited organisms toward the oropharynx. A final constituent of the mechanical defense of the respiratory tract is cough. This

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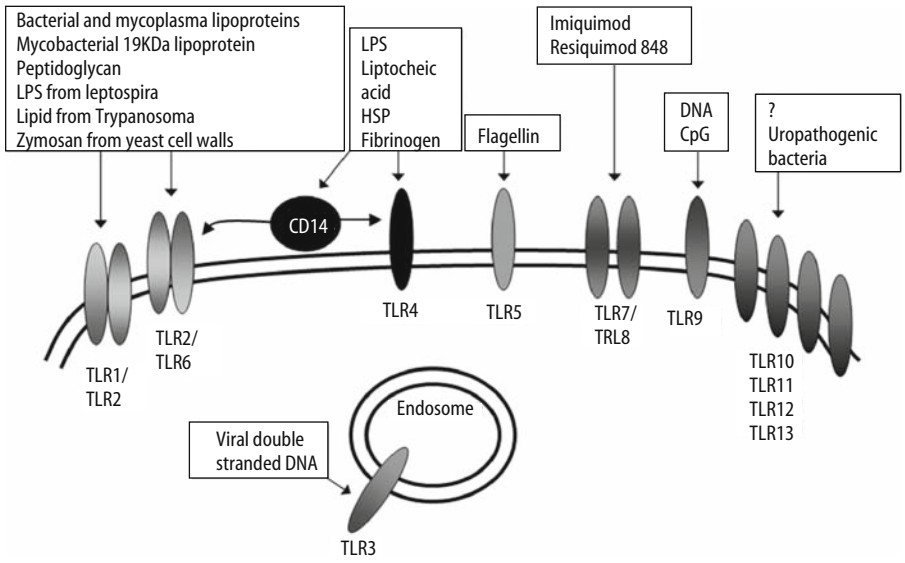

Figure 17.1. Toll-like receptors (TLR) and their ligands. LPS, lipopolysaccharide; HSPs, heat shock proteins.

potent expiratory maneuver is of fundamental importance in preventing material from being aspirated into the lungs.

The conducting airways also contain several antimicrobial substances, including immunoglobulins (IgG and secretory IgA), and complement that bind and enhance the elimination of microbial agents. In addition, airway epithelial and alveolar type (AT) II cells secrete several antimicrobial peptides. One of the best characterized families of antimicrobial peptides are the defensins, which are cysteine-rich peptides possessing broad antimicrobial activity [4]. An important recent discovery is the expanding role of respiratory airway epithelium in innate immune defenses by mechanisms that mimic those noted in phagocytic cells. Respiratory epithelial cells, including ATII cells, express TLR and are capable of expressing a variety of cytokines that amplify inflammation. The importance of innate immunity in epithelial cells was confirmed in mice with specific inhibition of nuclear factor (NF) κB activation that was restricted to distal airway epithelial cells. Mice lacking the ability to activate NFκB in epithelial cells exhibited impaired inflammatory response to inhaled LPS [5]. These data provide evidence that distal airway epithelial cells and the signals they transduce play a key physiologic role in lung inflammation in vivo. Alveolar type II cells also secrete surfactant proteins (SP)-A and D. Both SP-A and SP-D are collagen-like lectins (collectins) that agglutinate and/or opsonize pathogens and enhance their phagocytosis by innate immune cells such as alveolar macrophages and neutrophils [6]. Surfactant proteins A and D may have additional immunoregulatory functions [7] and also may exhibit direct bactericidal effects by inducing damage to the bacterial cell membrane [8]. The functions of SP-A and SP-D in host defense are listed in Table 17.1.

In the distal airspaces, alveolar macrophages are the first phagocytic cell type encountered by pathogens entering the lung. Macrophages have the capacity to induce the generation of large amounts of cytokines, chemokines, matrix metalloproteinases (MMP), nitric oxide, and potent oxidants that participate in antimicrobial defenses. In contrast, interstitial macrophages are located in the lung connective tissue and serve as both phagocytic cells and antigen-processing cells. Tumor necrosis factor (TNF)-α, a macrophage-derived multifunctional cytokine, is expressed early in both patients with and animal models of pneumonia [9]. Microbes also induce macrophages to generate potent chemokines that attract circulating neutrophils and monocytes into the lungs. Cytokines/chemokines amplify inflammatory responses and orchestrate the polarization and transition of innate to adaptive immunity that function to eliminate invading microorganisms [10]. Figure 17.2 summarizes the cellular and secretory peptides that are components of host defense against microbes in the lower respiratory tract. Disorders associated with impaired mechanical, innate, and adaptive host responses that may lead to the development of pneumonia in a susceptible host are listed in Table 17.2.

Table 17.1. Functions of lung collectins SP-A and SP-D in host defense.

	SP-A	SP-D
Agglutination	+	++
Opsonization	++	+
Reduced viral infectivity	+	++
Modulation of inflammation	+	+

Pathogenesis

The upper respiratory tract is normally colonized with nonpathogenic bacterial flora, but physical and immunologic host defenses generally ensure that bacteria that gain access to the lower respiratory tract are cleared. Pneumonia occurs because of an impairment of host defenses (as discussed earlier), invasion by a virulent organism, or invasion by an overwhelming inoculum of less virulent organisms. There are five main modes of pathogen entry into the lower respiratory tract.

Inhalation and Droplets

Inhalation of infectious particles is probably the most important pathogenic mechanism in the development of CAP, with particular importance in pneumonia of those caused by *Legionella* species and *Mycobacterium tuberculosis*. Contact with contaminated fomites also may be important in the acquisition of viral agents, especially respiratory syncytial virus. The viral agents that cause pneumonia proliferate and spread by contiguity to involve lower and more distal portions of the respiratory tract. Inhalation is also a common cause of pneumonia caused by contaminated ventilator tubes.

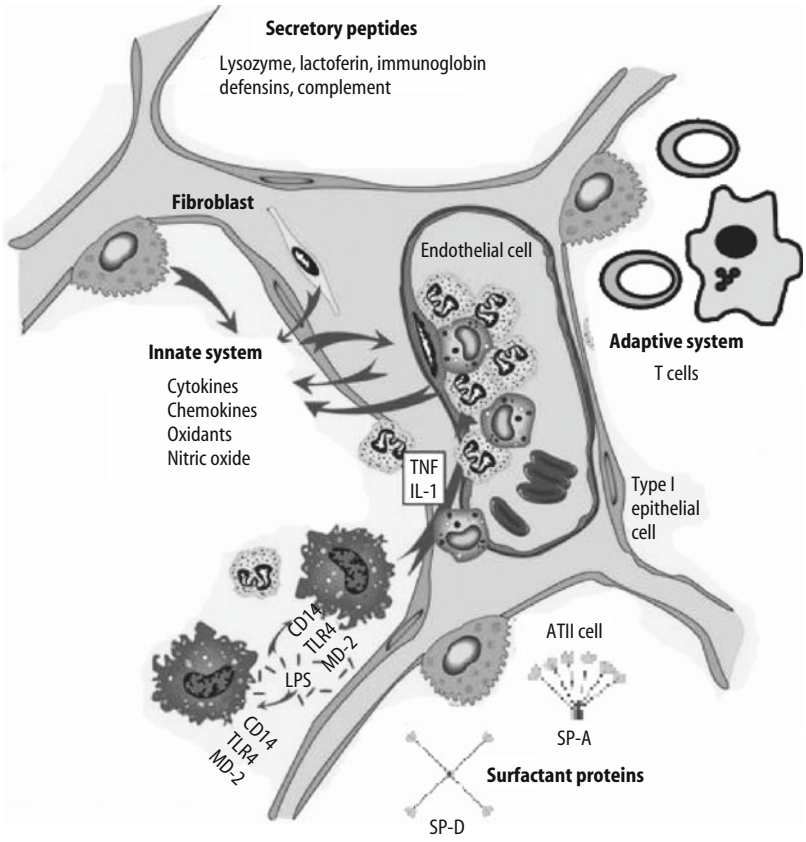

Figure 17.2. Cellular and secretory peptides involved in antimicrobial innate and adaptive host defense systems.

Aspiration

In addition to inhalation, pneumonia arises following the aspiration of microorganisms from the oral cavity or nasopharynx. Invasive disease most commonly occurs upon acquisition of a new serotype of the organism with which the patient has not had previous experience. Most episodes of VAP are thought to develop from the aspiration of oropharyngeal secretions containing potentially pathogenic organisms. Aspiration of gastric secretions may also contribute, although likely to a lesser degree. Tracheal intubation interrupts the body's anatomic and physiologic defenses against aspiration, making mechanical ventilation a major risk factor for VAP. The term *aspiration pneumonia* should be reserved for pneumonia or pneumonitis resulting from the aspiration of large amounts of gastric or oropharyngeal contents that may contain a large inoculum of relatively nonvirulent bacteria. The pathogens that commonly produce CAP or VAP, such as *Streptococcus pneumoniae*, Gram-negative bacilli, and *Staphylococcus aureus*, are relatively virulent bacteria so that only a small inoculum is required and the aspiration is usually subtle.

Hematogenous Spread

In immunocompromised individuals, an additional mode of pneumonia acquisition is bacteremia and sepsis. Hematogenous deposition of bacteria is responsible for some cases of pneumonia caused by *Staph. aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*.

Reactivation

Reactivation of pathogens can take place in the setting of deficits of cell-mediated immunity. Pathogens such as *Pneumocystis carinii/jiroveci*, *M. tuberculosis*, and cytomegalovirus (CMV) may remain latent for many years after exposure, with flares of active disease in the face of immune compromise. Reactivation tuberculosis occasionally occurs in immunocompetent hosts.

Table 17.2. Conditions associated with impaired pulmonary host defense.

Mechanical defenses	Phagocytic function	Cellular immunity (T cells)	Humoral immunity (B cells)
Impaired cough	Inherited	Inherited	Inherited
	Chronic granulomatous disease	Severe combined immunodeficiency syndrome	X-linked agammaglobulinemia
	Chediak-Higashi syndrome	DiGeorge syndrome	Common variable immunodeficiency
	Leukocyte adhesion deficiency	Wiskott-Aldrich syndrome	IgA deficiency
		Ataxia telangiectasia	IgG subclass deficiency
Impaired mucociliary function	Acquired	Acquired	Acquired
Primary ciliary dyskinesia	Neutropenia	Immunosuppressive medications	Steroids
Cystic fibrosis		Acquired immunodeficiency syndrome	Excessive pleural or peritoneal fluids losses
		Graft-versus-host disease	Nephrotic syndrome

Direct Injury and Inflammation

Direct inoculation rarely occurs as a result of surgery or bronchoscopy but may play a role in the development of pneumonia in patients supported with mechanical ventilation. The direct extension of infection to the lung from contiguous areas such as the pleural or subdiaphragmatic spaces is rare.

Pneumonia Types in the Pediatric Intensive Care Unit

Community-Acquired Pneumonia

Definitions and Main Features

Community-acquired pneumonia refers to pneumonia in a previously healthy person who acquired the infection outside a hospital. It is one of the most common serious infections in children, with an incidence of 34 to 40 cases per 1,000 children in the industrialized world [11]. A subset of these patients will require PICU admission. Admission to the intensive care unit should be considered for patients with persistent hypoxemia despite oxygen therapy, recurrent apnea, signs of respiratory fatigue with or without mental status changes, or evidence of compensated or decompensated shock. Infants less than 6 months of age and children with comorbid conditions such as bronchopulmonary dysplasia, cystic fibrosis, neuromuscular disorders, congenital heart disease, and immunodeficiency disorders have limited respiratory reserves and, therefore, are at increased risk for respiratory failure during a pneumonia episode.

For the adult population, the American and British Thoracic Societies have developed guidelines for hospital and ICU admissions for patients with severe CAP [12]. According to the American Thoracic Society Guidelines, admission to the ICU is needed for patients with severe CAP, defined as the presence of either one of two major criteria, or the presence of two of three minor criteria. The major criteria include need for mechanical ventilation and septic shock; the minor criteria include systolic blood pressure ≤90 mm Hg, multilobar disease, and a PaO_2/FiO_2 ratio <250. In addition, a Pneumonia Severity Index (PSI) score identifies adults at increased risk of medical complications and death [13]. However, similar guidelines or scores to grade the severity of pneumonia in children have not been developed.

Specific Pathogens

Children admitted to the PICU because of CAP are more commonly infected with bacterial than viral pathogens. *Streptococcus pneumoniae* is the most commonly identified bacterial cause of CAP in infants and children older than 1 month. Pneumonias caused by group A *Streptococcus* and *Staph. aureus* are less frequent. *Haemophilus influenzae* pneumonia has become uncommon following the widespread use of *Haemophilus* influenza type B immunization. Viruses are identified most often in children <5 years of age. Respiratory syncytial virus is the most common viral etiology during infancy, with adenovirus, influenza virus, parainfluenza virus, and the recently described human metapneumonovirus (14) also not infrequently detected. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are more common in older children and adolescents [11].

In May 1993 an outbreak of an acute febrile illness associated with respiratory failure, shock, and high mortality was identified by investigators from the Centers for Disease Control and Prevention (CDC) as being caused by a hantavirus. In the United States, 95% of the cases occurred west of the Mississippi after environmental exposure to infected deer mouse saliva, urine, or feces. In addition, a novel coronavirus was identified as the causative agent of severe acute respiratory syndrome (SARS), a new respiratory illness that affects adults and children, although the severity of the disease is less in children than in adults [15]. Another cause of severe pneumonia that should be considered is tuberculosis. A history of contact with a person with pulmonary tuberculosis is usually elicited. Finally, uncommon causes of CAP in otherwise healthy children are fungal infections including *Coccidiodes immitis*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*. These organisms should be included in the differential diagnosis as a cause of pneumonia only if there is a history of residence or travel to an area of endemic infection.

Occasionally, infection with *Strep. pneumoniae* [16] and *Mycoplasma pneumoniae* [17] can cause necrotic pneumonia secondary to an invasive organism or exaggerated host immune response. Compared to patients with pneumonia and parapneumonic effusions, children who developed necrotizing pneumonia exhibited a more protracted hospital course associated with higher rates of complications, including bronchopleural fistulas and need for thoracotomy for fistula repair or lobectomy. None of the necrotizing pneumonia patients were immune deficient [18].

Approach

The diagnosis of CAP is usually made based on the presence of respiratory symptoms (cough, retractions) in a febrile and tachypneic child. The presence of infiltrates on chest radiographs confirms the diagnosis of pneumonia. Infiltrates are generally either interstitial or alveolar. Although alveolar infiltrates are more commonly observed during bacterial pneumonia [19], in most studies, the pattern of infiltrates has not been shown to correctly differentiate viral from bacterial pneumonia [20]. Chest radiographs will also detect the presence of pleural effusions, pneumatoceles which are observed during staphylococcal pneumonia, or presence of air–fluid levels indicative of abscess formation.

After initial stabilization, diagnostic testing should be performed rapidly, avoiding delays in the administration of initial empiric therapy. In addition to a chest radiograph, an admitted patient should have a complete blood count and differential and routine blood chemistry testing (including glucose, serum sodium, liver and renal function tests, and electrolytes). All admitted patients should have oxygen saturation assessed by pulse oximetry and supplemental oxygen administered as needed. Arterial blood gas should be measured in any patient with severe illness to assess both the level oxygenation and the degree of carbon dioxide retention.

For critically ill patients with pneumonia, an aggressive approach to determine the causative microbial agent is warranted. Microbiologic confirmation is ultimately obtained for approximately 30%–50% of children with CAP [21]. If a pleural effusion is present, aspiration of pleural fluid for Gram stain and culture prior to starting antibiotics is valuable. Blood culture may reveal organisms in up to 30% of patients with bacterial pneumonia [22]. Sputum collection is usually not practical for infants and children, and bacterial organisms recovered from the nasopharynx do not accurately predict the etiology of pneumonia. However, recovery of viruses and other atypical pathogens from the nasopharynx is more predictive. Bacterial organisms recovered from tracheal secretions obtained through an

endotracheal tube may or may not reflect the causative agent(s) responsible for lower respiratory tract infection. Specimens are considered appropriate for examination if they contain ≤10 epithelial cells and ≥25 polymorphonuclear leukocytes under low power [23]. The primary purpose of tracheal aspirate samples is to visualize a bacterial morphology of an organism that was not anticipated so that appropriate drugs can be added to the initial antibiotic regimen (e.g., *Staph. aureus* or an enteric Gram-negative antibiotic). Bronchoalveolar lavage (BAL) has been shown to be a rapid, relatively safe, and relatively noninvasive diagnostic procedure to obtain lower respiratory tract samples for microbial identification and analysis.

Other techniques that can be used to identify pathogens include antigen detection of bacteria and viruses using immunofluorescence, polymerase chain reaction, and serology such as cold agglutination test for *M. pneumonia*. The specificity of the cold agglutination test for *M. pneumonia* is almost absolute, although the sensitivity is only about 50%. Detection of *Mycoplasma* IgM by enzyme-linked immunoabsorbant assay (ELISA) is a sensitive technique and should be considered for children [24].

Pneumonia in the Immunocompromised Host

Definitions and Main Features

Immunocompromised patients are those whose immune mechanisms are deficient because of congenital immune deficiency syndromes, acquired immunologic disorders, or exposure to cytotoxic chemotherapy and steroids. In addition, recipients of solid organ and hematopoietic stem cell transplantation (HSCT) are frequently given life-long treatment with immunosuppressive agents designed to prevent graft rejection or graft-versus-host disease. Patients who develop severe neutropenia (i.e., an absolute neutrophil count ≤500 cells/mL) or lymphopenia for prolonged periods of time are at greatest risk to develop a variety of infectious complications, including life-threatening pneumonia. The lung is the predominant site of opportunistic infection in the immunocompromised patient [25].

Pathogens

Immunosuppressed patients are predisposed to develop infections by ubiquitous microorganisms that do not normally cause disease in healthy people. They are also more susceptible to the usual causes of pneumonia, which can affect anyone. The sequence in which different organisms appear in the immunosuppressed and post-transplant recipients is fairly characteristic. Nosocomial bacterial infections remain the most common cause of pneumonia during the early post-transplant, neutropenic phase. *Staphylococcus aureus* and Gram-negative pathogens predominate. In addition, fungal infections with *Candida* and *Aspergillus* species are not uncommonly seen during a severe neutropenic phase. The second period, from 1 to 6 months after solid organ transplant, is the time when opportunistic infections more commonly associated with transplantation, including *Nocardia*, *P. carinii/jiroveci*, and CMV are observed [26]. During the third period, after 6 months, patients are categorized into different risk groups depending on the level of function of their allograft and the degree of immunosuppression they have received. Those who are on minimal immunosuppression therapy are subject mainly to the same pathogens as the rest of the community. Those with allograft dysfunction and ongoing heavy immunosuppressive therapy remain subject to all of the opportunistic infections seen during the second period. Lung transplant recipients who develop bronchiolitis obliterans and HSCT recipients who develop graft-versus-host disease remain especially at risk for infections [26].

Approach

Pulmonary infiltrates in the immunocompromised host may be caused by a variety of organisms, and may have noninfectious causes. Because progression to respiratory failure may be rapid, an aggressive approach to diagnosis and treatment is necessary to limit morbidity and mortality. Initial broad-spectrum therapy is important, with alterations of the empiric regimen once the clinical situation has stabilized and more diagnostic information has been obtained. In the immunocompromised host, BAL procedure should be performed promptly to rule out infectious etiologies. Table 17.3

Table 17.3. Evaluation of bronchoalveolar lavage in immunocompromised hosts.

Stains	Culture	Antigen determinations	Cytology
KOH	Bacterial	*Legionella*	Cell count and differential
Gram's	Routine aerobic	Respiratory syncytial virus	
Silver methenamine	*Legionella*	Cytomegalovirus	
Pneumocystis carinii	*Nocardia*		
Fungi	*Mycobacterium*		
Wright	Viral		
Chlamydia inclusions	Cytomegalovirus shell vial		
Hematoxylin and eosin	Respiratory syncytial virus		
Oil-Red-O	Influenza		
Lipid-laden macrophage index	Parainfluenza		
	Adenovirus		
	Enteroviruses		
	Fugal		
	Aspergillus		
	Candida		
	Chlamydia		

lists suggested BAL fluids analysis studies and cultures. Bronchoalveolar lavage is very helpful in the diagnosis of *P. carinii/jiroveci*, CMV, tuberculosis, and some fungal infections. However, the ability of BAL fluids analysis and culture to detect invasive aspergillosis, one of the most lethal infectious complication after transplantation, is limited [27]. The diagnostic yield for *Aspergillus* species infection has been enhanced by the recently developed ELISA that detects galactomannan, a fungal cell wall component released during invasive disease [28]. Histopathologic analysis and culture of open lung biopsy specimens may provide accurate determination for the cause of pulmonary infiltrates in pediatric patients [29]. However, open lung biopsy is associated with a significant surgical risk in critically ill patients. Open lung biopsy is most effective and least risky when performed early in the course of patients who develop nodular infiltrates that require rapid differentiation between fungal infections and more benign lesions [30].

Chemoprophylaxis against opportunistic infections is an important component of management of the post-transplant immunosuppressed patients. Before the widespread introduction of chemoprophylaxis, *P. carinii* pneumonia (PCP) was observed to be a common opportunistic infection among transplant recipients. With the administration of low-dose trimethoprim–sulfamethoxazole or an alternative prophylactic agent such as pentamidine, PCP can be effectively prevented [31]. Prophylaxis is also recommended for CMV in high-risk CMV seronegative recipients. Such prophylaxis includes intravenous ganciclovir for 14 days, followed by oral ganciclovir capsules for three months [32].

Aspiration Pneumonia

Definitions and Main Features

Aspiration pneumonia refers to the pulmonary consequences resulting from the abnormal entry of fluid, formula, or endogenous secretions into the lower airways. There is usually compromise in host defenses that protect the lower airways, including glottic closure, cough reflex, and other clearing mechanisms. Histories of seizure, anesthesia, or other episode of reduced level of consciousness, neurologic disease, dysphagia, or gastroesophageal reflux are all risk factors for aspiration. The risk of aspiration is especially high after removal of an endotracheal tube because of the residual effects of sedative drugs, the presence of a nasogastric tube, and swallowing dysfunction related to alterations of upper-airway sensitivity, glottic injury, and laryngeal muscular dysfunction [33]. Aspiration pneumonia may be classified into three clinical syndromes: chemical pneumonitis, bacterial infection, and airway obstruction. In animal models, development of chemical pneumonitis requires a 1 to 4 mL/kg inoculum of fluid with a pH of 2.5 to initiate an inflammatory reaction that may lead to pulmonary fibrosis [34]. Bacteria, present in the aspirated oropharyngeal and gastric secretions, may also lead to pneumonia. Aspiration pneumonia may involve particulate matter or foreign body, which, in addition to causing airway obstruction or reflux airway closure, may synergistically contribute to acid-induced lung injury [34].

Pathogens

True aspiration pneumonia, by convention, usually refers to an infection caused by less virulent bacteria, primarily anaerobes, which are common constituents of the normal flora in a susceptible host prone to aspiration. Pneumonia is commonly caused by oropharyngeal flora, including anaerobic Gram-negative bacilli (*Bacteroides fragilis*, *Fusobacterium nucleatum*, *Peptostreptococcus*, and *Prevotella*) and anaerobic Gram-positive bacilli (*Clostridium*, *Eubacterium*, *Actinomyces*, *Lactobacillus*, and *Propionibacterium*).

Approach

Aspiration usually occurs when the patient is supine during or immediately after feeding. In the supine position the right upper lobe is the most dependent part of the lung and is most frequently affected. Commonly, impaired airway protective responses are observed. The presence of tracheoesophageal malformations should be investigated if recurrent aspiration is noted in an otherwise healthy infant.

The clinical presentation and course of chemical pneumonitis after inhalation of gastric contents ranges from mild and self-limited to severe and life threatening, depending on the nature of the aspirate and the underlying condition of the host. In the absence of witnessed inhalation of vomit, diagnosis is difficult and requires a high index of suspicion in a patient who has risk factors for aspiration. In the absence of an obvious predisposition, the abrupt onset of a self-limited illness characterized by dyspnea, cyanosis, and low-grade fever associated with diffuse rales, hypoxemia, and alveolar infiltrates in dependent lobes should suggest aspiration [35]. If BAL is performed, assessment of lipid-laden macrophage index using Oil-Red-O stain is helpful in confirming the diagnosis [36]. The presence of foul-smelling putrid discharge in sputum or pleural fluid is regarded as diagnostic of anaerobic infection. Patients often have prolonged fever and productive cough, frequently showing blood in the sputum, which indicates necrosis (tissue death) in the lung. If aspiration is persistent, fibrosis and bronchiectasis may result.

A number of interventions (e.g., positioning, dietary changes, drugs, oral hygiene, tube feeding) have been proposed to prevent aspiration Patients with an observed aspiration should have immediate tracheal suction or bronchoscopy to clear fluids and particulate matter that may cause obstruction. The use of corticosteroids in the treatment of chemical pneumonitis is controversial [37], and antibiotics should not be used early in the course unless a superimposed bacterial infection is suspected.

Nosocomial and Ventilator-Associated Pneumonia

Definitions and Main Features

The National Nosocomial Infection Surveillance (NNIS) program sponsored by the CDC defines VAP as pneumonia in patients who have been on mechanical ventilation for >48 hr and have developed new and persistent radiographic evidence of focal infiltrates. In addition, patients had to have two of the following: temperature >38′C, leukocytosis (white blood cell >12,000/mm^3), and purulent sputum (>25 white blood cells/high-powered field on tracheal aspirate Gram stain). After blood stream infections, VAP is the second most common cause of nosocomial infections in PICUs. The mean VAP rate in children ranges from 6 to 12/1,000 ventilator days, accounting for 20%–50% of hospital-acquired infections [38,39]. Infections acquired in the PICU are associated with a significantly increased risk of death [40].

Pathogens

Nosocomial pneumonia and VAP are typically categorized as either early onset (occurring in the first 3–4 days of mechanical

ventilation) or late onset. This distinction is important microbiologically. Early-onset nosocomial pneumonia and VAP are commonly caused by antibiotic-sensitive, community-acquired organisms (e.g., *Strep. pneumoniae*, and *Staph. aureus*). Late-onset nosocomial pneumonia and VAP are commonly caused by anti-biotic-resistant nosocomial organisms (e.g., *P. aeruginosa*, methicillin-resistant *Staph. aureus*, *Acinetobacter* species, and *Enterobacter* species). During the winter respiratory viral season, all patients in a medical care environment are at risk for disease due to respiratory syncytial virus, parainfluenza, and influenza viruses. Legionnaire's disease is a multisystem illness with pneumonia caused by *Legionella* species usually present in contaminated water. Legionnaire's disease is less common in children than adults.

Approach

Compared with postmortem lung biopsies and culture results, the use of clinical criteria to diagnose VAP (lung infiltrates, leukocytosis, purulent secretions, fever) had a sensitivity of 69% and a specificity of 75% [41]. Clearly, a number of noninfectious causes of fever and pulmonary infiltrates can also occur in these patients, making the above clinical criteria nonspecific for the diagnosis of VAP. Lung infiltrates may be caused by pulmonary hemorrhage, chemical aspiration, or atelectasis. Fever may be caused by a drug reaction, extrapulmonary infection, or blood transfusion. Autopsy results in a series of patients with acute lung injury demonstrated that clinical criteria alone led to an incorrect diagnosis of VAP in 29% of clinically suspected cases [42]. These limitations have encouraged the use of invasive approaches to sample and culture material from the lower respiratory tract for accurate diagnosis of VAP.

Ventilator-associated pneumonia is most accurately diagnosed by quantitative culture and microscopic examination of lower respiratory tract secretions, which are best obtained by bronchoscopy and BAL [43]. Cultures of tracheal aspirates are not very useful in establishing the cause of VAP [44]. Although such cultures are highly sensitive, their specificity is low even when they are cultured quantitatively [45]. Combining clinical and bacteriologic evaluation is probably the best way to achieve the objectives of correctly diagnosing VAP and appropriately using antimicrobial agents. The main aims of this diagnostic approach are to rapidly identify patients with true lung bacterial infection, to select appropriate initial antimicrobial therapy, to adjust therapy based on antibiotic sensitivities, and to withhold antibiotics from patients without VAP. Guidelines for the prevention of VAP in children are lacking, but data extrapolated from adult studies support routine elevation of head of bed 30°, appropriate use of sedatives and muscle relaxants, and adequate oral and circuit hygiene [46].

Empyema

Definitions and Main Features

Empyema is the presence of purulent material containing polymorphonuclear leukocytes and fibrin in the pleural cavity. Empyema is usually a complication of inadequately treated bacterial CAP, although it may occur after trauma, thoracic surgery, or intrathoracic esophageal perforation. Although parapneumonic pleural effusions are noted in up to 34&–40% of children with pneumonia, empyema is rare, present in 1%–2% of cases [47]. The formation of an empyema can be divided into three stages: exudative, fibrinopurulent, and organizing. During the exudative stage, pus accumulates. This is followed by fibrin deposition and loculation of pleural fluid known as the fibrinopurulent stage. The organizing stage is characterized by fibroblast proliferation; at this time there is the potential for lung entrapment by scarring [48].

Typically, the pleural fluid in empyema is exudative, caused by protein leakage from the capillaries because of increased permeability and increased hydrostatic pressure during the inflammatory process. Although the distinction between transudates and exudates is sometimes difficult to make, several features favor an exudative process. If at least one of the following three criteria is present, the fluid is virtually always an exudate: (1) pleural fluid protein >2.9 g/dL or protein/serum protein ratio greater than 0.5; (2) pleural fluid lactate dehydrogenase (LDH)/serum LDH ratio greater than 0.6; and/or (3) pleural fluid LDH greater than two thirds the serum LDH [49,50].

Pathogens

The most common organisms that cause empyema in children are Strep. pneumoniae, *Staph. aureus*, and group A streptococci. *Haemophilus influenzae* is rarely encountered since the advent of the *H. influenzae* B vaccine. *Mycoplasma pneumoniae* and viruses can rarely result in exudative pleural effusions. In a series of 72 pediatric patients with empyema, 24% were secondary to anaerobic infection [51]. These data highlight the importance of anaerobic bacteria in selected cases of empyema in children and adolescents. In addition, tuberculosis should always be considered in the differential diagnosis, and a purified protein derivative test should be performed.

Approach

The differential diagnosis of patients with pleural effusions is shown in Table 17.4. The presence of fever associated with clinical signs of bacterial pneumonia is a clue to an underlying pneumonia as the cause of the effusion. A lateral decubitus radiograph, ultrasonography, or computed tomography may differentiate whether the fluid is loculated. A sample of the fluid should be obtained by thoracentesis in order to determine if the effusion is a transudate versus exudate. Pleural cultures are positive in approximately one half of pediatric patients with empyema. Blood culture and urine latex agglutination may help to identify a bacterial pathogen. A pneumatocele or pneumothorax seen on chest film suggests *Staph. aureus* as the cause of the empyema.

Until a specific organism is identified, empiric antibiotic therapy should be instituted. This might include a third-generation cephalosporin and antistaphylococcal β-lactamase–resistant penicillin. Antibiotics can be adjusted once an organism is identified. Antibiotic therapy should be intravenous until the patient becomes afebrile and then should be continued orally for an additional 2–3 weeks.

Table 17.4. Causes of pleural effusion.

Transudate	Exudate
Parapneumonic effusions	Empyema
Congestive heart failure	Neoplasms
Nephrotic syndrome	Connective tissue disorder
Cirrhosis	Pancreatitis
Ascites	Esophageal perforation
Hypothyroidism	Chylothorax

There is major debate as to the proper adjuvant treatment of children with empyema. Prospective, randomized and controlled studies of children with empyema are lacking. With the exception of starting appropriate or empiric antibiotics, there is no consensus on when and in whom to place a chest tube, instill fibrinolytic agents, or take to the operating room [52]. In 1992, Light suggested that chest tubes should be inserted if the pleural fluid is gross pus, if the Gram stain of the pleural fluid is positive, if the pleural fluid glucose level is below 40 mg/dL, or if the pleural fluid pH level is less than 7.00 [53]. If drainage with a chest tube is unsatisfactory, either urokinase or tissue plasminogen activator (tPA) should be injected intrapleurally [54,55]. If drainage is still unsatisfactory, a decortication should be considered [56]. A stage-related approach to the management of empyema is perhaps most efficacious and cost-effective [57]. In the exudative stage, conservative treatment using tube drainage may suffice. Fibrinolytic treatment may be useful during the fibrinopurulent stage. In contrast, aggressive treatment using surgical decortication may be necessary during the organizing stage.

With the advent of video-assisted thoracoscopy (VATS), these traditional approaches to management of empyema in children are being challenged. Video-assisted techniques offer distinct advantages in the accurate staging of the disease process, effectiveness of management of organizing pleural disease, and post-operative patient comfort [58]. In a retrospective study, the performance of early VATS (<48 hr after admission) in children with empyema was associated with significantly decreased length of hospital stay compared with performance of late VATS (>48 hr after admission) [59].

Children treated for empyema generally recover and have no residual sequelae. Radiographs at the time of discharge usually show pleural thickening that later resolves. Follow-up pulmonary function tests and physical examination are also usually normal or consistent with mild restrictive disease [60].

General Treatment Principles

Antimicrobial Therapy

Most epidemiologic investigations have clearly demonstrated that the indiscriminate administration of antibiotic agents to patients in the PICU has contributed to the emergence of multiresistant pathogens with potentially increased morbidity and mortality. The prevalence of penicillin-resistant strains of *Strep. pneumoniae*, methicillin-resistant *Staph. aureus*, vancomycin-resistant *Enterococcus*, and Gram-negative bacteria producing extended-spectrum β-lactamase is increasing. Despite these concerns, it is clear that patient survival may improve if pneumonia is correctly and rapidly treated. In adults, inappropriate initial antibiotic therapy is strongly associated with fatality [61]. Therefore, it may be concluded that empiric antibiotics for the treatment of severe pneumonia are indicated.

The choice of antibiotics is based on several factors, including the age of the patient, the type of pneumonia, and the local resistant patterns of predominant bacterial pathogens. Suggested choices for initial empiric antibiotic coverage for pneumonia in the PICU are listed in Table 17.5. Aspiration pneumonia occurring in the community can be treated with ampicillin-sulbactam. Empiric treatment for pneumonia in immunocompromised hosts requires broad-spectrum Gram-positive and Gram-negative coverage.

Table 17.5. Common bacterial causes and empiric antibiotic therapy for pneumonia in the pediatric intensive care unit.

	Community-acquired pneumonia	Ventilator-associated pneumonia
Usual pathogens	Infant	Gram positive
	Streptococcus pneumoniae	*Staphylococcus aureus*
		Methicillin-resistant *Staphylococcus aureus* (MRSA)
	Staphylococcus aureus	Gram negative
		Klebsiella pneumoniae
	Child and adolescent	*Pseudomonas aeruginosa*
	Streptococcus pneumoniae	*Escherichia coli*
	Mycoplasma, Chlamydia	*Serratia marcescens*
		Acinotobacter sp.
		Stenotrophomonas maltophilia
Recommended initial treatment	Infant:	Ticarcillin-clavulanate or Piperacillin-tazobactam + aminoglycoside
	Cefuroxime+ cloxacillin	Alternatives
	Child and adolescent	Vancomycin (if MRSA present)
	Cefuroxime + erythromycin	Ceftazidime+ aminoglycoside (if suspect *Pseudomonas*)

Immunocompromised patients are especially susceptible to a variety of life-threatening opportunistic viral and fungal pneumonias that require prompt diagnosis and aggressive treatment. For example, trimethoprim-sulfamethoxazole or pentamidine should be given for *P. carinii/jiroveci*, amphotericin B or caspofungin for *Candida* and *Aspergillus species*, acyclovir for herpes, amantadine for influenza, ganciclovir or foscarnet for CMV, and ribavirin for severe respiratory syncytial virus. Empiric regimens may need to be modified once results of cultures and antibiotic susceptibility testing are available.

Antiinflammatory Approach

The inflammatory response to infection is necessary for host defense but can contribute to the systemic toxicity and lung injury that may result from pneumonia. In some settings, adjunctive treatment of lower respiratory infections with antiinflammatory agents can reduce morbidity. Corticosteroids have a well-documented role in the management of *P. carinii/jiroveci* pneumonia. In a multicenter trial, infusion of hydrocortisone significantly decreased length of hospital stay and prevented mortality in adult patients with CAP [62]. Corticosteroids also may be effective under some circumstances in the treatment of inflammatory sequelae of respiratory tract infection, such as tuberculous pleurisy and bronchiolitis obliterans organizing pneumonia (BOOP). Strategies targeting specific cytokines have not been effective to date but remain active areas of investigation. Enhanced understanding of the interactions of pathogen components with TLRs may be helpful one day in controlling and containing infectious diseases.

Vaccines

Immunization has reduced the incidence of several serious childhood diseases. Immunization against influenza and increasingly resistant pneumococci can play a critical role in the prevention of pneumonia, particularly in immunocompromised patients.

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