**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 is prevalent in the out-of-hospital environment. 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
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 epithelial cells 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.

### 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.

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

<table>
<thead>
<tr>
<th>Function</th>
<th>SP-A</th>
<th>SP-D</th>
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<tbody>
<tr>
<td>Agglutination</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Opsonization</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Reduced viral infectivity</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Modulation of inflammation</td>
<td>+</td>
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</tr>
</tbody>
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### Figure 17.1. Toll-like receptors (TLR) and their ligands. LPS, lipopolysaccharide; HSPs, heat shock proteins.