CbpA, PspC, Hyl, pneumolysin, and the neuraminidases (Fig. 171-2). Adhesion coupled with inflammation induced by pneumococcal factors such as peptidoglycans and teichoic acids results in invasion. It is the inflammation induced by various bacterium-derived factors that is responsible for the pathology associated with pneumococcal infection. Cell wall–derived teichoic acids and peptidoglycans induce a variety of cytokines, including the proinflammatory cytokines interleukin (IL) 1, IL-6, and tumor necrosis factor, and activate complement via the alternative pathway. Polymorphonuclear leukocytes are thus attracted, and an intense inflammatory response is initiated. Pneumolysin also is important in local pathology, inducing proinflammatory cytokine production by local monocytes.

The pneumococcal capsule, consisting of polysaccharides with antiphagocytic properties due to resistance to the deposition of complement, plays an important role in pathogenesis. While most capsular types can cause human disease, certain capsular types are more commonly isolated from sites of infection. The reason for the dominance of some serotypes over others in IPD, as depicted in Fig. 171-3, is unclear.

HOST DEFENSE MECHANISMS

Innate Immunity As described above, intact respiratory epithelium and a host of nonspecific or innate immune factors (e.g., mucus, splenic function, complement, neutrophils, and macrophages) constitute the first line of defense against pneumococci. Physical factors such as the cough reflex and the mucociliary escalator are important in clearing bacteria from the lungs. Immunologic factors are critical as well: C-reactive protein (CRP) binds phosphorylcholine in the pneumococcal cell wall, inducing complement activation and leading to bacterial clearance; Toll-like receptor 2 (TLR2) recognizes both pneumococcal lipoteichoic acid and cell wall peptidoglycan; and in animal models, the absence of host TLR2 leads to more severe infection and impaired clearance of nasopharyngeal colonization. TLR4 appears to be necessary for the proinflammatory effect of pneumolysin on macrophages. The importance of TLR recognition is underlined by descriptions of an inherited deficiency of human IL-1 receptor–associated kinase 4 (IRAK-4) that manifests as an unusual susceptibility to infection with bacteria, including *S. pneumoniae*. IRAK-4 is essential for the normal functioning of several TLRs. Other factors that interfere with these nonspecific mechanisms (e.g., viral infections, cystic fibrosis, bronchiectasis, complement deficiency, and chronic obstructive pulmonary disease) all predispose to the development of pneumococcal pneumonia. Patients who lack a spleen or have abnormal splenic function (e.g., persons with sickle cell disease) are at high risk of developing overwhelming pneumococcal disease.

Acquired Immunity Acquired immunity induced via contact following colonization or through cross-reactive antigens rests largely on the development of serum IgG antibody specific for the pneumococcal capsular polysaccharide. Nearly all polysaccharides are T cell–independent antigens; B cells can make antibodies to such antigens without T cell help. However, in children <1–2 years old, such B cell responses are poorly developed. This delayed ontogeny of capsule-specific IgG in young children is associated with susceptibility to pneumococcal infection (Fig. 171-5). The extremely high risk of pneumococcal infection in the absence of serum immunoglobulin (i.e., in conditions such as agammaglobulinemia) highlights the important role of capsular antibody in protection against disease. Each serotype's capsule is chemically distinct; thus immunity tends to be serotype specific, although some cross-immunity exists. For example, conjugate vaccine–induced antibodies to serotype 6B prevent infection due to serotype 6A. However, cross-protection against serotypes within serogroups is not universal; for instance, antibodies to serotype 19F do not appear to confer protection against disease caused by serotype 19A. Antibodies to surface-exposed or secreted pneumococcal proteins (such as pneumolysin, PsaA, and PspA) also appear in the circulation with increasing age of the host, but their functional significance remains unclear. Data from murine models suggest that CD4+ T cells may play a role in preventing pneumococcal colonization and disease, and recent experimental data derived from humans suggest that IL-17-secreting CD4+ T cells may be relevant.

APPROACH TO THE PATIENT: Pneumococcal Infections

There is no pathognomonic presentation of pneumococcal disease; patients may present with a range of syndromes and with more than one clinical syndrome (e.g., pneumonia and meningitis). *S. pneumoniae* can infect nearly any body tissue, manifesting as disease ranging in severity from mild and self-limited to life-threatening. The differential diagnosis of common clinical syndromes such as pneumonia, otitis media, fever of unknown origin, and meningitis should always include pneumococcal infection. A microbiologically confirmed diagnosis is made in only a minority of pneumococcal cases since, in most circumstances (and especially in pneumonia and otitis media), fluid from the site of infection is not available for etiologic determination. Empirical therapy that includes appropriate treatment for *S. pneumoniae* is often indicated.

Algorithms for assessment and management of ill children have been developed for use in the developing world or in other settings where evaluation by a trained physician may not be feasible. Children who present with ominous signs such as an inability to drink, convulsions, lethargy, and severe malnutrition are categorized as having very severe disease without further evaluation by the community health care worker, are given antibiotics, and are immediately referred to a hospital for diagnosis and management. Children who present with cough and tachypnea (the latter defined according to specific age strata) are further stratified into severity categories based on the presence or absence of lower chest wall indrawing and are managed accordingly with either antibiotics alone or antibiotics and referral to a hospital facility. Children with cough but no tachypnea are categorized as having a nonpneumonia respiratory illness.

CLINICAL MANIFESTATIONS

The clinical manifestations of pneumococcal disease depend on the site of infection and the duration of illness. Clinical syndromes are classified as noninvasive (e.g., otitis media and nonbacteremic pneumonia) or invasive (e.g., bacteremic pneumonia). The pathogenesis of noninvasive illness involves contiguous spread from the nasopharynx or skin; invasive disease involves infection of a normally sterile body fluid or follows bacteremia.

Pneumonia Pneumonia is the most common serious pneumococcal syndrome and is considered invasive when associated with a positive blood culture. Pneumococcal pneumonia can present as a mild community-acquired infection at one extreme and as a life-threatening disease requiring intubation and intensive support at the other.

PRESENTING MANIFESTATIONS The presentation of pneumococcal pneumonia does not reliably distinguish it from pneumonia of other etiologies. In a subset of cases, pneumococcal pneumonia is recognized at the outset as associated with a viral upper respiratory infection and is characterized by the abrupt onset of cough and dyspnea accompanied by fever, shaking chills, and myalgias. The cough evolves from nonpurulent to productive of sputum that is purulent and sometimes tinged with blood. Patients may describe stabbing pleuritic chest pain and significant dyspnea indicating involvement of the parietal pleura. Among the elderly, the presenting clinical symptoms may be less specific, with confusion or malaise but without fever or cough. In such cases, a high index of suspicion is required because failure to treat pneumococcal pneumonia promptly in an elderly patient is likely to result in rapid evolution of the infection, with increased severity, morbidity, and risk of death.

FINDINGS ON PHYSICAL EXAMINATION The clinical signs associated with pneumococcal pneumonia among adults include tachypnea