182 *Haemophilus* and *Moraxella* Infections

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HAEMOPHILUS INFLUENZAE

MICROBIOLOGY

Haemophilus influenzae was first recognized in 1892 by Pfeiffer, who erroneously concluded that the bacterium was the cause of influenza. *H. influenzae* is a small (1- × 0.3-μm) gram-negative organism of variable shape; thus, it is often described as a pleomorphic coccobacillus. In clinical specimens such as cerebrospinal fluid (CSF) and sputum, *H. influenzae* frequently stains only faintly with safranin and therefore can easily be overlooked.

H. influenzae grows both aerobically and anaerobically. Its aerobic growth requires two factors: hemin (X factor) and nicotinamide adenine dinucleotide (V factor). These requirements are used in the clinical laboratory to identify the bacterium. Caution must be used to distinguish *H. influenzae* from *H. haemolyticus*, a respiratory tract commensal that has identical growth requirements. *H. haemolyticus* has classically been distinguished from *H. influenzae* by the hemolysis of the former species on horse blood agar. However, a significant proportion of isolates of *H. haemolyticus* have now been recognized as nonhemolytic. Analysis of various genotypic and phenotypic markers, including16S ribosomal sequences, superoxide dismutase, outer-membrane protein P6, protein D, and fuculose kinase, can be used to distinguish these two species.

Six major serotypes of *H. influenzae* have been identified; designated *a* through *f*, they are based on antigenically distinct polysaccharide capsules. In addition, some strains lack a polysaccharide capsule and are referred to as *nontypable* strains. Type b and nontypable strains are the most relevant strains clinically (Table 182-1), although encapsulated strains other than type b can cause disease. *H. influenzae* was the first free-living organism to have its entire genome sequenced.

The antigenically distinct type b capsule is a linear polymer composed of ribosyl-ribitol phosphate. Strains of *H. influenzae* type b (Hib) cause disease primarily in infants and children <6 years of age. Nontypable strains are primarily mucosal pathogens but occasionally cause invasive disease.

EPIDEMIOLOGY AND TRANSMISSION

H. influenzae, an exclusively human pathogen, is spread by airborne droplets or by direct contact with secretions or fomites. Colonization with nontypable *H. influenzae* is a dynamic process; new strains are acquired and other strains are replaced periodically.

The widespread use of Hib conjugate vaccines in many industrialized countries has resulted in striking decreases in the rate of nasopharyngeal colonization by Hib and in the incidence of Hib infection (Fig. 182-1). However, the majority of the world's children remain unimmunized. Worldwide, invasive Hib disease occurs predominantly in unimmunized children and in those who have not completed the primary immunization series. Certain groups have a higher incidence of invasive Hib disease than the general population, including African-American children and Native American groups. Although this increased incidence has not yet been accounted for, several factors may be relevant, including age at exposure to the bacterium, socioeconomic conditions, and genetic differences.

TABLE 182-1 CHARACTERISTICS OF TYPE b AND NONTYPABLE STRAINS OF *HAEMOPHILUS INFLUENZAE*

Feature	Type b Strains	Nontypable Strains
Capsule	Ribosyl-ribitol phosphate	Unencapsulated
Pathogenesis	Invasive infections due to hematogenous spread	Mucosal infections due to contiguous spread
Clinical manifestations	Meningitis and invasive infections in incompletely immunized infants and children	Otitis media in infants and children; lower respiratory tract infections in adults with chronic bronchitis
Evolutionary history	Basically clonal	Genetically diverse
Vaccine	Highly effective conjugate vaccines	None available; under development

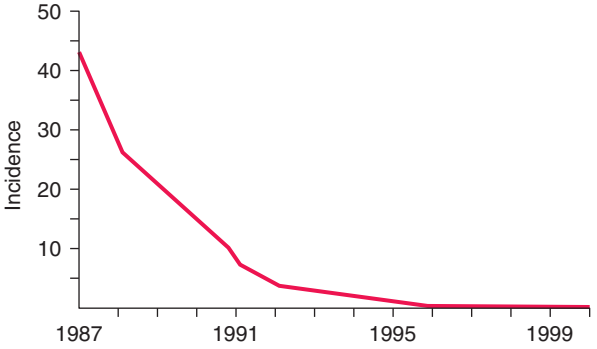

FIGURE 182-1 Estimated incidence (rate per 100,000) of invasive disease due to *Haemophilus influenzae* type b among children <5 years of age: 1987–2000. Fewer than 40 cases per year have been reported since 2000. *(Data from the Centers for Disease Control and Prevention.)*

PATHOGENESIS

Hib strains cause systemic disease by invasion and hematogenous spread from the respiratory tract to distant sites such as the meninges, bones, and joints. The type b polysaccharide capsule is an important virulence factor affecting the bacterium's ability to avoid opsonization and cause systemic disease.

Nontypable strains cause disease by local invasion of mucosal surfaces. Otitis media results when bacteria reach the middle ear by way of the eustachian tube. Adults with chronic bronchitis experience recurrent lower respiratory tract infection due to nontypable strains. In addition, persistent nontypable *H. influenzae* colonization of the lower airways of adults with chronic obstructive pulmonary disease (COPD) contributes to the airway inflammation that is a hallmark of the disease. Nontypable strains that cause infection in adults with COPD differ in pathogenic potential and genome content from strains that cause otitis media. In the middle ear, nontypable strains form biofilms. More resistant to host clearance mechanisms and to antibiotics than are planktonic bacteria, biofilms are associated with chronic and recurrent otitis media. The incidence of invasive disease caused by nontypable strains is low. Strains that cause invasive disease are genetically and phenotypically diverse.

IMMUNE RESPONSE

Antibody to the capsule is important in protection from infection by Hib strains. The level of (maternally acquired) serum antibody to the capsular polysaccharide, which is a polymer of polyribitol ribose phosphate (PRP), declines from birth to 6 months of age and, in the absence of vaccination, remains low until ~2 or 3 years of age. The age at the antibody nadir correlates with that of the peak incidence of type b disease. Antibody to PRP then appears partly as a result of exposure to Hib or cross-reacting antigens. Systemic Hib disease is unusual after the age of 6 years because of the presence of protective antibody. Vaccines in which PRP is conjugated to protein carrier molecules have been developed and are now used widely. These vaccines generate an antibody response to PRP in infants and effectively prevent invasive infections in infants and children.

Since nontypable strains lack a capsule, the immune response to infection is directed at noncapsular antigens. These antigens have generated considerable interest as immune targets and potential vaccine components. The human immune response to nontypable strains appears to be strain-specific, a characteristic that accounts in part for the propensity of these strains to cause recurrent otitis media and recurrent exacerbations of chronic bronchitis in immunocompetent hosts.