81 *Haemophilus influenzae* Infections

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Haemophilus influenzae is a common cause of a wide variety of childhood diseases that cause significant morbidity and mortality. It is the serotype b that is known to be more invasive and cause most of severe diseases. Before introduction of the conjugate HIB vaccine, the incidence of serious disease due HIB is 50–300/100,000 children below 5 years of age. *H. influenzae* type b (HIB) is the most common causative organism of bacterial meningitis accounting for 50–70% childhood meningitis. Ninety-one percent of HIB meningitis occurred in children less than 2 years of age. Many studies from Saudi Arabia have shown HIB to be the cause of 50–60% of childhood meningitis. In 2000, HIB was estimated to cause around eight million serious illnesses worldwide with an estimated 371,000 deaths. Conjugated HIB vaccine that is effective in early infancy has been introduced into the national vaccination program in more than 150 countries. It has resulted in significant reduction in the disease burden in these countries (*Fig. 81.1*).

In many of the developing countries this vaccine has not yet been introduced probably due to cost limitations or the misconception that HIB is not a major cause of disease in these countries. In Asia there are many studies that showed HIB to be a significant cause of serious illnesses (*Table 81.1*). Studies from some developing countries showed that infection due to *H. influenzae*, mainly type b, is far more common than developed countries. In Papua New Guinea, 11% of children 6–24 months of age were colonized with HIB. This study was confirmed by other studies from Gambia. In these two countries, *H. influenzae* combined with *Streptococcus pneumoniae* were the commonest cause of bacterial acute lower respiratory intact infections, which are the commonest cause of mortality in children <5 years of age.

Microbiology

H. influenzae is a Gram negative, facultative aerobic, nonmotile, and pleomorphic bacilli and coccobacilli that grew better in aerobic environment with CO2 enrichment. *H. influenzae* requires hematin (X) and NAD (V) factors for growth. These factors are available in chocolate agar media because the hemolyzed RBC in such a medium release hematin and NAD. There are encapsulated and nonencapsulated strains of *H. influenzae.* Encapsulated strains are grouped into six serotypes (A–F) according to their capsular determinants.

Pathogenesis

HIB is the most invasive among all *H. influenzae* strains. Only 3% of children are colonized with HIB, however this number increases to 10–15% in developing countries. HIB gains entry into the blood through translocation across the nasopharyngeal epithelium. This translocation is mediated mainly by adherence of the organism to a previously damaged or breached epithelium. The adherent factors are thought to be fimbriae and the adherence is made easy by releasing IgA protease that inhibits the action of the SlgA. Once translocation occurred, HIB gains access to the blood where it is protected from immune reaction by its capsule. In the blood, the organism multiplicates to a critical level of 10^5 colonies/mL that is required for the organism to cause disease and invade CNS and other tissues.

The entry into the CNS occurs through choroidal plexus, although it may occur through the dural traversing veins. Once in subarachnoid space, the organism elicits a cascade of inflammatory response that damage the BBB (see Chap. 69, "Meningitis").

Clinical Features

H. influenzae Type B (HIB)

Bacteremia

Isolated bacteremia can be caused by HIB. It has decreased significantly after the introduction of the vaccine. Patients usually present with high fever without any localizing signs. In patients with HIB bacteremia, meningitis should always be ruled out. Haemophilus bacteremia is more

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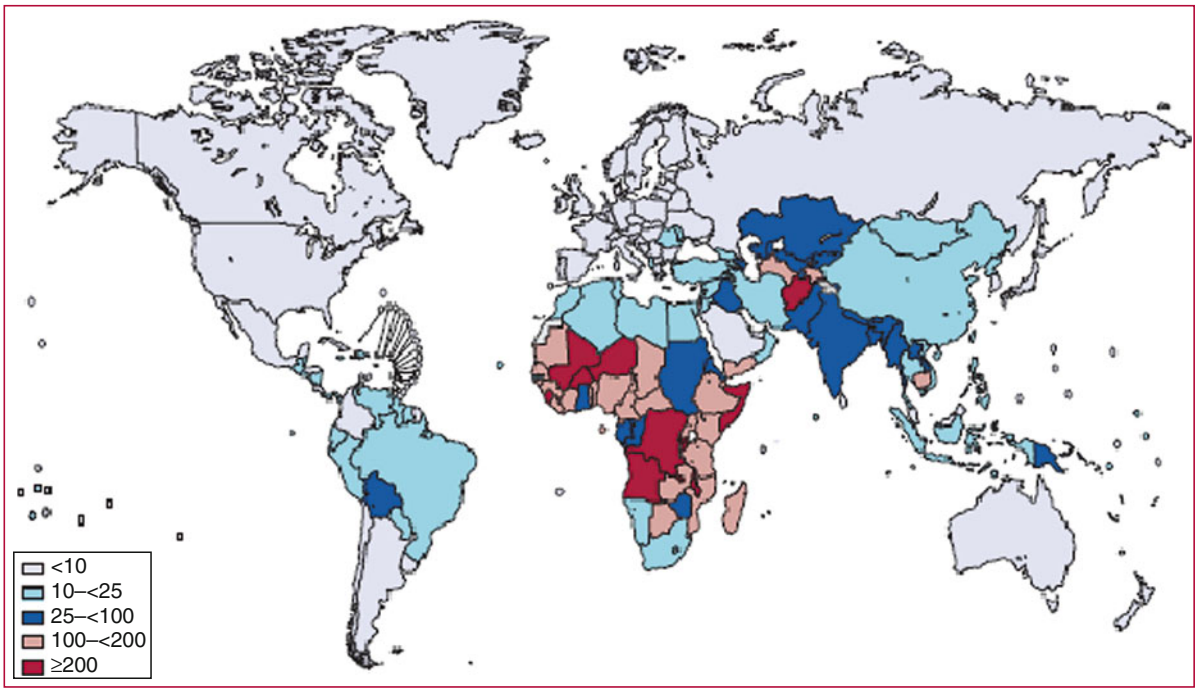

Figure 81.1
HIB mortality rate. HIB deaths in children aged 1–59 months per 100,000 children (HIV negative HIB deaths only) The boundaries shown and the designation used on this map do not imply the expression of any opinion by WHO concerning the legal status of any country, territory, city, or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement

Table 81.1
Incidence of invasive HIB disease in children aged less than 5 years, by country

Country	Treatment setting	Study design	Incidence (per 100,000)	Reference
Hong Kong	Urban	Retrospective	2.7	Lau (1995)
Japan	Regional	Retrospective	4.3–56.8	Sakata (2007)
South Korea	Regional	Prospective	6.8	Kim (2004)
New Caledonia	Rural	Retrospective	54.6	Anglaret (1993)
Philippines	Regional	Population based	95	Limcangco (2000)
Saudi Arabia	Regional	Prospective, population based	17	Al-Mazrou (2004)
Saudi Arabia	Urban, tertiary hospital	Retrospective	40	Almuneef (2001)
Singapore	Urban, single center	Retrospective	4.4	Thoon (2007)
Taiwan	Regional	Population based	5.6 in 1997, 3.2 in 2000	Shao (2004)
Thailand	Regional	Prospective	3.8	Perks-Ngarm (2004)
Vietnam	Regional	Population based	12	Anh (2006)
Indonesia	Rural	Prospective	67–158 (meningitis), 1,561 (pneumonia)	Gessner (2005)

Source: Michael B (2009) Burden of invasive disease caused by *Haemophilus influenzae* type b in Asia. Jpn J infect Dis 62:87–92

likely to be associated with invasive diseases than that of *S. pneumoniae*. Therefore patients with Haemophilus bacteremia should be hospitalized and investigated thoroughly for focal infections. Parenteral therapy with appropriate antibiotic is indicated.

Meningitis

HIB is the commonest cause of meningitis in children 3 months to 5 years of age in developing countries. The introduction of HIB conjugate vaccine has resulted in dramatic decrease in the incidence of this illness, however this vaccine is not yet universal in most of the developing countries. HIB meningitis results in 5% mortality rate and around 20% morbidity rate. The percentage of hearing loss among HIB meningitis (10%) is less than that of pneumococcus (28%) but because of higher percentage of childhood meningitis caused by HIB, the number of patients with hearing deficit due to HIB is more than any other organism. Other neurological defects include: MR 6%, paresis 5%, and seizure disorder 6%. Dexamethasone adjunctive therapy has been shown to decrease the incidence of hearing loss but not other neurological sequelae.

Epiglottitis

In contrast to other HIB invasive diseases that usually occur during the first 2 years of life, epiglottitis tends to occur more commonly in children 2–4 years of age. The affected child usually presents with abrupt onset of high fever, inspiratory stridor, difficulty in breathing, muffled voice, and drooling. The child is toxic and adopts a characteristic sitting position with protrusion of the jaw and extension of the neck to ease the breathing. There is usually no associated cough. Cautious examination of such children is required. The throat examination should not be attempted until assurance that adequate intervention methods and expertise in intubation are available if needed. This means that the patient should be examined in operation room in the presence of an otolaryngologist and anesthetist. Lateral neck radiography will show enlarged epiglottis (thumb sign), however the patient should not be moved to the radiology department unless his or her condition is stable and should be associated with an expert physician should intervention be required.

Cellulitis

Facial cellulitis in children 3 months to 5 years of age is commonly due to HIB. Periorbital cellulitis is the most common presentation.

Acute Lower Respiratory Tract Infections

HIB constitutes a major cause of lower respiratory tract infections in developing countries. In Gambia, it is estimated that the incidence of pneumonia due to HIB is around 300/100,000 children/year resulting in 40 deaths/100,000 children/year. It is assumed that this high incidence is due to early colonization with HIB.

Septic Arthritis and Osteomyelitis

HIB is a common cause of septic arthritis in children between 3 months and 5 years of age. It rarely causes osteomyelitis at any age group.

Miscellaneous Infection

HIB can cause infection at any organ including endocarditis, pericarditis, conjunctivitis, peritonitis, liver abscess, salpingitis, vaginitis, and brain abscess.

Other *H. influenzae* Serotypes

These are rare cause of childhood infections, however they can cause similar spectrum of disease as that of HIB. It is not known whether introduction of HIB conjugate vaccine will result in increase in incidence of infections due to other serotypes, however this was not proved by a study done in United States that showed no difference before and after 3 years of introducing HIB vaccine.

Nonencapsulated *H. influenzae* Infection

These are common causes of otitis media and sinusitis preceded only by *S. pneumoniae*. Most of these strains are b-lactamase producers. HIB conjugate vaccine does not confer immunity against them. There are increasing reports of these organisms causing neonatal sepsis. They also can cause invasive diseases.

Illustrative Case

A 5-month-old girl who has a ventriculoperitoneal shunt presented with a 3-day history of fever and vomiting. Computed tomography scan of the brain showed an increase of ventricular size indicating shunt malfunction. Cerebrospinal fluid culture grew nontypeable *H. influenzae*. Intravenous ceftriaxone was given for 3 days with no response. Shunt was removed and external ventricular drain was inserted and CSF was obtained in 3 consecutive days and came to be negative. Shunt was reinserted after 7 days and ceftriaxone was given for a total of 14 days and the patient responded well.

H. influenzae Biotype Aegypticus

This is a common cause of epidemic conjunctivitis in different parts of the world. It is also the cause of distinctive invasive disease that is only recognized in Brazil. It is called Brazilian purpuric fever (BPF). BPF is a septicemia disease that is characterized by high fever, toxicity, shock, and purpura arising within 7–10 days after resolving conjunctivitis that is caused by *H. influenzae* biotype aegypticus. It results in high mortality rate and usually spare CNS.

Diagnosis

H. influenzae infections can be diagnosed by clinical features and isolating the organism from the site of infection. Antigen detection studies including counter current immunoelectrophoresis and latex agglutination test can be helpful in identifying the organism in CSF, urine, and serum. Latex agglutination test has a 90–95% sensitivity and specificity in identifying HIB in CSF.

Therapy

Currently the empiric therapy of suspected invasive haemophilus infection is third generation cephalosporins (ceftriaxone 100 mg/kg/day once or twice daily or cefotaxime 150 mg/kg/day three or four times daily). This is because of the increasing incidence of ampicillin resistance among HIB that varies between 20% and 70% in different parts of the world. Chloramphenicol resistance is very low, however because of its potential hematological toxicity and the availability of safer medications, its use is decreasing. HIB resistance to chloramphenicol is mediated by the enzyme acyltransferase. It is very rare to have HIB resistant to the ampicillin and chloramphenicol combination. Otitis media and sinusitis are usually responsive to amoxicillin even if they are resistant in vitro. This is because of the high level achieved in middle ear. Therefore the initial drug of choice for otitis media and sinusitis remains to be amoxicillin.

Prevention

Immunization

HIB conjugate vaccine is now available and proven to be immunogenic in young infants. Since its inclusion in the primary series of childhood immunization in some parts of the world, it resulted in significant reduction of diseases due to HIB.

Prophylaxis

Household Contacts

1. Household contacts with children <12 months of age should be prophylaxed regardless of the immunization status.
2. Household contacts with children >12 months of age who receive the primary series and booster at 12 months or older do not need to be prophylaxed.
3. Household contacts with children <4 years of age who are incompletely vaccinated should be prophylaxed.

Nursing Schools and Day Care Centers

1. If two cases arise in the same center within 60 days, all the contacts should be prophylaxed if there are children who are unvaccinated or incompletely vaccinated.
2. In day care attended by children below 2 years of age and whose contact is more than 25 h/week, all contact should be prophylaxed if there are non-vaccinated or incompletely vaccinated children.
3. Day care attended by children >2 years of age need not be prophylaxed regardless of vaccination status.
4. Pregnant women need not be prophylaxed because of the potential risk of rifampin on the fetus.
5. Prophylactic drugs – Rifampin 20 mg/kg once daily for 4 days.

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