

HEMOPHILUS INFLUENZAE INVASIVE DISEASE

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Invasive *Haemophilus influenzae* (Hi) disease is caused by the bacterium *Haemophilus influenzae*. *H. influenzae* may be either encapsulated (typable) or unencapsulated (nontypable). Six antigenically distinct capsular types of *Haemophilus influenzae* (types a-f) have been identified that can cause invasive disease among people. Non-typable strains may also cause invasive disease, but are less virulent than encapsulated strains and are rare causes of serious infection among children.

Epidemiology

The mode of transmission presumably is person-to-person, by direct contact or through inhalation of droplets of respiratory tract secretions containing the organism, or in the neonate by intrapartum aspiration of amniotic fluid or genital tract secretions containing the organism.

Asymptomatic colonization by *H. influenzae* strains is common; nonencapsulated strains are recovered from the throat of 60% to 90% of children. Colonization by type b organisms is infrequent, ranging from 2% to 5% of children in the prevaccine era; widespread use of Hib conjugate vaccines has resulted in even lower colonization rates.

The exact period of communicability is unknown.

Before the introduction of effective vaccines, *Haemophilus influenzae* type b (Hib) was the cause of more than 95% invasive Hi diseases among children younger than five years of age. Hib was the leading cause of bacterial meningitis in the United States among children younger than five years of age and a major cause of other life-threatening invasive bacterial diseases in this age group.

Before the introduction of Hib conjugate vaccines for infants in late 1990, an estimated 20,000 persons developed invasive Hib disease annually. From 1989 to 1995, there was a 99% reduction in serotype b disease among children younger than five years of age, which coincided with the introduction and use of Hib conjugate vaccines among infants and children.

The incubation period is unknown.

Clinical Description

Invasive *H. influenzae* diseases include clinical syndromes of meningitis, bacteremia or sepsis, epiglottitis, pneumonia, septic arthritis, osteomyelitis, pericarditis, empyema, and abscesses. In contrast, syndromes of mucosal infections such as bronchitis, sinusitis, and otitis are considered noninvasive disease. The noninvasive syndromes are not nationally notifiable.

H. influenzae meningitis is primarily a disease of infancy. The infectious agent is usually *H. influenzae* type b. Other serogroups rarely cause meningitis. The onset is normally sudden and symptoms are those of fever, vomiting, lethargy, and meningeal irritation consisting of bulging fontanelle in infants or stiff neck and back in slightly older children.

Occasionally, nonencapsulated strains cause neonatal septicemia, pneumonia, and meningitis.

Laboratory Tests

Haemophilus influenzae is a pleomorphic Gram-negative coccobacillus. A positive blood or spinal fluid culture is considered diagnostic. If blood or spinal fluid culture is not positive, a positive gram stain from spinal fluid would be confirmatory.

Culture: The primary criterion for diagnosis is isolation of the organism from a normally sterile body site. Most hospital and commercial microbiologic laboratories have the ability to isolate *H. influenzae* from culture specimens. Normally sterile site specimens for isolation of invasive *H. influenzae* include cerebrospinal fluid (CSF), blood, joint fluid, pleural effusion, pericardial effusion, peritoneal fluid, subcutaneous tissue fluid, placenta, amniotic fluid, and other normally sterile sites. Isolates should be tested for antimicrobial susceptibility.

Serotype testing (serotyping): Serotyping is important for differentiation between unencapsulated (not typable), and encapsulated Hi strains, and for identification of the specific capsular type of encapsulated strains. Encapsulated strains can be separated into serotypes a- to f- based on six serologically distinct capsular polysaccharides using slide agglutination with specific antisera.

Ideally, efforts should be placed on getting all isolates from children typed at OPH lab, so that the investigators can focus on immunization data retrieval on only those cases confirmed as type b.

Microbiology laboratories should perform serotype testing of all *H. influenzae* isolates, particularly those obtained from children younger than 15 years of age. Although very few or none of the HI isolates may be serotype b as a result of declining Hib disease, laboratories should not discontinue routine serotype testing. Send cultures to the OPH laboratory for serotyping.

Antigen Detection: Latex agglutination (LA) - A rapid and sensitive method to detect Hib capsular polysaccharide antigen in CSF, serum, urine, pleural fluid, or joint fluid.

Since the type b capsular antigen can be detected in body fluids including urine, blood and CSF of patients, clinicians often request a rapid antigen detection test for diagnosis of Hib disease. Antigen detection may be used as an adjunct to culture, particularly in the diagnosis of patients who have received antimicrobial agents before laboratory specimens for culture were obtained. If the Hib antigen is detected in the CSF and there is not a positive result from culture or sterile site, the patient should be considered a probable case of Hib disease and reported as such. However, this test can be positive in urine and serum of persons without invasive Hib disease (e.g., in persons with asymptomatic carriage of Hib, recently vaccinated persons, or in persons with positive urine specimens from fecal contamination), and persons who are identified exclusively by positive antigen tests in urine or serum should not be reported as cases. Because antimicrobial resistance is increasingly recognized in serious bacterial infections, antigen tests are not a substitute for isolation of the organism.

Surveillance

Haemophilus influenzae invasive disease is a condition reporting required within 24 hours.

Information obtained through surveillance is needed to monitor the effectiveness of immunization programs, assess progress towards disease elimination, and monitor continued effectiveness of vaccines. The top priority for national surveillance is children under age 5 years, with children aged five to 14 years of next highest importance.

Case Definition

Clinical description

Invasive disease caused by *H. influenzae* may produce any of several clinical syndromes, including meningitis, bacteremia, epiglottitis, or pneumonia.

Laboratory criteria for diagnosis

Isolation of *H. influenzae* from a normally sterile site (e.g., blood or cerebrospinal fluid or, less commonly, joint, pleural, or pericardial fluid).

Positive antigen test results from urine or serum samples are unreliable for diagnosis of *H. influenzae* disease. False positive results may occur from asymptomatic nasopharyngeal carriage of Hib, recent Hib vaccination, or contamination of urine specimens by cross-reacting fecal organisms. Cases identified exclusively by these methods should not be reported.

Case classification

Probable: A clinically compatible case with detection of *H. influenzae* type b antigen in cerebrospinal fluid (CSF).

Confirmed: A clinically compatible case that is laboratory-confirmed.

Intervention

The purpose of investigation is to identify cases, to differentiate between the types of invasive disease, and to prevent transmission by identifying those most at risk and recommending appropriate prophylaxis. Rapid case identification is important for early administration of Hib vaccine or chemoprophylaxis to household and day care classroom contacts of cases.

Information to collect

The following data are epidemiologically important and should be collected:

- Demographic information: Date of birth is important
- Vaccination status (for type b or unknown serotype infections only), particularly important for children

Including:

- Date of each Hib immunization
- Manufacturer and lot number of vaccine(s) used
- Attendance in day care
- Clinical details, including:
 - Type of disease syndrome (e.g., meningitis, bacteremia, epiglottitis, arthritis, osteomyelitis, pericarditis, empyema, cellulitis, abscesses)
 - Date first positive culture obtained
 - Outcome of illness (died or survived)
- Laboratory information including
 - Serotype of isolate
 - Specimen source from which organism isolated (e.g., blood, CSF, pleural fluid, peritoneal fluid, pericardial fluid, joint fluid, placenta, amniotic fluid, other sterile site)
- Antibiotic susceptibility

Upon receipt of a report of *H-flu* meningitis, contact the physician and/or hospital to confirm the diagnosis.

Verify that the cerebral spinal fluid gram stain or culture of CSF or blood is positive. Note also the type of *H-flu*.

Identify all close contacts of the case.

Index case: The index patient also should receive rifampin prophylaxis only if ampicillin or chloramphenicol was used for treatment.

Household / Daycare contacts:

Chemoprophylaxis is not recommended for occupants of households with no children younger than 48 months of age other than the index case, and when all household contacts younger than 48 months of age have completed their Hib immunization series.

In households with

- **at least 1 contact younger than 48 months of age who is unimmunized or incompletely immunized against Hib,**
 - **or 1 contact younger than 12 months who has not completed the primary HiB immunization series**
- ➔ **Rifampin prophylaxis is recommended for all household contacts, irrespective of age.**

The exception to this recommendation is that all members of households with a fully immunized but immunocompromised child, regardless of age, should receive rifampin because of concern that the immunization series may not have been effective. Although the risk of secondary disease is low in an infant who has completed the primary two- or three-dose series, all members of a household with a child younger than 12 months of age (ie, who has not yet received the booster vaccine dose) should receive rifampin prophylaxis.

When indicated, prophylaxis should be initiated as soon as possible since the majority of secondary cases in households occur during the first week after hospitalization of the index patient. The time of occurrence of the remaining secondary cases after the first week suggests that prophylaxis of household contacts initiated seven days or more after hospitalization of the index patient, although not optimal, may still be of benefit.

Day care centers:

- **When 2 or more cases of invasive disease have occurred within 60 days and**
 - **Un-immunized or incompletely immunized children attend the child care facility,**
- ➔ **Rifampin prophylaxis to all attendees and supervisory personnel is indicated.**

When a single case has occurred, the advisability of rifampin prophylaxis in exposed child care groups with unimmunized or incompletely immunized children is controversial, but many experts recommend no prophylaxis.

In addition to these recommendations for chemoprophylaxis, unimmunized or incompletely immunized children should receive a dose of vaccine and should be scheduled for completion of the recommended age-specific immunization schedule (see Immunization, below).

If there is a case associated with a child care center(DCC) or private baby-sitter or if there is any unusual occurrence and request recommendations contact the owner/director of the DCC or private baby-sitter to notify her of the case and to determine if any other cases have occurred.

If no other cases have occurred, have the DCC owner/director send a letter home to the parents notifying them of the situation.

Instruct the DCC director to notify the health unit if a second case occurs.

If a SECOND case of invasive disease occurs within sixty (60) days, another letter is to be sent home to the parents indicating the need for prophylactic treatment with rifampin. (See attached sample letter).

Rifampin may be offered to day care center children and employees when a second *H. flu* case has occurred in the child care facility. For those child care center children and employees who wish to obtain rifampin via the health department, the following information will be required on each person receiving

rifampin in order for the Central Office Pharmacy to fill and expedite the prescriptions. Please be sure the information is correct and current in order to avoid any possible delays.

Name of child/employee, Date of birth, Present weight
 Address, Phone number
 Physician
 Physician's phone number

When the total list is compiled, please FAX the information to (504)568-8290 and notify the Infectious Disease Epidemiology Section. The medication will be shipped to the local health unit. Upon receipt of the filled prescriptions at the health unit, the nurse should make arrangements with the day care owner/director to issue the medication. A prescription receipt card will accompany each child/employee's Rx, along with instructions. Have the authorized person to sign the receipt card and return it to the Infectious Disease Epidemiology Section.

Dosage. Rifampin should be given orally once a day for four days (in a dose of 20 mg/kg; maximum dose, 600 mg). The dose for infants younger than one month of age is not established; some experts recommend lowering the dose to 10 mg/kg. For adults, each dose is 600 mg.

Immunization

The following Hib conjugate vaccines are currently available.

Licensed vaccine	Trade name	Manufacturer/Distributor
PRP-D	ProHIBIT®	Connaught Laboratories
HbOC	HibTITER®	Praxis/Lederle Laboratories
PRP-T	ACTHib®	Merieux/Connaught
OmniHIB®		SmithKline Beecham
PRP-OMP	PedVaxHIB®	Merck & Company

As of July 1997, four vaccines have been combined with Hib conjugate vaccines and licensed by the FDA following immunogenicity and safety studies. These combination vaccines decrease the number of injections needed for protection against vaccine-preventable diseases.

Licensed vaccine	Trade name	Manufacturer/Distributor
HbOC + DTP	TETRAMUNE™	Lederle Laboratories
PRP-T + DTP	ACTHib®	Pasteur Merieux/Connaught
PRP-T + DTaP	TriHIBit™*	Connaught Laboratories
PRP-OMP + HepB (RECOMBIVAX HB™)	COMVAX®	Merck & Co.

* As of July 15, 1997, TriHIBit™ was licensed for use only for the fourth dose of the DTaP and Hib vaccination series among children 15 to 18 months of age, and should be administered at least six months following the third DTP or DTaP dose.

Unvaccinated children should be vaccinated according to the following Table:

Table: Recommended schedule for Hib conjugate vaccine administration among previously unvaccinated children

Age (months) at Vaccine	Primary series	Booster
HbOC/PRP-T		
2-6	3 doses, 2 months apart	12-15 months
7-11	2 doses, 2 months apart	12-18 months
12-14	1 dose	2 months later
15-59	1 dose	NR ⁻
PRP-OMP		
2-6	2 doses, 2 months apart	12-15 months
7-11	2 doses, 2 months apart	12-18 months
12-14	1 dose	2 months later
15-59	1 dose	NR ⁻
PRP-D		
15-59	1 dose	NR ⁻

Based on the recommended schedule, infants should receive three primary doses of Hib conjugate vaccine with HbOC or PRP-T at ages two, four and six months; or two primary doses PRP-OMP at two and four months. A booster dose should be administered at age 12 to 15 months with any of the conjugate vaccines.

Treatment

Initial therapy for children with meningitis possibly caused by Hib is cefotaxime, ceftriaxone, or ampicillin in combination with chloramphenicol. Ampicillin alone should not be used as initial therapy since 10% to 40% of Hib isolates are ampicillin-resistant.

- For patients with uncomplicated meningitis whose infection responds rapidly, therapy for seven to 10 days administered intravenously in a high dose usually is satisfactory. Therapy for more than 10 days may be indicated in complicated cases.
- For treatment of other invasive *H. influenzae* infections, including non-type b capsular types, recommendations are similar but primarily are based on empiric experience.
- Dexamethasone is recommended for treatment of infants and children with Hib meningitis.
- Epiglottitis is a medical emergency. An airway must be established promptly by endotracheal tube or tracheostomy.
- Infected synovial, pleural, or pericardial fluid should be drained.
- For empiric therapy of acute otitis media, most experts recommend oral amoxicillin. Duration of therapy is five to 10 days. The five-day course is considered for children two years of age and older. Approximately 35% of *H. influenzae* isolates in the United States produce β -lactamase, necessitating a β -lactamase-resistant agent, such as an oral cephalosporin, a newer macrolide, or amoxicillin-clavulanate. In vitro, susceptibility testing of isolates from middle ear fluid specimens may help guide therapy in complicated or persistent cases.

Hospital precaution and isolation: Droplet precautions are recommended for 24 hours after initiation of antimicrobial therapy for invasive Hib disease.