REVIEW

Haemophilus Influenzae Infections

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ABSTRACT

***Haemophilus influenzae* is a serious bacterial pathogen especially in infants and children. Adequate understanding of the organism, its properties and antibiotic susceptibility, and of the epidemiology of diseases caused by it would assist the physician in selecting the most appropriate approach to prevent and treat infections caused by this organism. Newly licensed antibiotics and vaccines will help in controlling infections caused by *Haemophilus influenzae*.**

THE ORGANISM

Haemophilus influenzae is a pleomorphic gram negative coccobacillus. In vitro it requires factor X *(haematin)* and factor V (nicotinamide adenine dinucleotide) for growth. The organism occurs in either the encapsulated or the non-encapsulated forms. The encapsulated organisms are typed a through f depending on the polysaccharide in the capsule. Almost all serious diseases are caused by type b. The nontypable strains are responsible mainly for upper respiratory infections such as otitis media. Recently the nontypable strains were also reported to cause neonatal sepsis.

Most strains of *H. influenzae* type b (**Hib**) are susceptible to ampicillin. Almost all ampicillin-resistant Hib strains produce β-lactamase, but in some isolates the resistance is mediated by other means. The prevalence of ampicillin-resistant strains varies from 0 to 14% in published reports from Bahrain,[1] Kuwait,[2] Qatar[3] and Saudi Arabia,[4,5] whereas in the United States about one fifth of all isolates are ampicillin-resistant with a range of 16 to 48%.[6] Reports from Europe[7,8] reveal that 10 to 14% of **Hib** isolates are resistant to ampicillin. In Japan, 26% of **Hib** isolates are β-lactamase positive. The incidence of ampicillin-resistant **Hib** clinical isolates has been increasing, as observed in reports from the United States,[5] the United Kingdom[6] and Japan.[8] If the same trend develops in our region we should expect an increase in ampicillin-resistance in our **Hib** isolates.

Almost all strains of **Hib** are sensitive to chloramphenicol, although occasional chloramphenicol-resistant isolates are reported. Strains resistant to both ampicillin and chloramphenicol are extremely rare; one such strain was isolated from a patient in Saudi Arabia.[4] Two other strains were isolated from children with meningitis in Mexico[10] and the United States.[11]

Of the newer cephalosporins, cefotaxime, ceftriaxone and ceftazidime are active against ampicillin-susceptible and -resistant strains.[12] Ciprofloxacin, one of the new fluoroquinolone class of antibiotics, has a broad spectrum of activity against commonly isolated gram positive and gram negative bacteria including **Hib.**[12] The use of fluoroquinolones in children is not currently recommended because of the observed cartilage damage seen in juvenile animals receiving these agents.[12]

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EPIDEMIOLOGY AND PATHOGENESIS

Hib is the commonest causative agent of bacterial meningitis; it is a major cause of other serious bacterial diseases in infants and young children.[1,2,5,13,14] Host defence against **Hib** is mediated by antibodies to the capsular polysaccharide, polyribophosphate (PRP). Children younger than 18 months of age produce no or very small amounts of anti-PRP antibodies after either natural infection[15] or immunisation with capsule-derived PRP antigens.[16] The incidence of **Hib** disease, particularly meningitis is higher in children less than two years of age, probably because of the poor anti-PRP antibody production in this age group. Most cases of **Hib** disease are the result of upper respiratory tract colonisation after exposure to a healthy carrier followed by blood stream invasion by the organism.[17] Secondary spread is from contact with an ill child in the same household or to a lesser extent in day-care contact with an ill child.[18] The secondary spread accounts for less than 5% of all **Hib** cases.[19]

Nasopharyngeal carriage rate and secondary attack rate of **Hib** in household and day-care contacts of children with systemic **Hib** disease is significantly more than that in the general population, especially in children younger than four years of age.[20-22] The implications of these observations, ie the poor anti-PRP antibody response in young children and the risk of secondary **Hib** disease in the household and day-care contacts will be discussed further in the section on prevention.

It is known that the risk of invasive **Hib** disease in not uniform in the general population. Studies in the United States have shown that Alaskan Eskimos, Navajo and Apache Indians,[5] and blacks are at a higher risk of **Hib** disease.[15,22] There is no information on the risk of **Hib** disease in different parts of the Arab World. However, groups that are known to have increased risk of invasive **Hib** disease include children with sickle cell disease, complement or immunoglobulin deficiency, cancer patients, splenectomised individuals and patients on immunosuppressive therapy.[23] Infants and children with AIDS are also known to be more susceptible to severe or recurrent infections with encapsulated microorganisms, including **Hib.**[24]

DIAGNOSIS

This can be made by culturing the organism from blood or other body fluids. Routine microbiological techniques for isolation and identification of this organism such as growth on chocolate agar and requirements of both X and V factors are well known. Antibiotic susceptibility studies, and tests for β-lactamase production are also essential. Rapid diagnostic tests demonstrating **Hib** capsular polysaccharide antigen in blood, CSF, urine or other body fluids are available. These include countercurrent immunoelectrophoresis (CIE), latex particle agglutination, staphylococcal protein A co-agglutination (Co-A) and enzyme-linked immunosorbent assay (ELISA). Such tests are particularly helpful for quick diagnosis and in situations where the patient was on antibiotic therapy prior to attempts at bacteriologic diagnosis.

Other typable strains, ie other than type b, or nontypable organisms can rarely cause invasive diseases in children; particularly in neonates, adults with underlying chronic lung diseases or immunocompromised patients.[25,26] The isolation of nontypable *H. influenzae* from respiratory sites, such as from inflamed sinuses or middle ear fluid, is an evidence of the importance of this organism in the etiology of upper respiratory infections, especially acute otitis media and sinusitis.[27,28]

INFECTIONS CAUSED BY *HAEMOPHILUS INFLUENZAE* TYPE B

H. influenzae is the organism most commonly isolated from children with serious systemic bacterial infections.[1-3,5,13,14] The following is a description of the commonest manifestations of infection due to **Hib.**

Meningitis

Most studies from the Arab World[1-3,5] and elsewhere,[13,14] have demonstrated, that **Hib** is the commonest cause of meningitis in children. Almost all cases of meningitis due to **Hib** occur in children beyond the neonatal period and up to six years of age; most are in those less than two years of age. There is a slight male preponderance. Clinically the presentation of children with meningitis due to **Hib** is similar to that due to *Streptococcus pneumoniae* and *Neisseria meningitidis*. Concomitant with **Hib** meningitis, or as a consequence to the bacteraemia associated with it, children may have pneumonia,[29] endophthalmitis,[30] septic arthritis or osteomyelitis.[31]

Respiratory Infections:

Pneumonia

Reports show that **Hib** is an important cause of bacterial pneumonia in children.[13,14,29,32] Pneumonia due to **Hib** may be hard to distinguish from that due to *S. pneumoniae*. Clinically it may present as a mild, moderate or severe disease. The course of severe **Hib** pneumonia may lead to pleural effusion or pneumothorax in about one third of the patients. Pneumatoceles may rarely occur in the resolution phase of the pneumonia. Because of this, antibiotic therapy of pneumonia in young children must take into consideration the role of **Hib** in the aetiology of this infection in this age group.

Nontypable strains may be isolated from the sputum

of patients with underlying chronic lung disease such as bronchiectasis, chronic bronchitis or cystic fibrosis during exacerbations of the primary disease. Although the exact role of these nontypable strains is not completely determined, the evidence suggests that they are of prime importance during exacerbation of chronic bronchitis.[25]

Epiglottitis

The age group of children with **Hib** epiglottitis is one to seven years.[13,14,33] In most cases the children are about four years of age, in contrast to other forms of **Hib** disease, particularly meningitis, where the majority of cases are in children less than two years of age.[13,14,33]

The clinical picture is that of acute onset of fever and dysphagia in a child who is usually sitting up leaning forward, drooling and is in respiratory distress. Lateral neck X-ray reveals the swollen epiglottis, and is helpful in ruling out other conditions that may present in a similar fashion such as retropharyngeal abscess. Direct visualisation of the epiglottis should be attempted only in the presence of a person experienced in intubating sick children and with facilities and personnel available to perform emergency tracheostomy, if necessary. The epiglottis appears swollen, red and the airway can hardly be visualised because of the edema and the inflammatory process. This condition is the most acutely life-threatening **Hib** infection. Immediate management includes bypassing the obstructed airway preferably by intubation.[33] Epiglottitis is almost always due to **Hib.** The majority of patients are bacteraemic. Despite the frequent bacteraemia, most patients with epiglottitis do not have another focus of infection. Few patients may have concomitant meningitis or pneumonia. Laryngotracheitis can be readily distinguished from epiglottitis. Prognosis with appropriate antibiotic treatment and airway management is excellent.

Otitis Media and Sinusitis

Most cases of otitis media that are due to *H. influenzae* are caused by nontypable strains.[28] Some patients with **Hib** bacteraemia have associated otitis media. The organism is isolated from the middle ear fluid in 20% of children with acute otitis media. *H. influenzae* is also associated with acute sinusitis in children and adults.[27] The organism is isolated from the sinuses in 15-20% of children with acute sinusitis.

Cellulitis

Hib is responsible for about 15% of all cases of cellulitis in children. The majority of patients with **Hib** cellulitis are less than two years of age.[13,14] The commonest sites are the buccal and periorbital regions. Usually there is no prior history of trauma in contrast to orbital cellulitis due to *Staphylococcus aureus*. Children presenting with cellulitis have a history of upper respiratory infection that precedes the onset of cellulitis. Lesions do not have a distinct margin, they are tender and indurated. The violaceous discoloration seen in some patients is not pathognomonic of **Hib** cellulitis because it is not always seen in this condition and because it is occasionally seen in children with cellulitis due to other organisms particularly *S. pneumoniae*.[34] Aspirate from the cellulitis is frequently positive; if no material is obtained then another attempt at aspiration after the injection of 0.1 - 0.2 ml of nonbacteriostatic saline yields enough material for bacteriologic diagnosis. Blood cultures are often positive. The patients may have other foci of infection such meningitis or septic arthritis.

Skeletal infections

Although **Hib** accounts for only 20% of septic arthritis, it is the commonest cause of this condition in children less than two years of age.[13,14] Large joints are involved, some patients may have more than one joint affected. Joint fluid cultures are usually positive while blood cultures are less frequently so. In a series of 24 patients, 21 out of 24 joint fluid cultures were positive, while 16 out of 22 blood cultures were positive.[13] In the same series, 5 of 24 patients had associated infections; 3 had adjacent osteomyelitis and 2 had meningitis.

Hib is an uncommon cause of osteomyelitis in children.[13] About half of the patients with **Hib** osteomyelitis have another focus of infection such as adjacent septic arthritis or cellulitis or meningitis. Bone and joint infections with **Hib** are recognised to complicate the course of **Hib** meningitis. In a series of 202 children with **Hib** meningitis, 7 developed osteomyelitis or septic arthritis.[29]

Pericarditis

This is a rare manifestation of **Hib** disease.[13,35] Of all cases of bacterial pericarditis, about 5% are due to **Hib.**[13] The patients are usually between two and four years of age. Most patients have associated infections at other sites. Pneumonia and meningitis are the most commonly affected sites. Because of the high frequency of bacteraemia and the absence of contiguous focus of infection in most cases, it is believed that pericarditis is secondary to haematogenous dissemination.[35] Pericardectomy is preferred to pericardiocentesis or pericardotomy because it removes the risk of recurrent cardiac tamponade and constrictive pericarditis.[35]

Bacteraemia

Most patients with invasive **Hib** disease are bacteraemic.[13,14,28,32,33 35] Although **Hib** bacteraemia with no focus of infection is not common, localised infection, particularly meningitis may be preceded by occult bacteraemia.[36] Febrile children, particularly those younger than two years of age, who appear toxic and do not have an obvious focus of infection should be carefully evaluated and followed up preferably as in-patients, and should

undergo appropriate bacteriologic diagnostic tests.

Neonatal Infections

H. influenzae is an uncommon cause of neonatal infections such as septicaemia, pneumonia, meningitis and joint and bone infections. Nontypable strains are more commonly associated with these infections than type b.[13,25,26]

Other Infections

H. influenzae has been reported to cause urinary tract infection, epididymo-orchitis, uvulitis, cervical adenitis, glossitis, endocarditis and primary peritonitis. Such infections due to *H. influenzae* are rare.[13]

TREATMENT

Because of the seriousness of invasive **Hib** diseases (meningitis, pneumonia, cellulitis, epiglottitis, septic arthritis and pericarditis) the choice of initial therapy should include the use of agents that offer the best antibiotic coverage against the organism. Ampicillin-resistant **Hib** strains have been prevalent since 1974. The percentage of ampicillin-resistant strains varies in different regions.[1-9] The production of β-lactamase enzyme is responsible for most, but not all, ampicillin-resistant **Hib** strains. In some patients the isolated **Hib** strain from one site may be β-lactamase negative while it is β-lactamase positive from another site. So antibiotic susceptibility and tests for β-lactamase production should be performed on all isolates obtained from a single patient. Chloramphenicol is active against almost all **Hib** clinical isolates. Strains that are resistant to chloramphenicol produce a plasmid-mediated acetyltransferase. Only very rarely **Hib** is resistant to both ampicillin and chloramphenicol.[4,10,11]

Initial antibiotic therapy of invasive diseases presumably due to **Hib** should include a combination of ampicillin and chloramphenicol. After tests for β-lactamase production and antibiotic susceptibility testing are performed then one of the two can be continued alone for the total duration of therapy. Recent reports indicate that treatment of invasive **Hib** diseases with some of the newer cephalosporins (cefotaxime, ceftriaxone and ceftazidime) is equal in efficacy to ampicillin-chloramphenicol therapy.[12,37] So as an alternative to ampicillin-chloramphenicol combinations, and especially where ampicillin-resistant strains are increasing in prevalence, cefotaxime and ceftriaxone are being used with increasing frequency.[38] Factors that need to be considered when the choice of empiric antibiotic therapy is made include adequacy of antibacterial coverage, cost, frequency of administration, duration of therapy and adverse effects of the antimicrobial agents chosen.

PREVENTION

Immunisation

The presence of antibodies to PRP is of prime importance in preventing disseminated **Hib** infections. As mentioned earlier, anti-PRP antibodies are not detected in infants younger than 18 months of age. The incidence of serious **Hib** infection is high in children two years old or younger. The first **Hib** vaccine to be used was immunogenic in children older than 18 months of age, but not in ones younger than 18 months.[16] So, although the rate of infection due to **Hib** was observed to decrease in the **Hib** PRP vaccinees, it did so only in children older than 18 months. Since that time, several trials have been conducted, using PRP conjugated to other agents (diphtheria, tetanus or pertussis proteins). A recently published review,[39] describes all the available conjugate vaccines and summarises several studies on the efficacy of the various **Hib** PRP-conjugate vaccines. When given to infants two months of age or older, a significant decrease in the incidence of severe **Hib** infections was demonstrated. On the fourth of October, 1990, the United States Food and Drug Administration approved one of the currently licensed **Hib** PRP-conjugate vaccine for use in infants beginning at two months of age. Soon after,[40] the American Academy of Pediatrics recommended that all infants should receive the newly licensed **Hib** conjugate vaccine, starting at two months of age. It is prudent that we should soon include **Hib** vaccine in our routine immunisation list for all children, especially those who are known to be at increased risk of acquiring serious **Hib** infection, namely those infants and children with sickle cell disease and related haemoglobinopathies. Haemophilus vaccine, including the conjugate ones, are safe. About 10% of vaccine recipients develop minor local reactions (redness and swelling at the injected site). Serious adverse reactions are extremely rare.[39]

Chemoprophylaxis

Until recently, the chemoprophylaxis offered the only alternative to limit the spread of **Hib** disease in household and day-care contacts.[18,19] The risk of **Hib** disease in household contacts less than six years of age is similar to the risk of secondary meningococcal disease in household contacts of all ages.[41] The need to offer chemoprophylaxis to household and day-care contacts with **Hib** disease is as important as in cases of contact with meningococcal disease. Currently,[42] rifampin at 20 mg/kg/dose (maximum single dose 600 mg) daily for 4 days is recommended as the chemoprophylaxis agent of choice.

It is recommended for use by all household contacts, including adults in those households with at least one contact younger than four years of age. Prophylaxis should be initiated as soon as possible because most secondary

cases occur within one week after hospitalisation of the index case.[19-21] The index case in these families should also receive rifampin prophylaxis during hospitalisation just prior to discharge. The efficacy of rifampin in other situations such as day-care or nursery school contacts is not established. Most experts recommend the administration of rifampin to all infants and personnel when more than one case of invasive **Hib** disease occurs in a day-care centre within 60 days. Parents of all infants and children who have been in contact at home or in day-care centre with a child with invasive **Hib** disease should be advised to seek prompt medical evaluation if one of the contacts develops a febrile illness. Rifampin prophylaxis, when administered, should not substitute for prompt medical evaluation and treatment whenever indicated.

CONCLUSION

In this review, the characteristics of *Haemophilus influenzae* are presented, together with the various aspects related to infections caused by this organism. Adequate knowledge of these properties, the pathogenesis and epi-demiology of Hib infections are important. Changes in the antibiotic susceptibility, particularly the increase in the prevalence of β-lactamase producing, ampicillin-resistant strains are stressed. Various manifestations of *Haemophilus influenzae* infection in infants and children are reviewed; the importance of the organism as a pathogen in other patients such as neonates and those with predisposing factors such as sickle cell disease or chronic bronchitis is outlined. The use of new antimicrobial agents such as second and third generation cephalosporins and fluoroquinolones in the treatment of *Haemophilus* infection is reviewed. The role of vaccines, particularly those new ones with proven efficacy in young infants; and of chemoprophylactic agents, and their importance in the primary and secondary prevention of Hib infection is described.

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