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# Invasive *Haemophilus Influenzae* Type B Disease

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**ABSTRACT:** Invasive bacterial disease due to *Haemophilus influenzae* is a cause of sudden death in children. It must be considered by medical examiners when a child dies with a fulminant course and nonspecific symptoms. Three fatal cases are presented in children 7 weeks to 15 months of age. Two had meningitis and petechiae or purpura. All three had bilateral adrenal hemorrhage and a rapidly fatal course.

The potential for rapid and accurate diagnosis of *H. influenzae* infection is widely available due to latex agglutination technique against bacterial capsular wall antigens. Diagnosis is critical because of its public-health implications. Up to 50% of cases may be acquired in day-care settings. Chemoprophylaxis is recommended for household and day care contacts. With the recent introduction of *Haemophilus* b conjugate vaccines for routine administration to infants beginning at 2 months of age, a change in the epidemiology of the disease is anticipated.

**KEYWORDS:** pathology and biology, haemophilus influenzae type b, childhood diseases

Invasive bacterial disease due to *Haemophilus influenzae* type b (Hib) may come to the attention of medical examiners due to its fulminant course, nonspecific symptoms and high mortality rate. Rapid and accurate diagnosis of these cases is particularly critical because of public-health implications. Approximately 50% of cases of invasive Hib disease are acquired in day care settings [*1*]. Chemoprophylaxis is recommended for household and day care contacts regardless of their vaccination status. With the recent introduction of *Haemophilus* b conjugate vaccines for routine administration to infants beginning at 2 months of age a change in the epidemiology of the disease may be expected.

## Case Reports

### *Case 1*

A six-month-old white female presented to a community hospital with complaints of lethargy and fever. She had been well until 4 h prior to admission when her parents noted dyspnea and a temperature of 37.7°C. On admission she was dusky and hypotonic.

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Her white blood cell count was 8.4 × $10^3$ with 38% neutrophils, 11% band forms and 47% lymphocytes. Her spinal fluid had 1 WBC/mL, glucose 60 mg/dL, and protein 22 mg/dL. Gram stain of the spinal fluid revealed no bacteria. Upon arrival at the pediatric hospital she was covered with purpuric lesions. She died approximately 12 h after coming to medical attention.

At autopsy the infant weighed 7.6 kg with a crown-heel length of 70 cm. There was a diffuse blotchy purpura over her head, chest and abdomen. Her brain weighed 783 g. The leptomeninges were thin and translucent with no exudate identified grossly or microscopically. The adrenals were diffusely hemorrhagic with a combined weight of 8.7 g (mean 4.6 g ± 1.5). Culture of antemortem spinal fluid and blood grew *Haemophilus influenzae* type b.

*Case 2*

A 7-week-old white male became lethargic and irritable while at day care. He had been well until 5 days prior to admission when he was treated with antibiotics for an upper respiratory infection. The morning of admission he appeared pale to his parents, but otherwise normal. On admission his skin was pale, cool, and mottled. There was no pulse or blood pressure, but an occasional spontaneous respiration was noted. His white blood cell count was 7.0 × $10^3$, with 3% neutrophils, 26% band forms and 62% lymphocytes. He died 5 h after admission.

At autopsy the infant weighed 6.5 kg with a crown-heel length of 55 cm. Numerous petechiae were prominent around his orbits, neck, chest and abdomen. Petechiae were also present in the epicardium, adventitia of the great vessels and throughout the myocardium. The brain was soft and dusky with pus over the inferior and lateral aspects of the temporal lobes and inferior frontal lobes. Aspiration of the cisterna magna prior to autopsy revealed 10 mL of cloudy fluid. Gram stain of the fluid revealed numerous polymorphonuclear leukocytes and gram negative bacilli morphologically consistent with *Haemophilus*. Capsular antigen of *H. influenzae* type b was strongly positive by latex agglutination technique. Culture of the cerebrospinal fluid grew *H. influenzae*, beta-lactamase negative. There was bilateral adrenal hemorrhage with the combined weight of the adrenals being 20 g.

*Case 3*

A 15-month-old white male died shortly after arrival at an emergency room. Twelve hours prior to admission the child developed a fever for which he received acetaminophen. Upon admission he was apneic and cyanotic. White blood cell count was 4.5 × $10^3$ with 7% neutrophils, 14% band forms and 68% lymphocytes.

At autopsy the child weighed 9.5 kg with a crown-heel length of 79 cm. No purpura or petechiae were present. The combined weight of the adrenal glands was 13 g. Both were diffusely hemorrhagic. The leptomeninges were translucent with a thin layer of pus. Aspiration of the cisterna magna yielded cloudy fluid with many neutrophils and gram negative bacilli. The CSF culture grew *Haemophilus influenzae*, beta-lactamase negative. Capsular antigen of *H. influenzae* type b was demonstrated by latex agglutination.

## Discussion

*Haemophilus influenzae* is a small gram negative rod. Encapsulated strains are classified by the polysaccharides of the bacterial wall and are designated as types a through f. Almost all invasive disease in children is caused by type b. Formally, identification of the organism necessitated demonstration of growth requirement for X and V factors.

The potential for rapid and accurate diagnosis is widely available by use of latex agglutination technique against bacterial wall antigens.

*Haemophilus influenzae* causes a variety of clinical diseases, including acute purulent meningitis, epiglottitis, pneumonia, otitis media, conjunctivitis, cellulitis, pericarditis, and septic arthritis. It is the leading cause of bacterial meningitis in children 2 months to 5 years of age [*2*]. Before effective vaccines were available, 1 in 200 children developed invasive Hib disease by the age of 5 years with approximately two-thirds of all cases affecting children less than 15 months of age. Sixty percent of children with Hib had meningitis. The Waterhouse-Friderichsen syndrome due to *Haemophilus influenzae* is well described in children and adults and is associated with a high mortality [*4,5,6*].

As illustrated by the cases described, Hib disease may come to the attention of medical examiners because of its fulminant course. Case 1 demonstrates that at autopsy gram stain of spinal fluid and gross and microscopic examination of the leptomeninges may be negative. Postmortem cultures, or latex agglutination technique if available, may be the only means to make the correct diagnosis.

In the 1970s polysaccharide vaccines were developed and in 1985 were licensed for use in the United States for children at least 18 months old. Conjugate vaccines were later developed to overcome the T-cell independent characteristics of the first vaccines, and would thus be more effective in infants. At the end of 1990 the FDA approved the use of two of these conjugate vaccines for routine administration to infants beginning at 2 months of age. It must be noted that the efficacy of these vaccines is variable between ethnic groups with a range of 35 to 100%, with the lowest efficacy reported in Alaskan Natives [*3*]. Thus far, no adverse reactions to either type of vaccine have been reported.

Asymptomatic nasopharyngeal colonization is the major reservoir for Hib. The disease is most often transmitted from a colonized, asymptomatic or ill child, to a susceptible child by respiratory droplets. Obviously, day care is a setting where children are in close contact with one another. Studies have already demonstrated that day care attendees are at increased risk for contagious diseases such as rotavirus infection, hepatitis A, shigellosis, giardiasis, cryptosporidiosis, otitis media and upper respiratory tract infections. Similarly, it is estimated that as much as 50% of invasive *H. influenzae* disease is attributable to attendance at day care. It is incumbent upon medical examiners to make a rapid and accurate diagnosis of these cases and contact public health officials so that day care and household contacts may be treated with rifampin, the prophylactic agent of choice. Chemoprophylaxis is recommended for both the unvaccinated and vaccinated contacts because immune individuals may still asymptomatically carry and transmit the organism. Because the conjugate vaccines are more effective in protecting against colonization increased immunization of children with conjugate vaccines may also lower the rate of disease among unvaccinated contacts [*3*].

The American Academy of Pediatrics estimates that 30% of American 2 year olds have not received their required immunizations. In addition, they state that immunization rates may be less than 50% in some inner cities [*7*]. While some day care facilities are licensed and thus may require proof of immunization, there is no program to ensure that those not in day care or those in unlicensed settings receive their required shots before they reach school age.

It is really too early to predict the change in epidemiology of Hib disease that the introduction of the new vaccine schedule will cause. A recent review of the cases by age in Kansas City revealed surprising and confusing results. Since the introduction of the vaccine in 1985 for children older than 18 months, there has actually been a 50% decrease in the number of Hib meningitis cases among 5 to 8 month old infants, but a doubling of the cases in the older, presumably vaccinated group [*8*].

Immunization history and day care attendance are important questions for the investigator of a sudden death in a child. There must be a high index of suspicion and search

for infectious diseases at autopsy. One cannot assume that because a child is of an age to be vaccinated, that he has been, nor if he has been that he is immune. The medical examiner has the opportunity and duty to recognize diseases believed to be eradicated, report immunization failures, and notify public-health officials when contact tracing is appropriate.

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