

## Early Onset Nontypable *Haemophilus influenzae* Sepsis in a Preterm Newborn Infant

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Rec date: Jun 25, 2014, Acc date: Jul 21, 2014, Pub date: Jul 23, 2014

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### Abstract

We present a case of fulminant neonatal sepsis caused by nontypable *Haemophilus influenzae* and discuss some potential prevention measures. A 33-year-old pregnant woman delivered a 1,166 g male neonate at 27 weeks and 2 days of gestation. He died 5 hours after birth. *Haemophilus influenzae* was isolated from the amniotic fluid, maternal vaginal discharge, placenta, neonatal oral cavity, neonatal skin, and neonatal stool. These isolates were found to be nontypable by polymerase chain reaction and sensitive to ampicillin. Placental histopathology revealed acute chorioamnionitis without cord phlebitis or arteritis. An autopsy found no colonization of gram-negative cocobacilli in the organs including the lungs. These results suggest that acute intrapartum nontypable *Haemophilus influenzae* infection can cause fulminant and invasive neonatal sepsis. Intrapartum antibiotic prophylaxis may be useful for prevention.

**Keywords:** Antibiotics; Chorioamnionitis; Neonatal sepsis; Nontypable *Haemophilus influenzae*; Preterm delivery

### Introduction

*Haemophilus influenzae* is a common pathogen of infants and young children. Some strains possess a polysaccharide capsule and are associated with invasive diseases, such as meningitis, pneumonia and sepsis [1]. There are six capsular serotypes (a-f) of *Haemophilus influenzae*, of which serotype b (Hib) is by far the most common pathogen for invasive diseases. Although nontypable *Haemophilus influenzae* (NTHi) is commonly present in the normal flora of the upper respiratory tract, it is less invasive and infrequently involved in opportunistic respiratory tract infections. However, in nations where Hib immunization programs have been established, NTHi is responsible for most invasive *Haemophilus influenzae* infections and is associated with a high mortality rate [1]. In neonates, NTHi is responsible for most invasive diseases, such as sepsis and meningitis [2].

Herein, we report a case of NTHi sepsis in a preterm infant and discuss measures for preventing NTHi neonatal infection.

### Case Report

A 33-year-old gravida 5, para 1 Japanese woman had an uneventful antenatal course until 24 weeks of gestation. She suddenly became febrile (39°C) and complained of throat pain and nasal discharge. She spontaneously recovered three days later.

She visited a primary clinic at 27 weeks and 2 days of gestation because of vaginal fluid leakage and painful uterine contractions. She was transferred to our tertiary center on the same day. The cervix was fully dilated and bulging membranes were visible on admission. She was afebrile. Emergency laboratory tests showed leukocytosis of 15,000/μl and an elevated C-reactive protein of 1.36 mg/dl. Immediately after admission, she vaginally delivered a live male. He

weighed 1,166 g and Apgar scores were 4 at 1 minute and 7 at 5 minutes.

Placental histopathology revealed acute chorioamnionitis without umbilical phlebitis or arteritis. The patient received antibiotic therapy with flomoxef sodium (2 g IV BID.) for 5 days postpartum and was afebrile during the postpartum period.

The umbilical arterial pH value at birth was 7.3. The procalcitonin level in the umbilical venous blood was 7.76 ng/ml. He received full resuscitation in the delivery room. He was intubated and given surfactant (200 mg/kg). The neonate was transferred to the neonatal intensive care unit. We administered ampicillin (400 mg/kg/day IV) and gentamicin (7.5 mg/kg/day IV). We also started dopamine (5 μg/kg/min) and dobutamine (5 μg/kg/min). He had good oxygenation after surfactant administration therapy for the first hour of life. However, the blood pressure gradually decreased. He required 100% oxygen and high respiratory pressure support (PIP 20, PEEP 5) at 2.5 hours of life. Surfactant (200 mg/kg) was re-administered. Epinephrine (0.1 μg/kg/min) was also infused for persistent hypotension. Bicarbonate was also infused for metabolic acidosis (pH 7.1, base excess-13). Despite this therapy, he deteriorated and expired at 5 hours of life.

Autopsy revealed no colonization of gram-negative cocobacilli in the lungs, kidneys or liver. Brain postmortem was not allowed.

### Laboratory Analysis

*Haemophilus influenzae* was isolated from the amniotic fluid, maternal vaginal discharge, maternal and fetal surfaces of the placenta, neonatal oral cavity, neonatal skin, and neonatal stool. These isolates were found to be nontypable by polymerase chain reaction and sensitive to ampicillin.

## Discussion

We report a case of NTHi sepsis in a preterm infant. Although the neonate had fulminant sepsis, the colonization of gram-negative *cocobacilli* was not observed in the organs including the lungs at autopsy, as shown in Table 1.

Reference s	Mother			G.W (wks)	Birth weight (g)	outcome
	fever	PROM	antibiotics			
[4]	Yes	6 h	NA	23	680	death (1 h)
[5]	Yes	48 h	NA	23	610	alive
[4]	Yes	none	NA	24	680	death (1 h)
[4]	Yes	none	NA	24	690	death (7 wks)
[5]	Yes	17 h	NA	24	794	alive
[5]	No	none	NA	24	700	death
[6]	No	24 h	NA	24	590	death (7 days)
[7]	No	none	NA	25	810	death
[5]	Yes	41 h	NA	25	790	death
[4]	Yes	12 h	NA	26	650	alive
[4]	Yes	24 h	NA	26	780	alive
[5]	No	none	NA	26	720	death
[6]	No	none	NA	26	800	death (70 h)
[6]	No	72 h	NA	26	800	alive
[4]	Yes	12 h	NA	27	1030	alive
[6]	Yes	48 h	NA	27	862	alive
our case	No	Yes	none	27	1166	death (5 h)
[4]	No	7 days	NA	28	860	alive
[8]	No	33 h	Yes	28	1282	alive
[7]	Yes	none	NA	28	1315	death
[6]	No	none	NA	28	1260	alive
[4]	No	none	NA	29	1370	death (8 days)
[9]	Yes	36 h	Yes	29	1252	alive
[7]	NA	none	NA	29	1735	death
[5]	Yes	NA	NA	29	970	alive

PROM; premature rupture of membranes, G.W.; gestational weeks, NA; not available

**Table 1:** Nontypable *Haemophilus influenzae* sepsis in a preterm newborn infant <30 weeks of gestation

*Haemophilus influenzae* infections occur mainly in preterm, low birth weight infants, and are characterized by an early-onset and fulminant course [3-8]. NTHi colonizes the maternal genital tract, although its prevalence is low. This evidence suggests that NTHi is an

ascending infection during pregnancy and is also responsible for preterm birth. The mortality of NTHi neonatal sepsis is 40%, according to a population-based study done at Oxford [4]. The mortality rate was 90% for 20 infants with a gestational age of less than 30 weeks [9]. A *Haemophilus influenzae* infection is very similar to that of early onset Group B Streptococcal disease in that the infected infants are more likely to be preterm with maternal risk factors of prolonged ruptured membranes, maternal fever, and evidence of chorioamnionitis [10]. The use of intrapartum chemoprophylaxis with ampicillin may be effective in preventing transmission or invasive early neonatal sepsis by *Haemophilus influenzae*. As shown in Table 1, two neonates who received intrapartum chemoprophylaxis survived. In our case, NTHi was sensitive to ampicillin and the colonization of gram-negative *cocobacilli* was not observed in the organs. Therefore, if intrapartum chemoprophylaxis had been performed in our case, the fulminant sepsis might have been prevented. However, no measures for the prevention of NTHi have been established to date. This situation requires further evaluation.

Interestingly, despite the fulminant sepsis in our case, chorioamnionitis did not involve the umbilical cord vessels. This finding is similar to that of a previous report by Campognone et al. [3]. They noted that chorioamnionitis occurred in all placentas, but paradoxically, was more severe among survivors than among those who died.

Given the increasing prevalence of NTHi invasive disease, it is important for both obstetricians and laboratory staff to be aware of its potential risk.

## Acknowledgements

We thank Dr. K. Ubukata at the Kitazato Institute for Life Science, for capsule typing by PCR.

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