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Early-onset neonatal sepsis with *Haemophilus influenzae* in a premature low birth weight newborn – case report

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ABSTRACT

Prior to routine active immunization, *Haemophilus influenzae* was the leading cause of bacterial meningitis and other invasive bacterial disease among children. Although it is listed as one of the pathogenic causes of early-onset neonatal sepsis, it's a relatively infrequent cause of it. The onset of a clinical syndrome along with isolation of the bacteria in the first 72 hours of life defines neonatal sepsis and often presents as bacteremia, pneumonia or meningitis. We present the case of a preterm low birth weight infant with *Haemophilus influenzae sepsis.* Considering the high neonatal mortality and morbidity of these infections, cultures should be reconsidered. Prompt antibiotic therapy may not be enough in positive outcome of these patients.

Keywords: early-onset neonatal sepsis, *Haemophilus influenzae,* preterm mortality, multiple system organ failure

Abbreviations:

Ampl – amplitude
CDC – Center for Disease Control and Prevention
CRP – C-reactive protein
EOS – early onset sepsis
FiO2 – fraction of inspired oxygen
Freq – frequency
GA – gestational age
GA – gestational age
GBS – Group B Streptococcus
HFOV – high-frequency oscillatory ventilation,
Hib – Haemophilus influenzae type b
iNO – inhaled nitric oxide
IVH – intraventricular hemorrhage
LBW – low birth weight
MV – mechanical ventilation
NICU – neonatal intensive care unit
PDA – patent ductus arteriosus
PDE5 – phosphodiesterase-5 inhibitors
PIP/PEEP – positive inspiratory pressure/positive end expiratory pressure
PMean – mean airway pressure
PPV – positive pressure ventilation
PROM – prolonged rupture of membranes
RR – respiratory rate
SIMV – synchronized intermittent mandatory ventilation
Ti – inspiratory time

INTRODUCTION

Haemophilus influenzae is a Gram-negative, facultatively anaerobic coccobacillus which commonly colonizes the upper respiratory tract along with the urogenital tract, having both opportunistic and primary pathogenic characteristics [1]. The *H. influenzae* species are divided into typeable (encapsulated) and nontypeable (unencapsulated) strains based on the presence of a polysaccharide capsule. The most virulent type is the first one; Hib was the major cause of meningitis and epiglottitis in children before routine immunization [2]. Routes of transmission are represented by airborne transmission and

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direct contact; neonates can be infected vertically, via ascenscion of the bacteria in case of PROM, or via direct contact while passing through the infected birth canal [3].

The most common pathogenic causes of neonatal infection in the first 72 hours of life are represented by Group B Streptococcus and *E. coli.* Although *H. influenzae* can also lead to EOS, it is a relatively infrequent cause in most epidemiological studies [4,5]. However a significant concern is starting to appear regarding the morbidity and mortality among pregnant women and newborns by the invasive disease [6,7]. The invasive disease can involve not only the respiratory tract, but it can also manifest in forms of bacteremia, epiglottitis, septic arthritis, pericarditis and osteomyelitis [8,9]. Neonates often present nonspecific signs of sepsis in the first 24 hours. Risk factors include suspected maternal chorioamnionitis, PROM and premature delivery. Mortality is high and morbidities are represented by hearing loss, seizures or neurodevelopmental delays [10].

We present the case of EOS caused by *Haemophilus influenzae* in a premature low birth weight infant from a teenage mother with fatal outcome.

CASE REPORT

A 17-year-old female patient was admitted to the 1st Obstetrics and Gynecology Department of Targu Mures for premature rupture of membranes and onset of labor at 31/4 weeks gestation. Follow-up during pregnancy was partially realized by the local family physician, without any antenatal bacterial culture. The mother was gesta I, para I, without significant pathology in her personal history.

She presented fever and signs of infection, membranes were spontaneously ruptured 3 hours prior to admission, with a meconial and foul-smelling amniotic fluid. Paraclinical findings revealed leukocytosis (24.210/mm^3) with neutrophilia (83%). Urinalysis and vaginal swab were obtained; culture of the latter showed growth of *Haemophilus influenzae*. After examination of the gravida and blood test drawings, immediately antibiotic therapy with 2nd generation cephalosporins was begun along with tocolysis and antenatal corticosteroids. Unfortunately shortly after admission, monitoring started to show fetal distress therefore emergency C-section was performed.

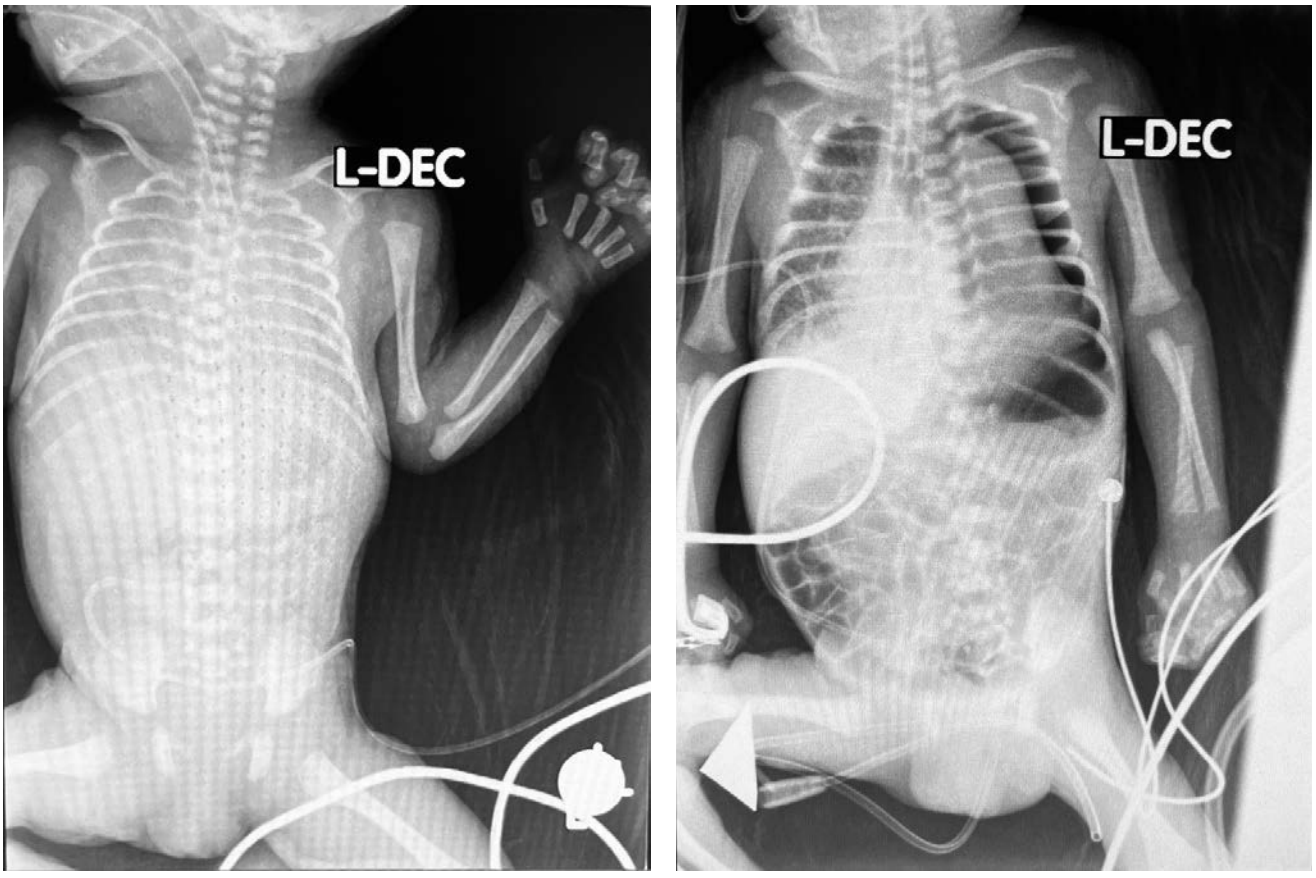
A female infant was delivered weighing 1650 g, length 44 cm, head circumference 27 cm. Since she showed poor respiratory effort at birth, she needed positive pressure ventilation first via T-piece resuscitator device and facial mask but considering no improvement in respirations or heart rate, she was intubated and ventilated via endotracheal tube coordinated with chest compressions for 30 seconds. She presented marked hypotonia and reduced reactivity to external stimuli. Giving the depressed respiratory and neurological status, after initial stabilization at the delivery room, she was admitted to neonatal intensive care unit for further investigations and treatment.

Clinical status at admission: critical general condition; cyanosis, marbled skin with generalized edema; axillary temperature 36.5°C; decreased air entry on auscultation of the chest and paradoxical thoracoabdominal movements, $satO_2$ 85-88% with 100% FiO_2 during mechanical ventilation; rhythmic heart sounds, heart rate 115-130/min, hypotension; soft abdomen without distension or tenderness, discrete edema of the abdominal wall; liver with 1 cm below the right subcostal margin, non-palpable spleen; anterior fontanelle flat and soft, marked hypotonia and reduced reactivity to external stimuli.

Therapeutic approach: after admission SIMV was initiated, catheterization of umbilical vein was performed, fluid resuscitation and total parenteral nutrition was begun, paraclinical tests and imagistics were obtained. Radiography of the chest revealed dense bilateral air space filling process with air bronchogram, 7 intercostal spaces on both sides, loss of cardiac silhouette (Figure 1a). Echocardiography showed severe pulmonary hypertension with dysfunction of left ventricle, large patent ductus arteriosus with bidirectional shunt, atrial septal defect. Initial laboratory findings: leucopenia (5670/mm^3, neutrophils 17.4%), positive C-reactive protein and elevated procalcitonin, severe mixed acidosis. After 24 hours blood culture came back positive for *Haemophilus influenzae.* First transfontanellar and abdominal ultrasound was performed shortly after admission and showed normal structures according to GA.

Evolution of the case: Therapy aimed the treatment of congenital pneumonia initially with conventional SIMV followed by high-frequency oscillatory ventilation due to poor response and need of high pressure parameters, surfactant administration with 200 mg/kg, associated antibiotic therapy with 2nd generation cephalosporins and aminoglycoside iv. In lack of iNO, pulmonary hypertension was treated with phosphodiesterase-5 inhibitors along with magnesium sulfate and double inotropic therapy (dopamine and adrenaline) was administered for maintaining contractility, blood pressure and end-organ perfusion. Respiratory complications appeared by development of a massive left pneumothorax which needed continuous pleural drain (Figure 1b). Ventilation parameters and venous blood gas are shown in Table 1.

Repeated transfontanellar ultrasound revealed bilateral grade III-IV intraventricular hemorrhage. Renal status deteriorated by the presentation of glomerulonephritis: macroscopic hematuria associated



a b

FIGURE 1. Thoracoabdominal radiography. a: after admission; b: 6 days of life

with oliguria and increasing creatinine levels. Coagulation disorder continued with upper digestive tract hemorrhage. Despite aggressive supportive treatment with intravenous albumin, blood transfusion, administration of fresh frozen plasma, continuous infusion with diuretics, the clinical status and general condition was stagnant. After an initial improvement in laboratory tests, acute-phase protein showed a tendency to increase, therefore antibiotic therapy was changed to meropenem. Respiratory status continued to worsen by the apparition of bilateral pneumothorax at 10 days of life, renal insufficiency associated with uncontrollable renovascular hypertension. Regardless of all attempts of ventilation, at 13 days of life constant hypoxia was seen followed by tendency to bradycardia leading to asystole unresponsive to cardiopulmonary resuscitation.

TABLE 1. Ventilation setting and blood gas in evolution

Day 1				Day 3*				Day 6**				Day 13***			
Blood gas		**SIMV**		**Blood gas**		**HFOV**		**Blood gas**		**HFOV**		**Blood gas**		**HFOV**	
pH	7.11	PIP/ PEEP (cmH_2O)	21/5	pH	7.14	PMean (mbar)	10	pH	7.03	PMean (mbar)	11	pH	6.93	PMean (mbar)	11
pCO_2 (mmHg)	73	RR (rpm)	60	pCO_2 (mmHg)	56	Freq (Hz)	9	pCO_2 (mmHg)	82	Freq (Hz)	6	pCO_2 (mmHg)	72	Freq (Hz)	6
pO_2 (mmHg)	18	Ti (sec)	0.35	pO_2 (mmHg)	44	Ampl (mbar)	18	pO_2 (mmHg)	23	Ampl (mbar)	20	pO_2 (mmHg)	18	Ampl (mbar)	23
BEecf (mmol/L)	-9.1			Lac (mmol/L)	1.4	FiO_2 (%)	100	Lac (mmol/L)	3.4	FiO_2 (%)	100	Lac (mmol/L)	7.4	FiO_2 (%)	100
				Beecf (mmol/L)	-9.9			BEecf (mmol/L)	-10.6			BEecf (mmol/L)	-17.6		
				HCO_3 (mEq/L)	19.1			HCO_3 (mEq/L)	18.1			HCO_3 (mEq/L)	14.1		

*Day 3 – switching conventional ventilation to HFOV
**Day 6 – massive unilateral pneumothorax
***Day 13 – last day of life

DISCUSSION

EOS is defined as the appearance of a clinical syndrome characterized by systemic signs of infection and positive blood culture in the first 72 hours of life [9]. Despite the fact that *Haemophilus influenzae* is not a common pathogen for EOS, a surveillance report from European Centre for Disease Prevention and Control reports an increase in invasive diseases as in 0.8 cases per 100.000 population with the highest incidence among infants under one year [11], CDC reports same incidence regarding infants [12,13]. A recent epidemiological study regarding the prevalence of *H. Influenzae* in England and Wales also underlines the increasing tendency of the invasive disease in the perinatal period [6].

Colonization of the vagina with this pathogen is rare and it's associated with fetal loss, premature birth and stillbirth [6,12]. Although PROM is a known risk factor for developing EOS [2], in our case membranes were ruptured only 3 hours prior admission, therefore a vertical transmission is likely. Furthermore, the infant's in utero status worsened before delivery, the presence of the foul-smelling amniotic fluid and the depressed clinical condition immediately after birth supports the in utero infection. Lack of a correct pregnancy follow-up and the omitted vaginal cultures also contributed to this poor outcome of pregnancy. Collins and coworkers found that mothers of neonates with *H. influenzae* EOS are more likely to be under 20 years old and primigravida [6], which is similar to our case. Since the mother presented at the hospital relatively late, the antepartum chemoprophylaxis was ineffective due to the short time for the antibiotics to act before delivery. In our case obstetrical complications were represented by premature rupture of membranes and onset of labor, maternal fever and fetal distress requiring emergency cesarean section. Affirmatively the mother did not present any respiratory symptoms before birth.

Infection with *H. influenzae* is more common among preterm and low birth weight infants and is represented by an early appearance of sepsis and poor outcome [3,6,12]. The depressed condition at birth, the need of full neonatal resuscitation at the delivery room and the critical condition in the first hours of life were similar to the case presented by Roy Chowdhury et al. and Rie Yamashita et al. but their case had a fulminant outcome with onset of death at few hours of life [2,16]. Two other cases by Warren S. et al. and Okubo S. et al. declared the same unstable postpartum state but with a favorable outcome [13,17].

Antibiotic profile of the mother's blood culture revealed sensitivity to 2nd and 3rd generation of cephalosporins but seemed to be resistant to ampicillin. After 5 days of cefuroxime with metronidazole and gentamicin her repeated culture came back negative. The infant's antibiogram on the other hand showed the same bacterial β-lactamase-non-producing *Haemophilus influenzae* strain but with a susceptibility to ampicillin and trimethoprim/sulfamethoxazole. The question of transmission can be raised based on the difference between the antibiotic susceptibility of the two strains. Recent studies searched for the difference between maternal colonization and neonatal blood culture by genomic analysis. A different antibiotic profile can mean other sources of infection beside maternal transmission. The study of Okubo et al. states that the vertical transmission of the infection is low but highlights the fact that mothers can be colonized by multiple strains and picking the exact strain for analysis is difficult therefore the growth of a different strain in case of multiple colonization or negative culture do not prove the absence of infection [14]. Chomkatekaew C et al. also studied the link between maternal colonization and EOS based on phenotypic antimicrobial resistance and found a medium rate transmission around birth [15].

Although ampicillin resistant *H. influenzae* strains are appearing, our neonate's culture revealed sensitivity to it. Initially we decided to go with a 2nd generation cephalosporin because of the mother's preceding antibiotic therapy and because of the depressed status of the infant and continued to carry on based on antibiogram. Sadly, the failure of cardiovascular, respiratory, and renal systems defined the outcome of the neonate.

CONCLUSION

Because of the poor outcome of the pregnancy and high mortality of the infants, infections with *H. influenzae* should be reconsidered. It's important for obstetricians and neonatologists to be aware of the increasing risk of infection with *H. influenzae*. The attending physicians should be warned of any growth of the bacteria in maternal or neonatal cultures. The early administration of antibiotics is crucial along with adjusting the appropriate antimicrobial therapy.

Patient consent:
The minor's legal guardian provided a written consent for the publication of this case report.

Author's contributions:
Conceptualization, SM. and SR.; methodology, GZS., TAN.; validation, CM., formal analysis, TAN.; investigation, TAN.; resources, TAN.; writing – original draft preparation, TAN.; writing – review and editing, SM., CM; visualization, SM., CM.; supervision, CM., SM.; project administration, SR.;. All authors have read and agreed to the published version of the manuscript.

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