Early-Onset Neonatal Sepsis with Extended Spectrum Beta-Lactamase Producing *Escherichia Coli* in Infants Born to South and South East Asian Immigrants: A Case Series

Kalsang Dolma, MD[1] Thanh L. Summerlin, MD[1] Hansa Wongprasert, MD[1] Charitharth Vivek Lal, MD[1] Joseph B. Philips III, MD[1] Lindy Winter, MD[1]

[1] Division of Neonatology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama

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Address for correspondence Kalsang Dolma, MD, Division of Neonatology, Department of Pediatrics, University of Alabama at Birmingham, 176F Suite 9380, Women and Infants Center, 619 South 19th Street, Birmingham, AL 35249-7335 (e-mail: kdolma@uabmc.edu).

Abstract

Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae represent a major worldwide threat. We present three cases of early onset ESBL *Escherichia coli* sepsis in infants born to families from South and Southeast Asia to inform the practitioner community about this emerging threat. Infants with suspected sepsis, whose mother is from Asia or Southeast Asia, should be suspected of having an infection with an ESBL-producing organism, and practitioners should strongly consider adding a carbapenem to their usual initial antibiotic regimen.

Keywords

- neonatal sepsis
- early onset sepsis
- extended-spectrum β-lactamases
- *Escherichia coli*

Extended-spectrum β-lactamases (ESBL) are plasmid encoded enzymes produced by Enterobacteriaceae and induce bacterial resistance by hydrolyzing β-lactam antibiotics.[1,2] ESBL-producing Enterobacteriaceae represent a major worldwide threat and contribute to morbidity and mortality among newborn infants, especially in other parts of the world with a pooled prevalence of 11%.[3] In the U.S., early onset sepsis (EOS) in neonates with ESBL organisms is rare. We present three cases of EOS with ESBL *Escherichia coli* (*E. coli*) in infants born to mothers, recently immigrated from South and Southeast Asia.

Case Series

Case 1

A 34-week expected gestational age (EGA) male was born to a 32 years/o Pakistani mother via spontaneous vaginal delivery, with rupture of membranes 12 hours before delivery. Pregnancy was complicated by gestational diabetes and severe pre-eclampsia. The mother received two doses of betamethasone and magnesium sulfate. Apgar scores were 6 and 8 at 1 and 5 minutes, respectively. The infant initially did well and was transferred to a step down unit on day 2. No antibiotics were administered during the initial Neonatal Intensive Care Unit (NICU) stay. At 62 hours of age, skin mottling, lethargy, abdominal distension, delayed capillary refill hypotension, and oliguria developed. A sepsis evaluation was initiated and ampicillin, gentamicin, and acyclovir were begun. Respiratory failure led to intubation and mechanical ventilation. Laboratory results revealed elevated C reactive protein (89.9 mg/L), leukopenia (1,004/μL), neutropenia (100/μL), and thrombocytopenia (71,000/μL), and severe metabolic acidosis with lactic acid of 16 mmol/L. Multiple doses of sodium bicarbonate ($NaHCO_3$) and fluid resuscitation did not improve the acidosis. The infant developed shock refractory to fluid boluses and vasopressors. Blood culture grew gram-negative rods within 7 hours of draw, and cefepime was added for extended gram-negative coverage. Cerebrospinal fluid (CSF) results revealed gram-negative meningitis. The infant developed pulmonary hemorrhage from disseminated intravascular coagulation (DIC) within 24 hours of presentation and continued to receive multiple blood products without improvement. He rapidly deteriorated despite vigorous resuscitative efforts and died. Blood and CSF cultures grew ESBL *E. coli*.

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Case 2

A 35-week EGA male twin 2 was born to a 26 years/o Vietnamese mother after an uncomplicated pregnancy. Maternal Group B Streptococcus (GBS) status was unknown, and mother received two doses of ampicillin prior to delivery. Mother had no signs of chorioamnionitis. The well-appearing infant was admitted to the well-baby nursery. At 60 hours, he developed hypothermia and new onset apnea. Rectal temperature was 94°F, and poor perfusion, and decreased activity were present. A sepsis evaluation was initiated and ampicillin, gentamicin, and ceftazidime were started. The infant was intubated with worsening respiratory status and persistent apnea. Pulmonary hemorrhage was noted during intubation. Chest X-ray showed near total opacification of the right lung. The baby was placed on conventional ventilation and multiple doses of endotracheal epinephrine were given without improvement. Multiple blood products were given for DIC. Blood gases showed a severe mixed acidosis. He deteriorated rapidly and died 4 hours after onset of symptoms. Blood culture grew ESBL *E. coli*.

Case 3

A 30-week EGA male infant was born to a 35 years/o Indian mother via spontaneous vaginal delivery. Pregnancy was complicated by gestational diabetes and prolonged rupture of membrane (48 hours). Maternal GBS status was unknown. She received four doses of ampicillin prior to delivery. There were no signs of chorioamnionitis; however, she developed a fever of 101.7°F on postpartum day 1 and was diagnosed with endometritis. Apgar scores were 7 and 8 at 1 and 5 minutes, respectively, and the infant was transferred to the NICU on room air. At 3 hours of age, he developed respiratory distress requiring continuous positive airway pressure (CPAP), which was escalated to conventional and then high frequency ventilation within the next 12 hours. Chest films showed generalized granular infiltration. Ampicillin, gentamicin, and ceftazidime were started. His status deteriorated with compensated septic shock, tachycardia, and lactic acidosis (11.6 mmol/L). DIC was present with pulmonary hemorrhage, thrombocytopenia, and coagulopathy. He received multiple normal saline boluses and blood products. Dopamine was added for hypotension. Blood culture grew gram-negative rods within 12 hours. Due to his ethnicity, meropenem was added due to high suspicion for ESBL gram-negative sepsis. Lumbar puncture was deferred due to unstable clinical status and significant coagulopathy (international normalized ratio [INR] of 4.1). Blood culture grew ESBL *E. coli* susceptible to meropenem and gentamicin, but resistant to all cephalosporins. Placental pathology revealed acute severe subchorioamnionitis. Given the severity of his illness with ESBL *E.coli* bacteremia and no initial CSF studies, he completed a 21-day course of meropenem for presumed meningitis associated with his bacteremia and sepsis.

Discussion

ESBLs induce bacterial resistance by hydrolyzing penicillins, first, second, and third generation cephalosporins and aztreonam, but not cephamycins or carbapenems. β-lactamase inhibitors such as, clavulanic acid, sulbactam, and tazobactam usually inhibit them.[4] Most ESBLs are derived from broad-spectrum β-lactamases TEM-1 and SHV-1. Mutations of these genes result in alteration of the amino acid configuration around the active site of β-lactamases.[4] Genes for ESBL are frequently encoded by plasmids.[1]

ESBL-producing organisms were first described in Europe.[5] In the U.S., the first cases of ESBL organisms were reported in the 1988, [6] and the incidence since.[7] A recent systematic review and meta-analysis have estimated a pooled prevalence of fecal colonization with ESBLs in healthy adults and children at 14% globally, with a higher prevalence of 22% in Southeast Asia and Africa.[8] Number of studies from South and Southeast Asian countries have also demonstrated a likewise prevalence in food, food producing animals, and environment.[8–12] Also, high colonization rates with ESBL-producing Enterobacteriaceae were found in travelers returning from South Asia.[13–16] Multiple countries report emergence of community-associated infections with ESBL-producing *E. coli*.[17–19] In the U.S., a recent prospective observational study showed an increase in the prevalence of ESBL-producing organisms, with 36.8% of all ESBL infections, caused by community-acquired ESBL producers.[20] A 2013 report of the Centers for Disease Control and Prevention, classified ESBL-producing Enterobacteriaceae as a serious threat requiring prompt and sustained action.

ESBL-producing organisms have been reported to cause neonatal sepsis in other parts of the world with heterogeneity among the geographical location.[3] ESBL infections in neonates have higher mortality rates compared with other pediatric populations.[3,21] The drug of choice for treatment of infections caused by ESBL-producing organisms is carbapenem. Among aminoglycosides, amikacin has the most activity against ESBL-producing strains and can be used if the organism is susceptible. Cefepime can also be used if the organism is susceptible.[22]

We observed 3 cases within a 6-month period, in 2017. All infants were born to families of South and South East Asian descent. These cases were managed with β-lactams and aminoglycosides without improvement. In our third case, early use of meropenem led to clinical improvement and survival. Infants with suspected sepsis, and whose mothers are from South and Southeast Asia, may have increased risk of infection with ESBL-producing organisms. Practitioners should consider adding meropenem to the initial antibiotic regimen in this patient population.

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Conflict of Interest

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Contributors' Statements

Authors K.D., T.L.S., and H.W. cared for the patient presented, reviewed the literature, and drafted the initial

manuscript. Authors C.V.L., J.B.P., and L.W. cared for the patient, presented, reviewed, and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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