ISSN: 2573-9565

Case Report

Journal of Clinical Review & Case Reports

Early-Onset Neonatal E. coli Sepsis in Term Infants in the Absence of Antenatal or Intrapartum Risk Factors for Infection

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Submitted:09 July 2020; **Accepted**: 14 July 2020; **Published**: 24 July 2020

Summary

Early-onset neonatal sepsis (EONS), an important cause of neonatal morbidity and mortality, is usually due to ascending infection from maternal genital tract or infected amniotic fluid. The most common organism is group B streptococcus (GBS), followed by Esc herichia coli (E. coli). Risk factors include maternal GBS colonization, chorioamnionitis, prolonged membrane rupture, prematurity, and intrapartum maternal pyrexia. The presentation of EONS can be varied, ranging from temperature instability to profound hypotension. We present two cases of E. coli EONS in term infants presenting as respiratory distress, without risk factors for infection.

The first case is a 34-year-old female, with history of one previous caesarean section (CS), who underwent a repeat CS at 37+1 week's gestation for obstetric cholestasis. Investigations performed on the second day of neonatal life in view of persistent respiratory distress, revealed E. coli bacteremia, complicated by septic shock. The mother developed fever on the first post-operative day due to E. coli bacteremia.

The second case is a 31-year-old GBS negative primigravida with gestational diabetes, who underwent an induction of labor at 38+ 3 weeks. She had a forceps delivery for fetal distress six hours after membrane rupture. On the second day of life, the neonate had retractions and poor feeding, and blood cultures grew E. coli. There were no risk factors for EONS. The neonate rapidly deteriorated and despite extracorporeal membrane oxygenation, passed away on the seventh day of life.

These cases illustrate the importance of E. coli as a cause of EONS and the need for a high index of suspicion due to the subtle presentation. Prompt recognition and treatment are important even in the absence of risk factors, as there is potential for rapid deterioration if treatment is delayed. In the presence of definite risk factors, broad-spectrum antibiotics should be considered for E. coli and GBS.

Keywords: Neonatal Early-Onset Sepsis, *E. coli* Infection, Term Birth, Puerperal Infection

Abbreviations

EONS: Early-onset neonatal sepsis
GBS: Group B streptococcus
CS: Caesarean section

Introduction

Early-onset neonatal sepsis (EONS) within 72 hours of birth is an important cause of neonatal morbidity and mortality. It is usually due to ascending infection from the maternal genital tract or from infected amniotic fluid [1]. The most common causative organism is group B streptococcus (GBS), followed by *Escherichia coli* (*E. coli)* [2-4]. *Listeria monocytogenes* is less common but an important cause of overwhelming neonatal sepsis [5].

The risk factors for EONS include maternal GBS colonization (including previous infant with invasive GBS disease or GBS bacteriuria in the current pregnancy), chorioamnionitis, prolonged rupture of membranes, preterm delivery, intrapartum maternal pyrexia, and inadequate intrapartum antibiotic prophylaxis (IAP) [6-9].

E. coli is commonly associated with EONS in preterm and very low birth weight (VLBW) infants, rather than term infants. [5], [10]. Although IAP has decreased the incidence of EONS due to GBS, its effect on the incidence of *E. coli* EONS is inconclusive with some studies showing a reduction in risk for term infants and others describing an increased incidence of penicillin-resistant *E. coli* infection with prolonged antenatal antibiotic usage [4, 11]. A study by Saez-Lopez showed that the prevalence of E. coli vaginal colonization in pregnant females was 13%, especially amongst those with premature preterm rupture of membranes [12].

The presentation of EONS in the neonate can also be varied and non-specific, ranging from subtle temperature instability, tachycardia, respiratory symptoms (tachypnea, grunting), irritability, lethargy, and poor feeding, to poor perfusion and profound hypotension [13].

We present two cases of *E. coli* EONS in term infants presenting as respiratory distress, without any obvious obstetric risk factors for infection. These cases illustrate the importance of *E. coli* as a cause of EONS, with a possible need to consider empirical antibiotic coverage for *E. coli* in addition to GBS. The subtle presentation of EONS as respiratory distress also emphasizes the need for a high index of suspicion for EONS even in the absence of risk factors for sepsis, and the importance of prompt recognition and treatment due to the potential for rapid deterioration of the neonate.

Case Presentation

Case 1

Our first case is a 34-year-old gravida 2 para 1, morbidly obese (body mass index [BMI] 44.1 kg/m2), Malay lady with a history of one previous emergency caesarean section (CS) at 37+6 weeks gestation for failure to progress in the first stage of labor. In the current pregnancy, the second trimester fetal anomaly scan detected a small to moderate ventricular septal defect (VSD). The antenatal course was uncomplicated until 34 weeks. A low vaginal swab screen at 34+6 weeks gestation was positive for GBS colonization.

She was admitted at 34+5 weeks gestation for unexplained antepartum hemorrhage. On admission, blood pressure at presentation was 150/93 mmHg and urine albumin was negative with no other clinical features of pre-eclampsia. She was found to have transaminitis as part of the pre-eclampsia investigations, with elevated alanine transaminase (ALT) level of 142 U/L (normal range 0-55 U/L) and aspartate transaminase (AST) level of 72 U/L (normal range 5-34 U/L), with a normal gamma-glutamyl transferase (GGT) level. The rest of the pre-eclampsia investigations were unremarkable, with a normal 24-hour urine total protein excretion and a normal platelet count. Her pregnancy-induced hypertension (PIH) was controlled with oral labetalol.

The differential diagnoses for her transaminitis were that of intrahepatic cholestasis of pregnancy, HELLP syndrome variant, or underlying fatty liver disease in view of her BMI. The screening tests for Hepatitis A, B, C, E, Cytomegalovirus (CMV), Epstein - Barr virus (EBV) and autoimmune hepatitis were negative. An ultrasound of the hepatobiliary system showed uncomplicated gallstones. Her serum bile acid was however elevated at 23 umol/L. She was started on ursodeoxycholic acid 500mg twice a day (BD), and serum bile acid level reduced to 10.7 umol/L the following day. Nevertheless, in view of persistently raised transaminases and concern of liver failure, decision was made for repeat CS at 37+1 weeks of gestation. There was no history of rupture of membranes or of maternal pyrexia prior to delivery. No placental histology or cultures were sent in view of an initial low suspicion of infection at delivery. The maternal serum bile acid and serum transaminases were noted to be normal on the first and second post-operative days (POD) respectively.

The baby boy was delivered as breech with Apgar scores of 7 and 9 at 1 and 5 minutes respectively and a birth weight of 3160 grams. The neonate was transferred to the neonatal intensive care unit (NICU) on continuous positive airway pressure (CPAP) in view of retractions and grunting attributed to respiratory distress from a delayed transition. The initial blood gas analysis showed respiratory acidosis, and a chest x-ray showed diffuse granularity in both lungs and a hypolucent area in the lateral right lower zone, suggestive of respiratory distress syndrome and a small right pneumothorax, respectively. The baby was intubated and given surfactant at 23 hours of life in view of persistent grunting with increasing fraction of inspired oxygen (FiO2) requirements and respiratory acidosis. The initial full blood count (FBC) and C-reactive protein (CRP) levels were unremarkable.

On the second day of life, investigations were performed for presumed neonatal sepsis in view of the persistent respiratory distress. Empirical intravenous (IV) benzylpenicillin and gentamicin was started as per protocol. A repeat of infective markers showed elevated CRP 11.9 mg/L (normal range 0-5.0 mg/L) and leukopenia 0.81 x 10^9/L (normal range 5.00 19.50 x 10^9/L). The neonate developed septic shock and disseminated intravascular coagulopathy (DIVC) with hypotensive episodes (lowest mean arterial pressure [MAP] 33-34 mmHg), requiring dopamine inotropic support, which was weaned off on the sixth day of life. The dosage of benzylpenicillin was escalated to the therapeutic dose for meningitis with addition of cefotaxime. In view of rising inflammatory markers (highest CRP 138.2 mg/L on the fourth day of life), persistent acidosis (bicarbonate level 12 mmol/L on the third day of life) and elevated lactate, antibiotics were further escalated to meropenem on the same day. The blood culture grew *E. coli* sensitive to meropenem, amikacin and cefepime. A repeat blood culture on the fifth day of life was negative. A lumbar puncture performed on the sixth day of life was a bloody tap with a negative culture. The resultant coagulopathy and thrombocytopenia (lowest platelet count 46 x 10^9/L at day 4 of life) were managed with fresh frozen plasma (FFP) and platelet transfusion. The baby was extubated to CPAP on the seventh day of life then to room air on the tenth day of life. Subsequently inflammatory markers showed a downward trend, and meropenem was de-escalated to cefepime on the eighth day of life. A total of three weeks of parenteral antibiotics were completed for presumed meningitis, and the neonate was discharged stable on the 23rd day of life with normal inflammatory markers CRP (<1 mg/L) and total white cell count (13.6 x 10^9/L).

The mother developed postpartum fever on the first POD with a maximum temperature of 39 degrees Celsius. Her inflammatory markers were markedly elevated with a CRP of 229.5 mg/L, procalcitonin of 1.87 ug/L, and total white count of 15.57 x 10^9/L. The post-operative antibiotic regime was escalated from

IV cefazolin to IV ceftriaxone and metronidazole. Maternal blood cultures confirmed E .coli bacteremia. The antibiotic was changed to meropenem as per the sensitivity. A computed tomography (CT) scan of the abdomen and pelvis ruled out intra-abdominal or pelvic fluid collections. A urine culture on the third POD grew *Enterococcus faecium and Enterococcus faecalis sensitive* to ciprofloxacin, ampicillin and nitrofurantoin. A vaginal swab culture taken on the fifth POD showed *E. coli* with identical antimicrobial sensitivities to the E. coli detected in the blood culture, and Enterococcus faecium sensitive to ampicillin.

The repeat blood cultures taken on the fifth and eighth POD and the urine cultures on the ninth POD were negative. Additionally, breast milk from bilateral breasts were also cultured on the ninth POD, which grew *Staphylococcus epidermidis*, a normal skin commensal. The antibiotics were subsequently oralised to ciprofloxacin 750 mg BD. The total parental antibiotics administered included one day of cefazolin, three days of ceftriaxone and metronidazole, and three days of meropenem, and four days of oral ciprofloxacin. The patient was discharged well on the 14th POD.

Case 2

The second case is of a 31-year-old GBS negative Indian primigravida, with no significant past medical history, who underwent an induction of labor for gestational diabetes on metformin 250mg BD at 38+2 weeks gestation. Her labor progressed uneventfully without any intrapartum pyrexia. After six hours of artificial rupture of the membranes and oxytocin augmentation, she had an assisted forceps delivery for a non-reassuring fetal status. The forceps delivery was complicated by a grade 3C anal sphincter tear that was managed appropriately with surgical repair and empirical antibiotics.

The baby girl was born in good condition with Apgar scores of 9 and 9 and 1 and 5 minutes, respectively, and a birth weight of 3360 grams. The arterial and venous cord blood cases at delivery were normal (Arterial pH 7.34, base excess [BE] -1.1 mEq/L, Lactate 3.31 mmol/L; Venous pH 7.29, BE -3.4 mEq/L, Lactate 3.85 mmol/L). The baby was commenced on CPAP for grunting and retractions at 10 minutes of life. The CPAP was weaned off at 18 minutes of life and the baby was sent to the special care nursery (SCN) for observation. The initial temperature was 37.7 degrees Celsius at 15 minutes of life. The baby remained clinically well and was transferred to general ward with the mother at six hours of life.

On the second day of life, at routine screening, the neonate was noted to have retractions and poor feeding with brownish regurgitation and therefore transferred back to SCN. The blood count showed leukopenia with total white count of 4.98 x 10^9/L and elevated CRP of 21.3mg/L. The blood gas showed compensated mild metabolic acidosis with raised lactate of 5.3 mmol/L. After obtaining blood cultures, empirical parental benzylpenicillin and gentamicin were commenced. At 25 hours of life, the baby was noted to have mild grunting with poor perfusion and widened pulse pressure. The antibiotics were escalated to meropenem, and ampicillin was added for *Listeria monocytogenes coverage.* The baby was transferred to NICU for CPAP for the respiratory distress. Repeat infective markers showed leukopenia of 2.41 x 10^9/L, thrombocytopenia of 91 x 10^9/L and worsening CRP to 56.5mg/L. The baby developed hypotensive episodes that required dopamine inotropic support and increasing ventilatory settings to maintain the oxygen saturations. At 36 hours of life, the baby developed bradycardia followed by asystole, requiring resuscitation with external cardiac compressions, seven doses of adrenaline, three fluid boluses of normal saline, along with a total of 62 mmol/kg of sodium bicarbonate, and three doses of calcium gluconate. Extracorporeal membrane oxygenation (ECMO) was activated and was successfully initiated at 38 hours of life and the baby was transferred to the cardiac intensive care unit (CICU). The circulation was restored after 1 hour and 44 minutes. A bedside echocardiography showed a structurally normal heart, with a normal ejection fraction of 65%, mild to moderate mitral regurgitation, large patent ductus arteriosus (PDA) 4.9mm with continuous left to right flow across PDA, and no atrial or ventricular dilatation, intracardiac thrombus or a pericardial effusion.

The blood culture of the neonate performed on the second day of life as part of the investigations for sepsis grew pan-sensitive *E coli.* Pan-sensitive *E. coli* was similarly found on a routine ear swab taken on the first day of life as part of infection control measures in the NICU. The urine culture performed on the third day of life was negative. As the neonate was hemodynamically unstable, a lumbar puncture was not performed.

The neonate's septic shock was complicated by DIVC, which required multiple units of FFP, packed cells, and cryoprecipitate transfusions. The baby also developed acute kidney injury requiring continuous renal replacement therapy.

A cranial ultrasound on the fourth of life showed bilateral sub-centimeter germinal matrix hemorrhages, and increased echogenicity of bilateral cerebral periventricular white matter. On the fifth day of life, the baby was noted to have absence of spontaneous breaths and movements on examination despite weaning off sedation and the pupils were non-reactive. A repeat cranial ultrasound performed the following day showed increased echogenicity related to a hypoxic ischemic injury, 4.5mm midline shift, reduced arterial flow, and dural venous sinus thrombosis. A CT scan of the brain on the seventh day of life revealed diffuse hypoattenuation of the brain parenchyma with loss of grey-white differentiation, associated with severe effacement of the cerebral sulci and ventricles, compatible with the provided history of cardiovascular collapse with resultant severe hypoxia. Following extensive discussion, the family decided to withdraw care on the seventh day of life, and ECMO and ventilatory support were disconnected.

Given the early-onset of pan-sensitive *E. coli* bacteremia in a full-term baby with unremarkable antenatal history, and poor response to broad-spectrum parenteral antibiotics, the neonate was also referred to immunologists for possible underlying immunodeficiency.

In contrast to the first case, the mother in this case was clinically well in the postpartum period. She had a maximum temperature of 38.4 degrees Celsius 1 hour postpartum, thereafter remained afebrile. She was given parenteral amoxicillin-clavulanate for 24 hours post partum as antibiotic prophylaxis after the third degree tear repair, which was subsequently oralised to complete one-week

duration. Although asymptomatic, maternal vaginal swab culture and urine culture were taken on the second day postpartum to evaluate for the source of *E. coli* in the neonate. The vaginal swab showed *E. coli* that was pan-sensitive to ampicillin, ceftriaxone, gentamicin and trimethoprim/sulfamethaxazole, but urine culture was negative. She was discharged well on the second postpartum day. An additional week of oral amoxicillin-clavulanate was prescribed following the results of the vaginal culture, to complete a total of two weeks of antibiotics.

Discussion

We present two cases of *E. coli* EONS in term infants presenting as respiratory distress, without any overt risk factors for infection. Both the cases had no antenatal or intrapartum risk factors for sepsis including prematurity, evidence of chorioamnionitis, antenatal or intrapartum maternal pyrexia, or any history of prolonged rupture of membranes. Chorioamnionitis manifested by uterine tenderness and/or foul smelling amniotic fluid has been reported as the most significant antenatal risk factor for *E. coli* EONS in a study [10].

E. coli EONS is more commonly seen in preterm and VLBW infants, and GBS is more common in term infants. The two cases discussed are of term infants, suggesting that E. coli should also be considered as an important cause of EONS regardless of gestation [5, 10].

In the first case, although the mother was positive for GBS vaginal colonization based on the antenatal vaginal swab, there was no evidence of ruptured membranes prior to delivery and the mode of delivery was by a CS. Hence, the possibility of genital tract colonization leading to an ascending infection is less likely. Though the vaginal swab culture taken on second POD was consistent with *E. coli,* this could be explained as secondary to endometritis following a caesarean delivery, rather than an undiagnosed chorioamnionitis. This is further supported by the fact that there were no clinical features suggestive of chorioamnionitis or maternal pyrexia in the antenatal period.

The second case was an elective induction of labor for gestational diabetes on metformin and the duration of membrane rupture to delivery was not prolonged at six hours. The vaginal swab taken at 35 weeks of pregnancy was negative for GBS with normal vaginal flora. During the course of investigation for the neonatal EONS with *E. coli,* the maternal vaginal swab performed on the second postpartum day showed light growth of *E. coli* with the same anti-microbial sensitivities to that of the *E. coli* in the neonatal blood culture. This could be as a consequence of contamination from the maternal gastrointestinal tract on account of a third degree tear sustained during the forceps delivery or secondary to true maternal genital colonization by *E. coli*, the incidence of which was noted to be 13% in literature [12]. As discussed, the mother was asymptomatic and did not have any overt risk factors for an *E. coli* infection. Of note, the maternal urine culture was negative for an *E. coli* infection.

The empirical antibiotic choices for EONS vary between institutions, but are typically IV benzylpenicillin and gentamicin as per the National Institute of Clinical Excellence (NICE) guidelines [14]. Some centers use ampicillin instead of benzylpenicillin with gentamicin for a comprehensive coverage, with benzylpenicillin or ampicillin providing cover against GBS along with *Listeria monocytogenes,* and gentamicin covering for *E. coli* [10]. A Spanish study over a 10 year period reported an increasing incidence of *E. coli* EONS and *E. coli* strains resistant to ampicillin and gentamicin in all age groups [15]. The study by Saez-Lopez also showed that the *E. coli* isolates resulting in obstetric infections had a higher percentage of ampicillin and gentamicin resistance. Similarly, as in the first case, the *E. coli* isolated from the mother and neonate were resistant to ampicillin and gentamicin, necessitating the use of meropenem. The stable burden of *E. coli* EONS emphasizes the need to reconsider empiric antibiotic choices especially in preterm and VLBW infants and in term infants with risk factors, especially in light of emerging *E .coli* resistance patterns [5, 10].

The two cases also highlight the subtle and non-specific presentation of EONS. Both cases presented as respiratory symptoms with grunting and retractions on the second day of life. The neonate in the second case was also noted to have poor feeding and regurgitation. There are numerous differential diagnoses and possible co-existing conditions that could account for respiratory distress, such as surfactant deficiency and pneumothorax as considered in the first case, and delayed transition as in the second case. However, there were subtle presenting features that triggered the investigations for sepsis in both the neonates. Despite antibiotic coverage with ampicillin and gentamicin, both the neonates rapidly deteriorated into septic shock. This emphasizes the need for a high index of suspicion for *E. coli* EONS and early investigation and consideration of empirical treatment with the usage of carbapenems such as meropenem.

Conclusion

The two cases presented illustrate the importance of *E. coli* as a cause of EONS, the subtle nature of its presentation in the neonate and the rapid deterioration to overwhelming sepsis with associated morbidity and mortality. It also emphasizes the need for a high index of suspicion for EONS with prompt recognition and treatment with broad-spectrum antibiotics, even in the absence of maternal risk factors, due to the potential for rapid progression if antibiotic treatment is delayed. In the presence of definite risk factors, a broad-spectrum antibiotic should be used in the intrapartum period and for empirical neonatal treatment to include coverage for *E. coli* in addition to GBS.

References

1. KM Puopolo, WE Benitz, TE Zaoutis (2018) Committee on Fetus and Newborn, and Committee on Infectious Diseases, "Management of Neonates Born at ≥35 0/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsi." Pediatrics 142: e20182894.
2. MJ Bizzarro (2005) "Seventy-Five Years of Neonatal Sepsis at Yale: 1928-2003." Pediatrics 116: 595-602.
3. J-H Wu, C-Y Chen, P-N Tsao, W-S Hsieh, H-C Chou (2009) "Neonatal Sepsis: A 6-Year Analysis in a Neonatal Care Unit in Taiwan." Pediatr Neonatol 50: 88-95.
4. P Kuhn (2010) "Incidence and distribution of pathogens in early-onset neonatal sepsis in the era of antenatal antibiotics:

Distribution of early-onset neonatal sepsis." Paediatr Perinat Epidemiol 24: 479-487.
5. SJ Schrag (2016) "Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014." Pediatrics 138: e20162013-e20162013.
6. GJ Escobar (2000) "Neonatal Sepsis Workups in Infants ≥2000 Grams at Birth: A Population-Based Study." Pediatrics 106: 256-263.
7. J Alexander (1999) "Chorioamnionitis and the prognosis for term infants." Obstet Gynecol 94: 274-278.
8. A Herbst, K Källén (2007) "Time between Membrane Rupture and Delivery and Septicemia in Term Neonates." Obstet Gynecol 110: 612-618.
9. KM Puopolo (2011) "Estimating the Probability of Neonatal Early-Onset Infection on the Basis of Maternal Risk Factors." Pediatrics 128: e1155-e1163.
10. BJ Stoll (2011) "Early Onset Neonatal Sepsis: The Burden of Group B Streptococcal and E. coli Disease Continues." Pediatrics 127: 817-826.
11. SJ Schrag, JL Hadler, KE Arnold, P Martell-Cleary, A Reingold, et al. (2006) "Risk Factors for Invasive, Early-Onset Esc herichia coli Infections in the Era of Widespread Intrapartum Antibiotic Use." Pediatrics 118: 570-576.
12. E Sáez-López (2016) "Vaginal versus Obstetric Infection Esc herichia coli Isolates among Pregnant Women: Antimicrobial Resistance and Genetic Virulence Profile." PLOS ONE 11: e0146531.
13. CB Wilson, V Nizet, YA Maldonado, JS Remington, JO Klein (2016) "Bacterial sepsis and meningitis," in Remington and Klein's infectious diseases of the fetus and newborn infant, Eighth edition. Philadelphia, PA: Elsevier, Saunders 2016: 217.
14. "NICE Clinical Guideline (2012) Neonatal infection (early onset): antibiotics for prevention and treatment." www.nice.org.uk/guidance/cg 149.
15. Natalia Mendoza-Palomar, Milena Balasch-Carulla, Sabina González-Di Lauro, Maria Concepció Céspedes, Antònia Andreu, et al.(2017) "Escherichia coli early-onset sepsis: trends over two decades." Eur J Pediatr 176: 1227-1234.