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CASE REPORT

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Should clinical suspicion shift to ampicillin resistance organisms in certain preterm premature rupture of membranes scenarios?: Case of early-onset sepsis caused by *E coli*

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Abstract

This case highlights the importance antibiotic stewardship, including reexamining current regimens use for intrapartum antibiotic prophylaxis, which may be accountable for the shift in organism responsible for some cases of early-onset sepsis.

KEYWORDS

ampicillin-resistant, *E coli*, early-onset sepsis, intrapartum antibiotics

1 | INTRODUCTION

Use of intrapartum antibiotic prophylaxis (IAP) for managing preterm premature rupture of membranes incorporates multiple doses of ampicillin and erythromycin. This regimen has been attributed to the recent increase in incidence of ampicillin-resistant strain of *Escherichia coli* in that has been implicated in early-onset neonatal sepsis. We describe a case of a male infant born at 30 weeks and 3 days to a 23-year-old gravida 2 para 1 mother that presented with preterm premature rupture of the membranes. The infant rapidly expired from early-onset sepsis due to unrecognized ampicillin-resistant *E coli*. This case highlights the importance antibiotic stewardship, including reexamining current regimens use for IAP, which may be accountable for the shift in organism responsible for some cases of early-onset sepsis.

Neonatal sepsis can be a rapidly progressive and frequently fatal condition caused by infection acquired before or during birth; when it occurs in neonates with in the first 3 days of life, it is referred to as early-onset neonatal sepsis (EOS). Although Group B streptococcus (GBS) is the most common cause for this condition, more recent data have shown that Escherichia coli (*E coli*) has become more frequent causative organism.[1] *E coli* is a gram-negative bacterium commonly found in the human gastrointestinal tract and is usually asymptomatic. However, within the scope of obstetrics, the impact of *E coli* in causing intrapartum and peripartum infection has been shifting, especially in patients who experience preterm premature rupture of membranes (pPROM) occurring prior to 34 gestational weeks.

Current recommendations for managing pPROM include administration of antibiotics to prolong the latency period. The standard regimen consists of 48 hours of intravenous

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ampicillin and erythromycin, followed by 5 days of oral amoxicillin and erythromycin[2] along with GBS prophylaxis, if appropriate. The use of this regimen has been linked to a drop in the incidence of GBS sepsis and prolongation of the latency period; however, recent evidence suggests that this may be a causative factor for the observed increase in the incidence of *E coli* sepsis.[3,4] Among *E coli* infections, the ampicillin-resistant strain has become more prevalent and has been statistically linked with the antenatal antibiotics.[4] While not as symptomatic to the mother, neonatal sepsis from this organism has a higher mortality rate compared with sepsis caused by GBS,[5] especially in infants who are classified as very low birth weight (VBLW) or low birth weight (LBW). We describe a case of early-onset neonatal sepsis with *E coli* that resulted in neonatal mortality. It is important that obstetricians and pediatricians become more aware of the increased incidence and the risk factors associated with *E coli* sepsis so that a high degree of clinical suspicion can be maintained.

2 | CASE REPORT

Our patient was 30 weeks and 3 days male infant born to a 23-year-old gravida 2 para 1 mother. He was delivered by Cesarean section, due to placental abruption following pPROM. Four days prior to delivery, the mother presented to the labor and delivery unit with premature rupture of membranes. She was initially given betamethasone for pulmonary maturation and intravenous magnesium sulfate for neuroprotection. For latency period prolongation and GBS prophylaxis, a course of intravenous ampicillin (2 g q 6 × 48 hours) and azithromycin (500 mg q 6 × 48 hours) followed by oral ampicillin and erythromycin was initiated. At the time of admission, a cervical culture was taken, which was positive for Group B Streptococcus.

On admission, the maternal leukocyte count was 12.3 k/μL. She was afebrile but mildly tachycardic with a heart rate of 110 beats per minute. Leading up to the Cesarean delivery, the mother complained of increasing abdominal pain and contractions accompanied by vaginal bleeding, which was clinically indicative of placental abruption. The mother remained afebrile, but the leukocyte count measured 4 days after admission increased to 21.9 k/μl. Fetal heart rate monitoring started to exhibit a Category 2 tracing, which in combination with the clinical suspicion of placental abruption, resulted in the mother being taken for emergency Cesarean section. The baby was delivered in breech position, with clear amniotic fluid. He was dried and stimulated with reciprocal response. Apgar scores were calculated to be nine in the first and nine in the fifth minute of life. Although quite premature and weighing 1588 g, he was appropriate for his gestational age. Oxygen through nasal continuous positive airway pressure (CPAP) was started along with administration of Ampicillin, Gentamycin, and Penicillin. Vital signs at that time were Temperature 99.7 F, Pulse 180 beats per minute, Respiratory Rate 48 breath per minute, Blood Pressure 72/26 mm Hg, 90 SaO2. The baby was admitted to the Neonatal ICU with the diagnosis of respiratory distress and in order to rule out sepsis. Postdelivery, the mother had an unremarkable post-operative course and remained afebrile.

The neonate's laboratories where done at admission and showed a leukocyte count of 3.4 k/μl and a CRP of 1.37(units). Two hours into the neonatal ICU stay, the baby was unable to tolerate the nasal CPAP and sustained oxygen desaturations accompanied by bradycardia. Vitals taken at that time were P148, RR 60, BP 46/24, and 87 SaO2. Oral intubation was conducted and vital signs stabilized. An arterial blood gas (ABG) was indicative of reparatory acidosis with values of pH 7.11, pCO2 81, HCO3 25.7. A chest X-ray was done and showed haziness in bilateral lung fields suggestive of respiratory distress syndrome (show X-ray). In response to the chest radiograph, paired with the clinical findings, surfactant was given, but no clinical improvement occurred.

Shortly afterward, the baby started to decompensate and required high ventilator settings. Blood pressures started to drop. The echocardiogram showed bidirectional shunting across the atrial septal defect and a PDA consistent with pulmonary hypertension. The patient was promptly started on dopamine, dobutamine, and norepinephrine. Blood pressures stabilized, but the baby did not respond to ventilation. The baby expired later in the night despite extreme measures including fluid resuscitation. Subsequently, the peripheral blood cultures came back positive for gram-negative bacillus, later identified as Escherichia Coli, and gram-positive cocci in clusters. The antibiotic sensitivities of the Escherichia Coli displayed resistance to ampicillin but sensitivity to cephalosporins. An autopsy was later conducted at the hospital and revealed gram-negative bacilli in multiple areas of the lungs with significant congestion, hemorrhage and focally hyaline material deposits in both lungs. Further pathological testing established that the gram-negative bacilli were morphologically consistent with the previously cultured *E coli* including the same antibiotic resistance pattern. In summary, the report supported that the cause of death for the patient was overwhelming sepsis and pneumoniae due to ampicillin-resistant *E coli*.

3 | DISCUSSION

Certain risk factors predisposed the neonate described in this case report to an infection from *E coli* including the prolonged time gap between the pPROM and the delivery, as well as prematurity and his low birth weight. The

administration of latency antibiotics may have also been a contributing factor. In accordance with the ACOG recommendation, expectant management was the appropriate course due to the neonate being premature.[1] Expectant management entails administration of magnesium sulfate for neuroprotection, corticosteroids to prevent complications associated with prematurity, and an intrapartum antibiotic prophylaxis (IAP) regimen to prolong the latency period to delivery.[6]

Since the implementation of intrapartum antibiotic prophylaxis as standard practice, the incidence of GBS related sepsis has declined significantly while the incidence of *E coli* related sepsis has increased. A review of data regarding very low birth weight (VLBW) infants in the Neonatal Research Network compared two population cohorts, one from 1991-1993, and the other from 1998-2000 before and after the implementation of IAP respectively. The findings demonstrated an increase in the incidence of *E coli* bloodstream infections from 3.2 per 1000 live births in the 1991-1993 cohort to 6.8 per 1000 live births in the 1998-2000 cohort.[1] The authors of the article concluded that the use of IAP unintentionally allowed for the organism to build up resistance to the antibiotic used. Similarly, an article published in the New England Journal of Medicine which looked at the pathogens responsible for early-onset sepsis in very low birth weight infants, reported that after the implementation of national programs to reduce vertical transmission of GBS infection, a change in the predominant organism was observed. While the investigators saw a reduction in the prevalence of EOS sepsis caused by GBS in the postimplementation period (1998-2000) as compared to the preimplementation period (1991-1993), an increase of incidence in EOS due to *E coli* was observed during the postimplementation period.[4]

Historically, the predominant organisms associated with EOS have changed over time. Gram-negative organisms, especially *E coli*, were the most common causes of cases of neonatal sepsis reported at Yale University from the late 1940s to the mid-1960s.[1,7] Gram-negative organisms remain the most frequently reported cause of neonatal sepsis in developing countries.[7,8] That, in addition to the long-time lapse between rupture of membranes and delivery, proved to be strong risk factors for developing EOS.[4] The use of IAP in the mother, although appropriate in our patient, may have predisposed the patient to the organism possibly not covered by the regimen. Additionally, the use of intrapartum antibiotic for latency has increased the incidence of ampicillin resistance in organisms that subsequently may cause sepsis.[9]

Antibiotic resistance has increasingly become a major public health issue. Certain bacteria, gram-negative organisms in particular, already have high intrinsic abilities that allow them to be resistant to antibiotics. In addition, they also exhibit ways to acquire resistance through new mechanisms that may be transferred from other pathogens. A population-based study that examined ampicillin administration in relation to *E coli* resistance in neonates found that 67% of their *E coli* were ampicillin resistant. Furthermore, within that group, it was found that 92% of isolates occurred in mothers had been treated with intrapartum ampicillin, in comparison with the 18% who had not received ampicillin.[9] In a study by Stoll et al that examined changes in pathogens causing early-onset sepsis in VLBW, 85% of *E coli* isolates (28 out of the 33 that were found to have *E coli* sepsis) were resistant to ampicillin. Similarly, the mothers of infants with ampicillin-resistant strains of *E coli* were significantly more likely to have received intrapartum ampicillin than were those with ampicillin-sensitive strains (93% vs 20%).[4] A recent Pediatrics & Neonatology article associated ampicillin resistance bacteria with the increases in its virulence factors within the organism, such as adhesion molecules (F1, P, and S fimbriae), iron-sequestering systems, hemolysin, capsules (K1, K5), lipopolysaccharide O-antigen, and others.[8] Based on this evidence, this pathogenic pathway could have explained the presence of this organism in our patient as the mother had been treated antenatally with ampicillin.

Neonatal symptoms secondary to sepsis are difficult to distinguish from symptoms that are typical complications of prematurity, thus making the diagnosis elusive. As noted by Stoll et al, who reported symptoms associated with EOS *E coli* sepsis in 30 infants, the predominant symptom observed was respiratory distress within the first 4 hours after birth (73% of the patients). Furthermore, the initial chest radiographs were abnormal in 19 of those 30 neonates and the remainder were interpreted as possible meconium aspiration, respiratory distress syndrome, wet lung, or pneumonia.[9] Symptomology consistent with these diagnoses in premature neonates, such as apnea, bradycardia, and cyanosis, may also be the first indications of sepsis. Therefore, identifying infants with EOS is more challenging and requires heightening vigilance and clinical suspicion.[10] The clinical features and risk factors discussed occurred more often in the deceased than in the survivors of the study. Additional features that contribute to an increased rate of death are as follows: history of rupture of the membranes for 36 hours or more, maternal intrapartum ampicillin therapy, birth weight of 2500 g or less, metabolic acidosis at birth, features of respiratory distress syndrome, neutropenia, and cerebrospinal fluid cultures positive for the presence of E coli (this was not seen in the discussed patient).[9]

Although sepsis, in general, has always been potentially fatal, research has identified *E coli* as more likely to lead to death compared with GBS. Mortality among infants with *E coli* early-onset sepsis was higher than in those with GBS early-onset sepsis (10% of the patient population vs 4% patient population, $P < .001$). However, there is no difference in the length of survival between both groups (53% of the GBS group died compared with the 44% in the *E coli* group

died within 7 days of a positive culture).[1] In the Stoll et al study, after adjusting for gestational age, the morbidity of the infants with gram-negative EOS had a significantly higher risk of respiratory distress syndrome (63% vs 43%), severe intraventricular hemorrhage or periventricular leukomalacia (32% vs 12%), and bronchopulmonary dysplasia (62% vs 35%) than the infants with gram-positive EOS.[4]

One feature of gram-negative EOS that makes it more fatal than its GBS counterpart is the additional virulence factors that the organism develops. One study that explored the interspecies genetic distribution and prevalence of virulence factors in *E coli* strains from pregnant women and neonates found that the flora that induced the sepsis originated from the intestinal flora; however, these pathogens also acquired additional virulence factors allowing it to specifically thrive in the vaginal vault and cause chorioamnionitis. The specific subtype was discovered to contain the ECOR B2 gene and the K1 capsular antigen along with other factors.[5] As discussed above, resistance to ampicillin has also been found to be associated with acquired virulence factors.

Given the high mortality rate associated *E coli* EOS in neonates, the question then arises whether any changes to the standard IAP should be implemented. A high degree of clinical suspicion is necessary to diagnose *E coli* EOS. As in the case described, in a case of prematurity and prolonged-time between membrane rupture and delivery, along with administration of IAP, an ampicillin-resistant *E coli* should be on the differential diagnosis when a neonate fails to improve clinically after administration of Ampicillin. In this setting, we believe that the neonate should be treated with an antibiotic regimen geared toward the ampicillin-resistant *E coli*. One such regimen is a second-generation cephalosporin in combination with erythromycin, which has been found to be as effective as ampicillin/sulbactam combination commonly used for sensitive organisms.[11] In terms of prophylactic treatment for this specific clinical scenario, providing an alternative regimen in facilities where ampicillin-resistant *E coli* are more predominant is a possible approach, but also runs the risk of creating a more broadly resistant organism in the future.

4 | CONCLUSION

Universal use of IAP has lowered the incidence of GBS EOS while increasing the incidence of EOS associated with *E coli*. Neonatal symptoms can be elusive and difficult to distinguish from prematurity; thus, a high degree of clinical suspicion is required to make the diagnosis. As demonstrated in this case, ampicillin-resistant *E coli* EOS should be suspected when the infant fails to improve clinically after administration of ampicillin, especially in a setting of prematurity, low birth weight, prolonged rupture of membranes, or use of IAP. Further research and population-based studies on the incidence of EOS and unintended consequences associated with universal IAP may help to modify current IAP protocols to cover for EOS associated with *E coli*.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

A. Bandu and N. Lakhi: contributed to the writing of the manuscript. A. Barone and S. Parab: contributed the overall planning and content of the manuscript. All authors approved the final manuscript.

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