

Youngest survivor of perinatal infection by *Eikenella corrodens*: case analysis and literature review highlighting the merits of placental swab culture

A. Garvey¹, J. Powell², B. Murphy², N. O'Connell², M. Imcha¹ and R. K. Philip¹

1) University Maternity Hospital Limerick, Limerick, and 2) University Hospital Limerick, Limerick, Ireland

Abstract

Eikenella corrodens has been noted as a causative organism in both neonatal and perinatal sepsis. Positivity of blood cultures at birth among preterm infants may be influenced by the maternal use of peripartum antimicrobials and a normal C-reactive protein result within the first 24 hours need not always reflect the absence of fetal invasion by the highly pathogenic organisms. For these reasons, supportive and adjunctive approaches such as appropriately collected placental swabs for culture would be of value in optimizing the antimicrobial choice for sick preterm infants during the early neonatal period. Fetal infection by *E. corrodens* detected by placental swab culture influencing antimicrobial management of an extremely premature infant with sepsis is described. Management of the youngest premature survivor with the lowest birthweight among the reported cases in English language of neonatal *E. corrodens* infection is summarized and literature is reviewed. The value of placental swab, which is often underused, is highlighted in this review.

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Keywords: Chorioamnionitis, *Eikenella corrodens*, extremely low birthweight, neonatal sepsis, perinatal infections, placental swab

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Corresponding author: R.K. Philip, Division of Neonatology, Department of Paediatrics, University Maternity Hospital Limerick, Limerick V94 C566, Ireland
E-mail: roy.philip@hse.ie

with clinical features of sepsis soon after birth. Value of placental swabs, which are often underused, is highlighted and we have reviewed all published reports of neonatal *E. corrodens* infections.

Introduction

Eikenella corrodens is a Gram-negative rod associated with human gastrointestinal (particularly oral cavity) or upper respiratory tracts. Less commonly, it has been known to be a contributing agent in meningitis, endocarditis, head and neck infections, intra-abdominal infections and gynaecological infections [1–4]. Association of *E. corrodens* infection with preterm labour, chorioamnionitis and early neonatal mortality has been reported [5–11].

We describe a case of *E. corrodens in utero* fetal infection detected by a positive placental swab culture influencing antimicrobial management of an extremely-low-birthweight infant

Case

A 36-year-old Irish Caucasian, G3 P0+2 attended our hospital for antenatal care. She had gestational diabetes mellitus which was diet controlled. Her past medical history was positive for hypertension, asthma, the drainage of a Bartholin's cyst 10 years ago and she had had a termination of pregnancy 16 years previously. In this pregnancy, her antenatal viral serology including human immunodeficiency virus and hepatitis B/C viruses was negative and immunity to rubella virus was demonstrated. She had also previously delivered a baby prematurely at 21/40 associated with acute, severe chorioamnionitis which merited maternal treatment with intravenous amoxicillin and metronidazole. She conceived approximately 1 month after the above described fetal loss. In the current pregnancy, she had a

cervical suture placed at 14/40 gestation. She was admitted at 21⁺⁴/40 for bed rest due to shortening of the cervix with funnelling. A mid-stream urine at 22/40 grew group B streptococcus and she received a 5-day treatment course of an oral amoxicillin/clavulanic acid combination. Antenatal steroids (betamethasone) were given at 23⁺⁴ and she received a loading dose of magnesium sulphate before delivery.

A baby girl was born by emergency lower segment caesarean section due to preterm breech in labour with bulging, intact membranes at 24⁺⁶ weeks of gestation. Birthweight was 570 g. Baby was intubated post-delivery and received one dose of surfactant (Beractant $\alpha^{\text{®}}$) in theatre. Apgar scores were 7, 7 and 8 at 1, 5 and 10 minutes, respectively. Umbilical vascular access was obtained and a septic work up, including a full blood count, C-reactive protein (CRP) and blood cultures, was performed. On the day after delivery, mother was febrile with a white blood cell count of $9.05 \times 10^9/\text{L}$ and her CRP reached 310 mmol/L.

The baby was initiated on ventilatory support, specifically synchronized intermittent mandatory ventilation but she developed respiratory acidosis with CO_2 retention soon after delivery, which improved with a second dose of surfactant. Tachycardia, tachypnoea, increased capillary refill time and desaturations (SaO_2 of 75%) were also observed at this time and high-frequency ventilation was initiated. She remained hypoxaemic (PaO_2 of 3 kPa) initially and point-of-care echocardiography at 3 h of age showed evidence of persistent pulmonary hypertension of newborn. However, following initiation of high-frequency ventilation and before introduction of inhaled nitric oxide (iNO) she improved with PaO_2 reaching 8.2 kPa. Her systemic blood pressure remained stable at 28–34 mmHg and as her metabolic acidosis persisted she received two, 10 mL/kg boluses of 0.9% NaCl and maintenance acetate in her patient-specific total parenteral nutrition.

She was initially commenced on intravenous benzylpenicillin (standard dose 25 mg/kg) and intravenous gentamicin (5 mg/kg) at 2.5 h of life. She was also commenced on prophylactic fluconazole as a preventive strategy for invasive candidal infections among extremely-low-birthweight infants, which was the unit policy. Her initial CRP taken at 2.5 h of life was 25 mmol/L and full blood count showed white blood cell count $5.01 \times 10^9/\text{L}$ with neutrophil count of $1.35 \times 10^9/\text{L}$. Following this result, her benzylpenicillin was changed to high-dose (50 mg/kg). Her CRP was repeated at 24 h of life and had increased to 87 mmol/L. A lumbar puncture was performed for cerebrospinal fluid (CSF) studies and intravenous cefotaxime (50 mg/kg) was added to her current antimicrobial regimen.

Although her blood cultures were sterile at 36 and 48 h, antimicrobials were continued pending final results of blood and CSF cultures, as her clinical features were consistent with

sepsis and secondary persistent pulmonary hypertension of newborn. Her CSF cultures were sterile with $<5/\mu\text{L}$ leucocytes, glucose was 4.1 mmol/L and protein was 1.64 g/L. CSF showed negative PCR results for group B streptococcus and *Escherichia coli*.

Placental swab culture results became available on day 3 and both the maternal and fetal surfaces revealed 0–4/high-power field leucocytes and grew *E. corrodens*, which was sensitive to cephalosporins, penicillin and clindamycin. She received a total of 10 days of intravenous benzylpenicillin and 7 days cefotaxime. A repeat blood culture was performed on day 4 of life and was reported sterile. Maternal expressed breast milk was commenced on day 1 of life, which was continued along with donor expressed breast milk until maternal supply was established. She remained on synchronized intermittent mandatory ventilation with pressure support for 4 days, Nasal continuous positive airway pressure for 18 days and high/low-flow humidified oxygen for 11 days. Her cranial ultrasound scans were normal and she showed appropriate growth parameters during the neonatal course and during follow up for the given gestation.

Discussion

Early-onset neonatal sepsis is one of the most important causes of neonatal morbidity and mortality worldwide. *Eikenella corrodens* is a rare cause of early-onset neonatal sepsis with only seven case studies previously described in English literature [5–11].

Eikenella corrodens is a fastidious, facultative, anaerobic, Gram-negative organism that is part of the normal human oral flora. It has the peculiar characteristic of creating a depression or pit on the agar medium and hence is referred to as the corroding bacillus. *Eikenella corrodens* is oxidase positive, catalase negative, non-motile and non-spore forming and does not have a capsule. It grows slowly on both blood and chocolate agar and growth is enhanced in carbon dioxide conditions (3%–10% CO_2). Culture typically requires longer than 2 days to recognize the pinpoint colonies, which are greyish and small with an almost greenish discoloration on blood agar. Colonies may have an odour resembling hypochlorite. Following growth of placental swabs on blood and chocolate agar, identification of the pitting organism is confirmed by Gram stain and matrix-assisted laser-desorption/ionization time of flight mass spectrometry [12,13].

In the 12-year period from April 2004 to March 2016, a total of 1200 placental specimens were cultured in the Microbiology Laboratory from University Maternity Hospital Limerick. While offering clinical and microbiological benefits in high-risk perinatal contexts, the value of performing routine placental cultures for all pregnancies appears limited [14]. Placental swabs

TABLE 1. Summary of published literature on neonatal *Eikenella corrodens* infections

Case	Maternal risk factors	Maternal signs and symptoms	Maternal treatment	Gestational age	Birthweight	Newborn signs and symptoms	Newborn treatment	Newborn outcome
Hu et al. [6]	None	WBC 19 000/mm ³	None	33 weeks	1395 g	Positive blood culture at 30 min of life. WBC 2990/mm ³ , ANC 388, respiratory distress	Ampicillin 100 mg/kg IV every 12 h for 14 days; Gentamicin 4 mg/kg IV every 36 h for 10 days; Cefotaxime 50 mg/kg every 12 h for 5 days	Infant survived and improved clinically on antimicrobial therapy.
Andres-Gomez et al. [11]	None reported	Temperature 38°C, positive cervical and vaginal cultures	None	28 weeks	1035 g	Positive cultures from blood, pharynx, nose, ear and umbilical cord. WBC 16 000/mm ³ (80% neutrophils)	Ampicillin 50 mg/kg IV every 8 hours for 2 weeks	Infant survived and improved clinically on antimicrobial therapy.
Kostadinov & Pinar [8]	Bleeding gums	Placental histology showed acute necrotizing chorioamnionitis	None	23 weeks	590 g	Positive blood and lung cultures post-mortem; bronchopneumonia and funisitis on autopsy	None	Infant died shortly after birth
Sporcken et al. [9]	Oral sex during pregnancy	WBC 15 200/mm ³ , temperature 38.9°C, positive cervical and amniotic fluid cultures	Cephalothin 4 g per day and metronidazole 2 g per day started 18 h before delivery	24 weeks	570 g	Positive cultures from blood, axilla, groin, mouth, throat, nose, ear and anus, intracerebral haemorrhage, bronchopneumonia and acute enteritis on autopsy	None	Infant died shortly after birth
Garnier et al. [5]	None	38.9°C, premature labour, CRP 105, WBC 25 000/mm ³	Not documented	32 ⁺⁶ weeks	1830 g	Tachycardia, hepatomegaly, Positive gastric aspirates	Cefotaxime (8 days) and Gentamicin (3 days)	Favourable
Garnier et al. [5]	None	37.8°C, premature labour, CRP 105, positive placental cultures	Not documented	30 weeks	1800 g	RDS, infectious alveolitis, hypotension, tachycardia, neonatal jaundice, positive gastric aspirates	Cefotaxime (10 days) and Gentamicin (2 days)	Favourable
Sawyer et al. [10]	None	Premature labour, mother otherwise well	Single dose ampicillin 1 h before delivery	27 weeks	1000 g	RDS, WBC 4800/mm ³ , blood cultures positive, CSF WBC 990/mm ³	Ampicillin and gentamicin (7 days) and cefotaxime (21 days)	Infant survived and improved clinically on antimicrobial therapy.
This study	None reported	Hx chorioamnionitis in previous pregnancy, WBC 9.05 × 10 ⁹ /L, CRP 310, preterm labour	IV Benzylpenicillin 6 h before delivery	24 ⁺⁶ weeks	570 g	Raised CRP 25, positive placental cultures	Benzylpenicillin (7 days) and Cefotaxime (5 days)	Favourable

Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; IV, intravenous; RDS, respiratory distress syndrome; WBC, white blood cell count.

for all severely premature babies was also not the standard of care in our hospital until the end of 2015 due to their perceived low yield; however, placentas from all extremely-low-birthweight babies are now swabbed.

This is the first positive report of confirmed *E. corrodens* identified from placental, fetal, neonatal or peripartum maternal specimens. Perhaps the newer and more sensitive molecular methods, automation and culture techniques could be playing a role in the identification of uncommon, yet clinically significant organisms [13].

Of late, interesting evidence is emerging to suggest that hematogenous spread of bacteria is colonizing the placenta [15–17]. Positive placental cultures may provide the clinician with valuable information on which to base therapy; however, it is confirmed only in a small number of placentas with histological evidence of chorioamnionitis and funisitis [14]. Correlation between the bacteriological and histopathological findings in placentas from women with suspected or proven chorioamnionitis has been established with concordance in about 70% of the examined placentas [18].

There are several ways to perform placental swabs. A suggested technique involves the careful cleansing of the placenta, before incision is made to reach and identify the interface between the chorion and amnion membranes and at this interface, a swab can be collected [19].

Positive culture result from the maternal side of the placenta alone, especially in a vaginal delivery, would be of limited value, particularly if the isolated bacteria is from the normal vaginal flora. However, isolation of highly pathogenic bacteria from the fetal side offers higher correlation with chorioamnionitis [18]. The current method of placental swabbing and culture technique is highly specific but not sensitive [14].

Recent studies have suggested that bacteria associated with the placenta, a 'placental microbiome', may be important in reproductive health and disease. However, a challenge in working with specimens with low bacterial biomass, such as placental samples, is that some or all of the bacterial DNA may also derive from contamination [20].

In this case, it is possible that the treatment of the mother with amoxicillin/clavulanic acid combination before delivery could have contributed to the sterile blood cultures in our patient. It is known that bacteraemia could resolve rapidly after the initiation of appropriate antibiotic therapy and source control [21]. Benzylpenicillin diffuses across the placenta into the fetal circulation at levels 10%–30% of those found in maternal plasma. High concentrations are also attained in the amniotic fluid [22]. The terminal half-life of benzylpenicillin in neonates <32 weeks has been estimated to be about 3.9 hours [23] so trace levels with the potential to inhibit positive growth on culture media may be present more than 24 h after cord

clamping. Consideration should be given to adopting alternative diagnostic techniques as adjuncts such as cord-blood novel biomarkers and placental swab cultures for neonatal culture negative sepsis [14,24–31].

Eikenella corrodens cases documented in the literature to-date describe babies born at a mean age of 30 weeks of gestation [5–11]. Five of seven babies improved clinically with antimicrobial therapy and had a favourable outcome. Interestingly, these babies were all born with a birthweight >1000 g. The two reported cases of death occurred in infants of 24 and 23 weeks of gestation [8,9]. All of the mothers except one had evidence of infection including raised inflammatory markers and presence of a fever, and risk factors including poor oral hygiene and history of oral sex during pregnancy were only reported in two women. Interestingly, in the case described by Sawyer *et al.*, the mother was well with no risk factors identified. This baby subsequently had positive blood cultures and raised white blood cell count in CSF studies. Table 1 summarizes the reported feto–maternal and neonatal *E. corrodens* infections. Our patient was born at 24⁺⁶ weeks gestation, but in this case we had a high index of suspicion for infection causing preterm birth given the history of chorioamnionitis in a previous delivery and so treated empirically and promptly with antibiotics, which was likely a contributing factor in the good clinical outcome of our patient.

Conclusion

Eikenella corrodens has been noted as a causative organism in both neonatal and perinatal sepsis. As the positivity of blood cultures at birth among preterm infants could be influenced by the maternal use of peripartum antimicrobials and a normal CRP result within the first 24 hours need not always reflect the absence of fetal invasion by the highly pathogenic organisms, supportive and adjunctive approaches such as appropriately collected placental swabs for culture would be of value in optimizing the antimicrobial choice of sick preterm infants during the early neonatal period [14].

Our patient, the youngest premature survivor of *E. corrodens* infection with the lowest birthweight documented in the literature to date, presented with culture-negative sepsis following preterm delivery at 24⁺⁶ weeks of gestation and her successful outcome was aided by placental swab cultures and appropriate antimicrobial use.

Transparency declaration

All authors report no conflicts of interest relevant to this article.

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