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Necrotizing enterocolitis following treatment of congenital syphilis with penicillin in a term newborn

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Abstract

Necrotizing enterocolitis is a disease process of intestinal disruption which has been associated with gastrointestinal microbial alterations after antibiotic exposure. Treatment guidelines and antibiotic exposure for congenital syphilis have historically been based on limited evidence. This case presents a term infant who developed necrotizing enterocolitis after treatment for congenital syphilis.

Keywords

Necrotizing enterocolitis, term infant, congenital syphilis, syphilis

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Introduction

Necrotizing enterocolitis (NEC) is a disease process of the gastrointestinal tract that results in significant morbidity and mortality among neonatal infants. NEC occurs primarily among premature infants and is uncommon among term infants with an incidence inversely proportional to gestational age.[1] Hospital mortality rates among neonates with NEC have been reported to range from 20% to 30%.[2] While the pathophysiology of NEC is not completely understood, it is thought to be associated with several risk factors and involve a multifactorial process that results in an inflammatory process of intestinal disruption.[3] Risk factors that have been identified include prematurity, low birth weight, early formula feeding, antibiotic exposure, and alterations in microbial colonization of the gastrointestinal tract.[4,5]

Previous studies have suggested an associated risk of NEC from prolonged antibiotic use and the alteration of gastrointestinal flora.[6–10] The mechanism of NEC from antibiotic exposure may result from an alteration of the diversity of the microbiome, a delayed colonization of normal flora, or a development of overgrowth of pathogenic organisms.[11] While antibiotic administration may be necessary among those with high risk of invasive bacterial infections, the potential risk of adverse consequences and necessity of antimicrobial stewardship signify the importance of limiting antibiotic exposure to no more than the needed length of treatment. To date, focus has mainly been on the risk of NEC following prolonged antibiotic exposure in low birth weight early preterm neonates, but the risk of duration of antibiotic exposure must also be considered in the treatment of diseases in term newborns.

Congenital syphilis is a disease where the duration of treatment may lead to prolonged antibiotic exposure in a neonate. Treatment of congenital syphilis has largely been based on clinical experience and there is limited evidence on the optimal dose or duration of penicillin or other alternative antibiotics in neonates.[12,13] The Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) have developed recommendations to help guide treatment, but optimal treatment and duration may vary across clinical practice as some experts have differing treatment opinions. With congenital syphilis cases continuing to increase, adverse events attributed to current treatment regimens should continue to be reported to guide future clinical guidelines.[12]

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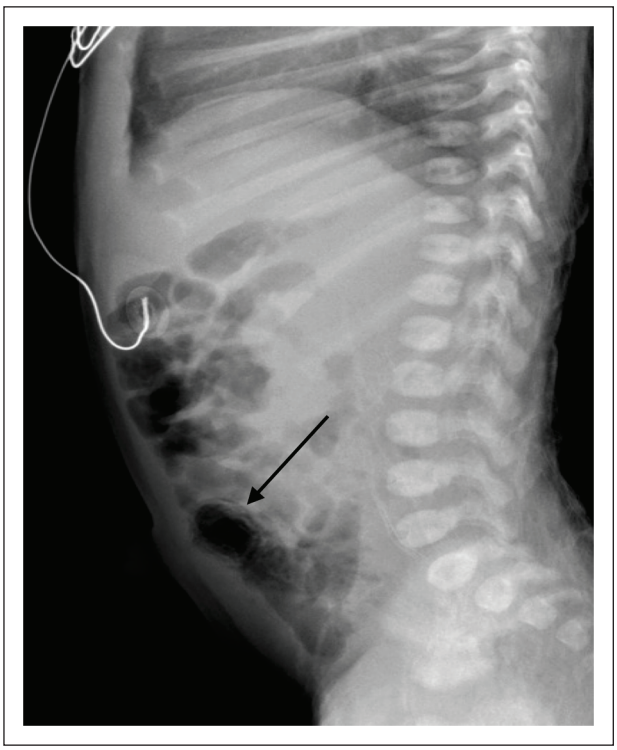

Figure 1. Lateral abdominal radiograph with pneumatosis intestinalis indicated by black arrow.

Due to the rarity of NEC among term infants, studies have mainly been limited to case reports or small case series.[1] As such, we present a case NEC in a term infant after antimicrobial exposure for congenital syphilis with penicillin.

Case presentation

Our institution does not require ethical approval for reporting individual cases without any identifiable private health information. A 2.77-kg female was born via spontaneous vaginal delivery to a 22-year-old mother following a 37-week 4-day gestation. Maternal history was complicated by Group B *Streptococcus* (GBS) and possible latent syphilis of unknown duration. Other prenatal infectious laboratory results were unremarkable. Mother received three total doses of bicillin, with the final dose being 2 days prior to delivery. Mother's rapid plasma reagin (RPR) titer had a decrease from 1:32 to 1:4 dilution prior to delivery. Mother's partner was incarcerated with unknown sexually transmitted disease status. Mother did not receive adequate GBS prophylaxis prior to delivery.

The infant was vigorous at birth with APGAR scores of 8 and 9 at 1 and 5 min, respectively. The neonate was transferred to the neonatal intensive care unit (NICU) shortly after delivery for work-up of exposure to reactive maternal syphilis. This infant was placed in adoptive care following delivery, so breast milk was not available. The baby bottle fed ad lib with a milk-based newborn formula, eating 15–45 mL every 3 h. Initial physical examination was unremarkable without findings consistent with congenital syphilis. Initial laboratory work included a normal complete blood count (CBC) and liver function tests. RPR was reactive at 1:2. Cerebrospinal fluid (CSF) was obtained with 131 white blood cells (WBCs)/μL and 49,000 red blood cells (RBCs)/μL. CSF venereal disease research laboratory (VDRL) was not obtained due to hemolysis. Initial ophthalmology examination showed no signs of ocular syphilis. Bone survey resulted in no long bone abnormalities that would be consistent with congenital syphilis.

Without an adequate VDRL sample and with a concern of inadequately treated maternal syphilis, the case was discussed with infectious disease consult service. The multidisciplinary consensus was to complete a full 10-day course of Penicillin G IV for possible congenital syphilis. The neonate was started on penicillin G every 12 h at 50,000 U/kg for 7 days and then changed to every 8 h for 3 days (total 10-day course). On day 10 of treatment with penicillin, the infant developed bloody clots in her diaper. Physical examination at this time revealed mild abdominal distension with noted irritability with palpation, bowel sounds were diminished, heart was without murmur, and lungs were clear bilaterally. An abdominal radiograph revealed pneumatosis intestinalis with no free or portal venous air (Figure 1). Subsequently, feeds were held, a replogle was placed for decompression and blood and urine cultures were obtained. Penicillin was discontinued and vancomycin and piperacillin/tazobactam were started due to concern for NEC. Laboratory results revealed a WBC count of 12.31 K/μL, hemoglobin of 17 g/dL, platelets of 309 k/μL, and C-reactive protein of 0.7 mg/L. Infant was noted to be mildly acidotic with a bicarbonate of 18 mmol/L on a renal function panel that subsequently normalized over 48 h. There was no evidence of hemolysis and prothrombin time and partial thromboplastin time were normal. Replogle was maintained on low intermittent suction for 48 h with up to 10 mL/kg/day of non-bilious output residuals that improved after 2 days of bowel rest. Replogle was then placed to gravity. Vancomycin was discontinued after 48 h as the blood culture had no growth. Piperacillin/tazobactam was continued for 7 days. The infant remained afebrile during the illness. The infant had guaiac-positive stools for 5 days following treatment and bowel rest. Pneumatosis persisted on serial radiographs obtained every 12 h with resolution by 72 h of treatment. After completing treatment for NEC, a cranial ultrasound was obtained on day of life 23, which was normal. An echocardiogram was not performed during the hospital stay as the infant's physical examination was normal. The infant resumed feeds with a milk-based formula on day 5 of illness and the replogle was subsequently removed. The infant showed good consistent weight gain prior to discharge and did not have further issues. Infant was discharged to follow-up with infectious disease.

Discussion

This case presents the development of bloody stools prompting a work-up for NEC in a term infant following treatment of suspected congenital syphilis.

Studies have suggested that prolonged antibiotic exposure alters the gastrointestinal flora and increases the risk of NEC in newborn infants.[5–9] This alteration in the diversity of the microbiome and delay in colonization of normal flora leads to overgrowth of pathogenic organisms.[11] Tapiainen et al.[12] have recently demonstrated that even narrow-spectrum β-lactam antibiotic, penicillin, can markedly alter the colonization and microbiome of newborns potentially leading to harmful effects on the intestinal microbiome comparable to wider spectrum of antibiotics. Short et al.[13] previously reported that early perinatal infection and antibiotic exposure were associated with a majority (63%) of cases of NEC in a retrospective review of 39 term infants. Bacteremia (41%) was the most common reason for infants to be treated with antibiotics while congenital syphilis was present in a small number ($N=3$) of infants.[13] One case study has described the development of NEC following the treatment with penicillin in a preterm infant of 29 weeks gestation with a history of congenital syphilis and echogenic bowel though the pathophysiology is unclear.[14] The development of NEC in this infant was thought to be secondary to either the activation of the immune system with inflammation of intestinal wall from spirochete migration or secondary to the treatment of penicillin resulting in the release of endotoxin-like compounds from spirochetes.[14] The causality of NEC in infants from either the inflammatory insult of the infection or alteration in microbiome from the treatment remains to be seen. As exposure of antibiotics to infants is necessary, clinical awareness of adverse events associated with potentially altering a newborn's microbiome must be recognized.

Congenital syphilis is a disease of the newborn in which treatment has largely been based on clinical experience and there is limited evidence on the optimal dose or duration of penicillin in neonates.[15,16] The CDC has published guidelines to categorize infants as those who are more or less likely to have disease.[17] These categories include confirmed or highly probable congenital syphilis, possible congenital syphilis, congenital syphilis less likely, and congenital syphilis unlikely.[17] The recommended treatment by the CDC include aqueous crystalline penicillin G 100,000 U/kg/day to 150,000 U/kg/day, administered as 50,000 U/kg/dose intravenously every 12 h during the first 7 days of life and every 8 h thereafter for a total of 10 days; or procaine penicillin G 50,000 U/kg/dose intramuscularly in a single daily dose for 10 days; or benzathine penicillin G 50,000 U/kg/dose intramuscularly in a single dose.[17] Dosing and duration of treatment varies on positive identification of syphilis in mother, adequate maternal treatment, and evaluation of syphilis in the neonate.[17]

Duration and optimal treatment remain controversial especially among asymptomatic exposures and may vary across clinical practice. Clinical providers may determine that a full course of penicillin is indicated to infants who are asymptomatic with normal laboratory and physical evaluation but maternal treatment was inadequate; while an alternative practice is to give a single dose of benzathine penicillin G with close follow-up.[17,18] The differing best practice treatment likely results from the lack of evidence regarding the effectiveness and safety of treatment of newborns with confirmed, highly probable, or possible congenital syphilis.[15] Recommendations on duration and dosing of treatment have been mainly based on non-randomized and historical studies on the treatment of suspected congenital syphilis in infants with small sample sizes and follow-up rates that were very low with no reportable adverse events.[19] Because of low-quality evidence and best practice treatment that differs among practice experts, practitioners may opt for a longer course of antibiotics to reduce the chance of latent syphilis.[15–17] Such prolonged exposure to antibiotics can lead to serious adverse events including NEC. To guide the need for future studies, adverse events must be reported based on the current recommended treatment.

Conclusion

We report a case of an adverse event of NEC in a term infant following a full 10-day course of penicillin treatment of suspected congenital syphilis in an asymptomatic newborn. Future studies are recommended to evaluate the current practices of congenital syphilis against treatment failure as well as consideration of other treatment alternatives.

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Author contributions

C.P.P., M.B., and G.W. composed and edited this manuscript.

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Ethical approval

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Informed consent

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