A case late-onset Group B streptococcus infection in fraternal twins

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The case

A 29-year-old G1P0 married Caucasian female presented to the Labor and Delivery unit due to preterm premature rupture of membranes (PPROM). Gestational age was 32 weeks and 2 days

by 1st trimester ultrasound which correlated with her last menstrual period, and this ultrasound also confirmed dichorionic diamniotic twin pregnancy.
Maternal Screening:

- Blood Group A+/ Antibody negative
- HIV: negative
- Rapid plasma reagin: negative
- Hepatitis B & C: negative
- Gonorrhea/chlamydia: negative
- Group B Streptococcal (GBS): unknown
- COVID-19 polymerase chain reacton: negative

She received antenatal corticosteroids and penicillin.

A maternal request was made for vaginal delivery.

Twin A	Twin B
Male Spontaneous vaginal delivery PPROM for 36 hours Amniotic fluid clear Apgar scores 9/9/9 at 1/5/10 minutes respectively Birth weight 1.87 kg (50th %tile) Height 45 cm (80th %tile) Head circumference 33 cm (>97th %tile) Placenta – meconium pigment in chorion, intraplacental hematoma, no chorioamnionitis or villitis	Female Spontaneous vaginal delivery ROM at delivery Amniotic fluid clear Apgar score 9/9/9 Birth weight 1.77 kg (50th %tile) Height 44.5 cm (75th %tile) Head circumference 29.5 cm (50th %tile) Placenta - normal

Table 1. Displaying Twin A and Twin B delivery data.

Both infants were transferred to neonatal intensive care unit (NICU) for apnea and started on caffeine. Sepsis rule-out with 48 hours of ampicillin and gentamicin was given until blood cultures were reported negative. Maternal GBS screen done on admission was also negative. Twin A had a head ultrasound (HUS) on day of life (DOL) 1 due to macrocephaly which revealed Right Grade 1 Intraventricular hemorrhage (IVH). Twin B had a routine HUS on DOL 3, which was normal. Both twins were treated with phototherapy for indirect hyperbilirubinemia of prematurity. They were transferred to the NICU-B, a step-down unit on DOL 3, and were progressing as expected.

Both babies were in the process of being discharged on DOL 23 when their mother noticed that Twin A was not breastfeeding well and alerted the medical staff. On physical examination, he was pale, lethargic, and ill-appearing. His vital signs were significant for hypothermia of 35.7°C, tachycardia to 211 beats per minute (bpm), and low blood pressure of 40/15 mmHg.

Immediately, a lab workup was done. An intravenous (IV) access was secured for fluids and empirical antibiotics with oxacillin and tobramycin x1 dose, which was then switched to vancomycin and cefepime.

CSF Analysis	
Appearance	Clear
Supernatant	Xanthochromic
WBC	63 /mm^3
RBC	53 /mm^3
Protein	>300 mg/dL
Glucose	<20 mg/dL
Gram Stain	Few white blood cells Heavy growth of gram-positive cocci
Microbiology	Positive for *Streptococcus agalactiae*

Blood Culture – *S. agalactiae*

Urine Culture – Negative

Nasopharyngeal Culture – *Klebsiella oxytoca*

Breastmilk culture – *Klebsiella oxytoca* and *Staphylococcus epidermidis*

Table 2. Displaying culture results taken immediately after the acute decompensation of Twin A.

He was transferred to NICU-A, the highest acuity unit, where he continued to deteriorate. Blood and cerebral spinal fluid (CSF) cultures resulted positive for *Streptococcus agalactiae*, GBS. Now confirmed to have GBS meningitis and sepsis; antibiotics were appropriately switched to penicillin G with gentamicin for synergy. Septic shock and disseminated intravascular coagulation symptomatology ensued. He required ample pressure support and multiple transfusions of packed red blood cells (PRBCs), platelets, and fresh-frozen plasma, as well as a bicarbonate infusion to correct for acidosis. He then developed intractable seizures confirmed on electroencephalography (EEG), requiring multiple antiseizure medications. Repeat HUS showed evolving Right Grade 1 IVH. Eventually, he required intubation and mechanical ventilation.

During this time, consultations were made with pediatric infectious disease, neurology, and palliative care teams. Given his grave prognosis, a family conference was held. His parents were adamant that they did not want their baby to suffer anymore. A decision was made not to increase care beyond current support. Parents were allowed to hold their son. He died on DOL 25, approximately 48 hours after his acute decompensation.

<u>Where is Twin B?</u>

She remained stable and continued to feed well. She was without any signs or symptoms of sepsis and was well-appearing. However, due to the sudden deterioration of her twin, a complete blood count (CBC) and C-reactive protein (CRP) were performed and were within normal limits. Her newborn screening test was within normal limits, and she passed the hearing screen. She was discharged on DOL 23 as previously planned and appropriate anticipatory guidance was given to both parents.

About 4 days after hospital discharge at DOL 29, the mother presented with Twin B to the emergency department (ED) after she seemed more tired than usual with approximately a 5ml decrease in oral intake per feed and making "grunting" noises. On arrival, her vital signs were temperature of 37.2^{o}C, heart rate of 174 bpm, blood pressure of 88/51 mmHg, respiratory rate of 54 breaths per minute, and 100% oxygen saturation on room air. A workup was performed, including CBC, blood, urine, and CSF cultures. Intravenous ampicillin and gentamicin were given empirically, and she was admitted to the pediatric floor.

CBC	
Hemoglobin	10.1 g/dL
Hematocrit	28.3 %
Platelets	288 x10^3mcL
WBC Count	5.7x10^3mcL
Neutrophils	82%
Bands	1%
C-Reactive Protein	6.9 mg/dL

CSF Analysis	
Appearance	Clear
Supernatant	Clear
WBC	0 /mm^3
RBC	1 /mm^3
Protein	73 mg/dL
Glucose	56 mg/dL
Gram Stain	Gram-positive cocci
Microbiology	Positive for *Streptococcus agalactiae*
Blood Culture	Positive for *S. agalactiae*
Urine Culture	Negative

Table 3. Displaying initial admission lab results for Twin B Female

Hospital course for Twin B

She was admitted for suspected GBS meningitis and sepsis from the ED, which was subsequently confirmed. Pediatric infectious disease was consulted and recommended treatment for 14 days with meningitic doses of ampicillin every 6 hours with 48 hours of gentamicin on-board for a synergistic effect. Her repeat HUS was normal and repeat blood culture after 48 hours of antibiotics and on day 7 of admission were negative. The CSF culture was not repeated based on her clinical status. She was well-appearing throughout her hospital course and was gaining weight at approximately 35g per day and developing appropriately. Her initial inflammatory marker, CRP of 6.9mg/dL, declined to 1.2mg/dL by day 12 of antibiotics. She was discharged home after about 2 weeks, now DOL 44, with a follow-up appointment with the pediatrician in 48 hours and audiology.

Return of Twin B

About 5 days after hospital discharge, on DOL 50, she returned to the hospital for increased fussiness and irritability, starting about 9 hours before arrival to the ED. Her parents said she was feeling warm, but her rectal temperature was 37.7^{o}C at home. Parents gave her simethicone, but the fussiness and irritability continued. They brought her for evaluation given the prior history of GBS meningitis and recent discharge.

In the ED, vital signs were significant; febrile to 38.5°C, tachycardia at 184 bpm; blood pressure 97/46 mmHg; and tachypnea rate 64 breaths per minute with 100% oxygen saturation on room air. She received 20cc/kg saline boluses x2 and Tylenol with improvement in vital signs. Lab workup included CBC, comprehensive metabolic panel (CMP), urine, and blood Culture. Lumbar Puncture (LP) was attempted 4 times in the ED, but the team was unable to obtain CSF. Given the recent history of GBS bacteremia and meningitis, she received meningitic doses of ampicillin and ceftriaxone empirically and was transferred to the floor for further workup and management. Once on the floor, CSF was obtained for culture and chemistry.

CBC	
Hemoglobin	7.8 g/dL
Hematocrit	24 %
Platelets	613 x10^3mcL
WBC Count	13.8x10^3mcL
Neutrophils	75%
Bands	0%

C-Reactive Protein	16.9 mg/dL
Procalcitonin	6.05 ng/mL

CSF Analysis	
Appearance	Clear
Supernatant	Clear
WBC	11 /mm^3
RBC	2 /mm^3
Protein	88 mg/dL
Glucose	31 mg/dL
Gram Stain	Gram-positive cocci
Microbiology	Positive for *Streptococcus agalactiae*

Blood Culture	Positive for *S. agalactiae*
Urine Culture	Negative

Table 4. Displaying Lab results at the time of the second admission for Twin B Female

She had recurrent GBS meningitis and bacteremia.
Pediatric infectious disease was once again consulted, recommendations given:

- Treat with ampicillin and ceftriaxone for 21 days after cultures are negative
- Susceptibility testing of GBS isolates to ampicillin
- Re-culturing maternal breastmilk
- Echocardiogram for vegetations
- HUS and brain MRI
- Repeat audiology testing
- Rifampin treatment for 4 days after completion of therapy to eradicate potential mucosal colonization

<u>Results of workup</u>

- Echocardiogram done on this 7-week-old infant with sepsis and bacteremia to assess the cardiac anatomy and function and evaluate for intracardiac vegetations. The following is the summary:
    1. Patent foramen ovale with trivial left to right shunt.
    2. Normal biventricular size, wall thickness and systolic function.
    3. No indirect evidence of pulmonary hypertension was noted.

4. No intracardiac vegetations seen.

- HUS - Normal Echoencephalogram
- MRI of brain - Unremarkable non-contrast MRI of the brain. No evidence of hydrocephalus, fluid collections, or acute ischemia.
- Maternal breastmilk resulted positive for *S. agalactiae*.
- ETEST® for ampicillin susceptibility turned out not susceptible.
- Repeat blood culture after days 2, 3, and 4 of antibiotics were negative.
- Repeat CSF culture on day 10 of antibiotics was negative.
- Audiology screen was normal

She was maintained of IV ceftriaxone for the duration of treatment via a peripherally inserted central catheter (PICC) line. She was transfused 10cc/kg of PRBCs for increasing tachycardia without increasing inflammatory markers or clinical deterioration. This anemia was likely iatrogenic due to frequent blood sampling. After discussing the results of labs with parents, they decided to formula feed from now on. Although inpatient, she was also being seen by physical therapy, child life, and nutrition. She showed good response to therapy and continued to gain weight and develop adequately. She was discharged on DOL 75 with discharge medications, including rifampin, for 4 days to treat oral mucosal colonization from breast milk and daily multivitamin with iron. Follow-up appointments were made with her pediatrician, audiology, cardiology, neurology, and physical therapy.

<u>The discussion</u>

GBS is a major cause of neonatal morbidity and mortality as it remains one of the leading causes of neonatal sepsis and meningitis.[1] GBS is a gram-positive diplococcus, a common colonizer of the gastrointestinal and genital tracts in pregnant women, and this colonization is often asymptomatic in pregnancy.[2]

The age of onset classifies GBS in neonates.[1]

- Early-onset GBS – Presents from birth through DOL 6 but generally presents within the first 24 hours after delivery.[3]
- Late-onset GBS – Usually occurs at 4 to 5 weeks of life and may present from DOL 7 to 3 months of life.[4]

The most common pathogenesis of early-onset GBS infection is vertical transmission by ascending colonization from the maternal gastrointestinal and genitourinary flora. Then infection occurs with subsequent colonization and invasion of the fetal compartment or fetal aspiration of infected amniotic fluid.[5] This transmission primarily occurs shortly before or during labor and delivery. Late-onset GBS infection may be acquired vertically as well, but horizontal transmission from colonized household contacts, hospital contacts, and breast milk is also a practical pathogenesis.[6]

The incidence of early-onset GBS declined in the United States, and this is predominantly because of maternal GBS screening and intrapartum antibiotic prophylaxis (IAP), which was done in this case. In contrast, the incidence of late-onset GBS disease has remained approximately unchanged over the last 30 years.[2] This is not surprising as IAP is only effective during labor and delivery and does not necessarily eradicate GBS colonization.[7] Thus, even after women are given IAP, they may continue to be GBS colonized postpartum.[8]

Twin A had rapid clinical deterioration from meeting discharge criteria in just 48 hours prior to demise. He manifested profound septic shock and meningitis with intractable clinically observed seizures despite multiple medications. Although HUS was done immediately and repeated during his acute decompensation, an early MRI may have provided more details and possible pathology. In hindsight, perhaps the macrocephaly diagnosed prenatally on obstetric ultrasound played a more significant role in his disease susceptibility, prognosis, rapid progression, and eventual mortality.

Horizontal transmission from colonized contacts plays a significant role in the pathogenesis of late-onset GBS, whether from parents or hospital staff. In this case it remains a likely possibility, especially given that maternal GBS screen resulted negative, IAP was administered, and both twins had prolonged hospitalization from birth to DOL 23 before clinical deterioration. It can even be hypothesized that maternal breast milk could have been the agent of horizontal transmission.

Regarding Twin B, an important clinical question has been raised. What to do in twins or other multiples when invasive GBS infection occurs in 1 sibling, but the other sibling/siblings remain (or appear to remain) asymptomatic?

When invasive GBS infection occurs in an infant of multiple births, siblings should be observed carefully for signs of infection.[1] Whether this observation should be in hospital and for what duration, or with the parents after thorough anticipatory guidance and counseling is yet to be determined.

The unaffected sibling is likely colonized with GBS, given shared contacts and medical history, but there is no evidence to support a full antibiotic course in the absence of confirmed GBS disease.[9]

However, some experts decide on a conservative approach of empirical evaluation and antibiotic therapy even in the asymptomatic sibling when the index case has invasive GBS disease.[10] This then leads to the discussion of adequate duration of treatment when there is no identified source of infection in the sibling.

Another important takeaway from this case is the importance of prompt CSF testing for sterility after antibiotic treatment, despite the patient's clinical appearance.

Patient outcome

Follow-up with Twin B at 15 months revealed that she was developmentally appropriate. Her vision and hearing are normal. EEG and brain MRI at age 1 year were normal. She qualified for early intervention based on her prematurity and significant course of meningitis and currently attends physical therapy and occupational therapy. The family has since relocated to another state but has future fertility desires.

Future directions

There are limitations to GBS screening and IAP, especially because the exact delivery time cannot be predicted, particularly in the premature population. Universal antenatal testing of pregnant women for GBS colonization is obtained at 36 - 37 $^{6}/_{7}$ weeks gestation and on presentation in all preterm pregnancies.[11] If administered to pregnant women and all sexually active females, the GBS vaccine is a promising solution and could potentially prevent these infections, especially late-onset disease. Clinical trials are currently being done on multivalent glycoconjugate GBS vaccines.[12] As is more evident in recent times, vaccine prevention remains a better solution than disease treatment, so we look forward to the GBS vaccine in the near future.

Conclusion

The above case presentation serves as a reminder of the critical importance of prompt evaluation and empirical treatment of neonates at risk of invasive bacterial infection. There is an increased relative risk of invasive GBS infection in the twin of an affected patient, and therefore, clinical hypervigilance must be maintained.

In invasive GBS disease, especially GBS meningitis, response to therapy and potential complications must be monitored clinically through serial neurologic examinations, repeat CSF analysis, and neuroimaging. In this patient with recurrent GBS meningitis, there is a high risk of permanent neurological sequelae, which so far, our patient has seemingly escaped.

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