Accepted Manuscript online: 2022-02-04 Article published online: 2022-03-14

Early-Onset Fulminant Sepsis in a Preterm Neonate due to *Streptococcus gallolyticus*: A Case Report and Literature Review

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AJP Rep 2022;12:e117–e122.

Abstract

Streptococcus gallolyticus is an uncommon cause of neonatal infections. We describe the first case of fulminant lethal neonatal sepsis due to *S. gallolyticus* reported in literature. Our patient was an extremely low birth weight premature infant born to a mother with prolonged rupture of amniotic membranes and chorioamnionitis. We also review the cases of neonatal *S. gallolyticus* infections reported in literature. Fifty-eight percent neonatal *S. gallolyticus* infections presented in the first week of life. Importantly, *S. gallolyticus* meningitis is more commonly reported with early-onset infections compared with group B streptococcal meningitis, which is more common with late-onset infections. *Streptococcus gallolyticus* should be included in differential for neonatal sepsis, particularly in the presence of meningitis in the first week of life. Most cases are sensitive to penicillin; however, cases of reduced sensitivity to penicillin have also been reported.

Keywords

- neonatal sepsis
- *Streptococcus bovis*
- *Streptococcus gallolyticus*
- *Streptococcus pasteurianus*
- neonatal meningitis
- chorioamnionitis
- preterm

Streptococcus gallolyticus is a group of bacteria that belong to the nonenterococcal group D streptococci previously known as *S. bovis/S. equinus* complex (SBSEC).[1] *Streptococcus gallolyticus* has been reported as a cause of adult gastrointestinal tract infections and infective endocarditis for decades but is an uncommon cause of neonatal infections.[1,2] However, over the past decade, there have been increasing reports of neonatal sepsis, meningitis, and intrauterine infections due to *S. gallolyticus.* Here, we report an unusual case of a preterm, extremely low birth weight (ELBW) male neonate who developed fulminant early-onset sepsis due to *S. gallolyticus*. To the best of our knowledge, no prior cases of fulminant lethal sepsis due to *S. gallolyticus* have been reported to date. We also review the cases of neonatal *S. gallolyticus* infections reported in literature.

Case Presentation

A male infant was born at 26 weeks of gestation to a 25-year-old G5 now P5 mother with good prenatal care. Pregnancy was complicated by chronic hypertension and premature prolonged rupture of membranes 12 days before delivery for which the mother received 7 days of latency antibiotics (48 hours of intravenous ampicillin followed by 5 days of oral amoxicillin and a single dose of azithromycin) that was completed 5 days prior to delivery. She developed chorioamnionitis prior to delivery for which she received one dose of ampicillin.

Mother had a history of trichomonas infection during pregnancy which was treated. Her other prenatal infectious laboratories including group B streptococcal (GBS) culture

received
December 20, 2021
accepted after revision
January 28, 2022

DOI https://doi.org/10.1055/a-1762-0096.
ISSN 2157-6998.

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

were negative. The infant was born via spontaneous vaginal delivery with a birth weight of 950 g. In the delivery room, the infant required positive pressure ventilation and intubation. APGAR scores were 6, 3, and 4 at 1, 5, and 10 minutes, respectively. The infant was then admitted to the neonatal intensive care unit (NICU).

The infant's arterial cord blood gas pH was 6.96 with a pCO_2 of 76 mm Hg and a base excess of −15.9 mmol/L. His venous cord blood gas pH was 7.17 with a pCO_2 of 42 mm Hg and a base excess of −12.7 mmol/L.

The infant had mixed metabolic and respiratory acidosis on admission (pH 6.9) and required high ventilator support. The respiratory acidosis improved with ventilator adjustments and surfactant administration; however, he had persistent metabolic acidosis. He also had leukopenia (white blood cell count $1.5 \times 10^3/mm^3$), thrombocytopenia (platelet count was $89 \times 10^3/mm^3$), and an elevated C-reactive protein level of 21.1 mg/L. Blood culture was sent on admission and the infant was prescribed ampicillin and gentamicin.

Around 4.5 hours of life, the infant became hypotensive and rapidly deteriorated despite fluid resuscitation and receiving pressors (dopamine and dobutamine). A repeat blood culture and tracheal aspirate were obtained, but the infant died at 5.5 hours of life after he remained unresponsive to resuscitative efforts.

Parents declined an autopsy. Both blood cultures resulted positive for gram-positive cocci within 12 hours of incubation, which were further identified as *S. gallolyticus* using MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight) biotyper. Unfortunately, genotyping was not possible in our laboratory, and hence, we were unable to further classify this pathogen. The tracheal aspirate culture was negative. Placental pathology confirmed acute chorioamnionitis of the fetal membranes.

Discussion

This is the first case of *S. gallolyticus* in an ELBW infant leading to fulminant sepsis. *Streptococcus gallolyticus* has been often used interchangeably with *S. bovis* in literature.[2] Over the years, SBSEC has undergone numerous taxonomical changes. Based on their ability to ferment mannitol, *S. bovis* has been classified in the older literature into two biotypes, mannitol-fermenting biotype I and mannitol nonfermenting biotype II. Biotype II has been divided further into subtypes 1 and 2 based on starch and bile-esculin hydrolysis and trehalose acidification.[1,3–5] The most recent taxonomic classification uses genetic methodology to classify SBSEC into four species *S. gallolyticus* (further divided into subsp. *gallolyticus*, *pasteurianus*, and *macedonicus*), *S. alactolyticus*, *S. infantarius* (divided into subsp. *infantarius* and *coli*), and *S. equinus*.[1,3–5] ►**Fig. 1** shows a simplified taxonomical classification of *S. bovis*.

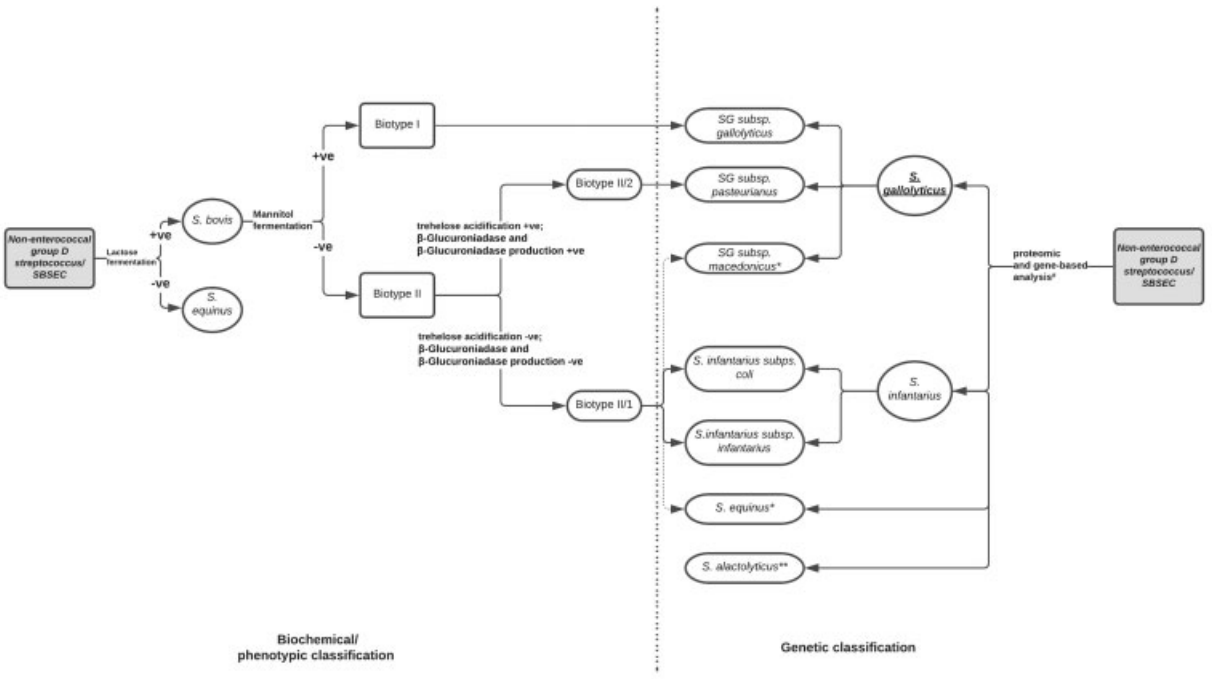

Fig. 1 Taxonomical classification of *S. bovis*: This figure shows the correlation between the previously used biochemical/phenotypic classification and the new genetic classification of nonenterococcal group D *Streptococcus*. Reconstructed based on the description by Dekker and Lau,[1] Schlegel et al,[4] and Jans et al.[5] #Methods used for analysis include MALDI-TOF (proteomic-based), 16s rRNA, sodA, and groEL sequencing (single-gene-based) and/or whole genome sequencing.[1,5] **Streptococcus equinus* and *S. macedonicus* likely belong to biotype II/1 based on phenotypic data.[5] **Phenotypic data for *S. alactolyticus* is variable, and hence, biotypic classification is not possible.[5] BE, bile-esculin; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; SBSEC, *Streptococcus bovis/Streptococcus equinus* complex; SG, *Streptococcus gallolyticus*; subsp., subspecies.

Streptococcus gallolyticus is prevalent in the bowel flora in humans. In adults, *S. gallolyticus* subsp. *gallolyticus* is commonly associated with infective endocarditis, bacteremia, gastrointestinal infections including hepatobiliary infections, and colon cancer.[1–3] *Streptococcus pasteurianus* has been commonly associated with meningitis.[1] Although uncommon, *S. gallolyticus* subsp. *gallolyticus* and *S. pasteurianus* have emerged as important causes of neonatal sepsis in recent years. *Streptococcus gallolyticus* subsp. *macedonicus* has not been associated with infections in humans.

Streptococcus infantarius has been associated with noncolonic cancers and is an uncommon cause of adult sepsis.[1] Only two cases of neonatal infections with *S. infantarius* subsp. *coli* (also known as *S. lutetiensis*) have been reported in literature.[6]

To review the cases of neonatal invasive *S. gallolyticus* infections reported in the English literature, we performed a MEDLINE search and found 66 cases of neonates ($\leq$ 28 days old) reported to be infected by *S. bovis*. Twenty-nine cases were classified only as *S. bovis* and four cases as *S. bovis* biotype II. Infections with *S. pasteurianus* (*S. bovis* biotype II/2) has been much more commonly reported compared with that with *S. infantarius* (*S. bovis* biotype II/1) in both neonates and adults, thus making it likely that the cases without further identification beyond *S. bovis*/*S. bovis* biotype II belong to the *S. gallolyticus* species. However, due to lack of certainty, these cases ($n = 33$) were not included in this review. Of the remaining 33 cases, two cases were reported as *S. lutetiensis* infection and one case as *S. alactolyticus* infection and hence were also not included. We analyzed the remaining 30 cases of neonatal *S. gallolyticus* infections reported in literature before November 30, 2021, and the present case ($n = 31$) (►**Table 1**).[2,7–21] Of the 30 cases reported in literature, only 10 cases were reported from the United States.[10,13,14,21]

Fifty-eight percent of the patients presented during the first week of life. There was a slightly higher incidence of early-onset ($\leq$ 6 days) ($n = 17$; 55%) and late-onset infections ($>$ 6 days) ($n = 14$; 45%) due *S. gallolyticus*. Gestational age was unknown for one infant and 12 of 30 (40%) infants were premature (gestational age 26–36 weeks). Presenting symptoms included respiratory distress, apnea, metabolic acidosis, fever, lethargy, abdominal distension, loose stools, congestion, poor feeding, and seizures. In five cases, further identification beyond S. *gallolyticus* was not performed. When classification was available, *S. pasteurianus* was more common than *S. gallolyticus* subsp. *gallolyticus* (25 vs. 1).

Meningitis was reported in 19 patients (18 due to *S. pasteurianus* and 1 due to *S. gallolyticus* subsp. *gallolyticus*). Hede et al[13] hypothesized that *S. gallolyticus* infection in neonates follows the pattern of early- and late-onset GBS diseases. However, unlike GBS infection, *S. gallolyticus* infection was associated with a higher rate of meningitis (63%), and early-onset *S. gallolyticus* infection was more likely to be associated with meningitis compared with late-onset infection (76 vs. 43%).[22] Meningitis was more commonly reported in term neonates (16 of 18; 89%) compared with preterm neonates (2 of 12; 17%).

In one patient, bacteremia was associated with infective endocarditis, and in another patient with liver abscess.[2,18] Park et al[15] reported a case of urinary tract infection due to *S. pasteurianus* in the absence of pyuria.

Most patients were treated with a penicillin and/or a third-generation cephalosporin and the duration of antimicrobial therapy ranged from 7 days to 8 weeks (median: 14 days; average: 15 days). Although all patients had a severe clinical course, most patients had a favorable outcome. All patients, except this case, survived the acute infection. One patient had to be rehospitalized 2 weeks postdischarge due to partially treated meningitis but had no long-term neurological sequalae.[15] Only one patient with meningitis was reported to have long-term neurological deficits.[13]

This is the first reported case of fulminant lethal sepsis due to *S. gallolyticus*. Our patient was an ELBW preterm infant with history of prolonged rupture of amniotic membranes (12 days) and acute chorioamnionitis which may have resulted in the particularly severe course in this case.

The exact route of *S. gallolyticus* infection in neonates remains uncertain. It is presumed that like GBS, *S. gallolyticus* infection occurs either vertically via transvaginal transmission or postnatal horizontal transmission.[13] Fikar and Levy[23] reported positive rectal and vaginal cultures from the patient's mother 2 weeks following the onset of symptoms in a neonate with *S. bovis* meningitis. In another report, mother of the infant with *S. pasteurianus* meningitis grew *Escherichia coli* and Group D *Streptococcus* in the urine culture collected on fourth postpartum day.[12] A case of intrapartum infection and postpartum bacteremia without neonatal infection has also been reported.[24] Floret et al[9] and Saegeman et al[16] reported clusters of neonatal infections due to *S. pasteurianus* in their respective NICUs, likely due to horizontal transmission from health care workers. In one case series, one of the four patients had history of maternal contact with chicken who died 1 week prior to patient's birth; however, postmortem testing of chickens was not performed.[10]

Similar to GBS, *S. gallolyticus* is often sensitive to penicillin; however, cases with reduced susceptibility to penicillin have been reported including two cases of neonatal meningitis due to *S. pasteurianus*.[3,8,10] This organism is also susceptible to aminoglycosides, cephalosporin, and vancomycin, and high rates of resistance to quinolones, macrolides, and tetracyclines have been reported.[3]

Conclusion

Streptococcus gallolyticus must be considered an important differential for neonatal sepsis particularly, in the presence of meningitis in the first week of life when maternal GBS is negative. Appropriate identification and classification of the organism are important to further understand the epidemiology of neonatal infections due to *S. gallolyticus*. Culture sensitivity should be performed to determine appropriate antibiotic for treatment due to the increasing rates of reduced susceptibility to penicillin. Although no mortality was reported in previous cases of neonatal *S. gallolyticus* infections, this case shows that *S. gallolyticus* in ELBW infants may be lethal.

Table 1 Summary of the neonatal cases of *Streptococcus gallolyticus* reported in literature

Reference	Number of pts reported	Birthweight (kg)	GA (wk)	Delivery type	Age of presentation	Organism	Clinical symptoms	Sites organism isolated from	Diagnosis	Final antibiotic therapy course	Final disposition
Gavin et al (2003) [21]	1	3.925	Term	Vaginal	3 d	SG subsp. *pasteurianus*	Fever, seizures	Blood + CSF	Bacteremia, meningitis	Penicillin G × 14 d	Survived
Onoyama et al (2009)[7]	1	3.19	Term	Vaginal	4 d	SG subsp. *pasteurianus*	Fever, decreased activity	Blood + CSF	Bacteremia, meningitis	Cefotaxime × 14 d	Survived
Khan (2009)[8]	1	Not reported	Not reported	Not reported	3 d	SG subsp. *pasteurianus*	Apnea, lethargy	Blood + CSF	Bacteremia, meningitis	Penicillin and gentamicin × 14 d	Survived
Floret et al (2010)[9]	5[a]	Not reported	Preterm	Not reported	13–56 d	SG subsp. *pasteurianus*	Gastrointestinal symptoms in all pts including abdominal distension and diarrhea	Blood	Bacteremia	Cefotaxime × 10 d	Survived
Klatte et al. (2012) [10]	4	Not reported	Term	Vaginal	2–13 d	SG subsp. *pasteurianus*	Pt 1: congestion, respiratory distress, increased sleepiness Pt 2: fever, seizures Pt 3: lethargy, seizures Pt 4: fever, congestion, lethargy	CSF in all pts Blood in pts 2–4	Meningitis: all pts Bacteremia: pts 2–4	Pts 1 and4: Cefotaxime × 14–16 d Pts 2 and 3: ampicillin 14–16 d	Survived
Nagamatsu et al (2012)[11]	1	3.092	40	Vaginal	8 d	SG subsp. *pasteurianus*	Seizures, fever, inconsolability, decreased oral intake	CSF	Meningitis	Ampicillin, panipenem/ betamipron × 20 d	Survived
Thatrimontrichai et al (2012)[12]	1	3.188	39	Vaginal	3 d	SG subsp. *pasteurianus*	Fever, lethargy, poor oral intake, bulging fontanelle	CSF	Meningitis	Cefotaxime × 14 d	Survived
Hede et al (2015) [13]	2 (twins)	Pt 1: 2.12 Pt 2: 1.47	32	C-section	3 wk	SG subsp. *pasteurianus*	Pt 1: lethargy, irritability, respiratory distress, poor feeding, loose stools, seizures Pt 2: respiratory distress	Pt 1: blood + CSF Pt 2: blood	Meningitis in both pts Sepsis in pt 1 Bacteremia in pt 2	Ampicillin × 10–20 d	Both pts survived, but pt 1 was reported to have long-term neurologic deficits
Kennedy et al (2015)[14]	1	3.05	37	Vaginal	4 d	SG subsp. *gallolyticus*	Fever, lethargy, irritability.	Blood + CSF	Bacteremia and meningitis	Ampicillin × 14 d	Survived
Park et al (2015)[15]	1	3.6	38	Vaginal	28 d	SG subsp. *pasteurianus*	Fever, lethargy	CSF + blood + urine	Meningitis, UTI, bacteremia	Ampicillin + cefotaxime × 21 d	Survived, but rehospitalized 2 wk later due to fever and seizures, requiring 31 additional d of ampicillin
Saegeman et al (2016)[16]	1	Not reported	30	Not reported	7 d	SG subsp. *pasteurianus*	Sepsis	Blood	Sepsis	Penicillin, duration unknown	Survived
Yamamura et al (2018)[17]	1	3.68	Term	Vaginal	27 d	SG subsp. *pasteurianus*	Fever, lethargy, irritability, cold extremities	Blood + CSF	Sepsis, meningitis	Ampicillin × 22 d	Survived
Nguyen et al (2019)[18]	2	3.25–4.19	39–40	Vaginal	< 24 h	SG subsp. *Pasteurianus*	Pt 1: respiratory distress Pt 2: respiratory distress, sepsis	Blood	Pt 1: sepsis, infective endocarditis, meningitis Pt 2: sepsis	Pt 1: cefepime × 28 d, gentamicin × 14 d Pt 2: cefepime and clindamycin × 14 d	Survived

Table 1 (*Continued*)

Reference	Number of pts reported	Birthweight (kg)	GA (wk)	Delivery type	Age of presentation	Organism	Clinical symptoms	Sites organism isolated from	Diagnosis	Final antibiotic therapy course	Final disposition
Chen et al (2021)[19]	3 (pt 2 and 3 were twins)	1.86–2.58	Pt 1: 35 Pts 2 and 3: 37	Pt 1: C-section Pts 2 and 3: not reported	2–5 d	SG subsp. *Pasteurianus*	Pt 1: apnea, desaturation Pts 2 and 3: fever, tachypnea, desaturation	Pt 1: blood Pt 2: blood + CSF Pt 3: blood	Sepsis, meningitis	Ampicillin + cefotaxime × 14 d	Survived
Geetha et al (2021)[2]	1	3.77	36	Vaginal	< 24 h	SG subsp. *pasteurianus*	Respiratory distress, sepsis	Blood	Liver abscess, sepsis	Cefotaxime × 5 wk, coamoxiclav for 3 wk	Survived
Sim et al (2021)[20]	4	1.81–3.37	Pts 1–3: term; Pt 4: 34	Pts 1–3: vaginal Pt 4: C-section	1–23 d	SG	Pts 1 and 2: respiratory distress Pts 2–4: fever Pts 3 and 4: lethargy/poor feeding	Pts 1–4: blood Pts 1 and 2: CSF	Sepsis: all pts Meningitis: pts 1 and 2	Ampicillin, clindamycin, or vancomycin × 7–14 d	Survived
This case	1	0.95	26	Vaginal	< 24 h	SG	Respiratory distress, sepsis	Blood	Sepsis	n/a	Died at 5 h

Abbreviations: CSF, cerebrospinal fluid; GA, gestational age; GBS, group B *Streptococcus*; pt, patient; S., *Streptococcus*; SG, *Streptococcus gallolyticus*; subsp., subspecies; UTI, urinary tract infection.
[a]Exact number of neonates (≤ 28 days) unknown.

Conflict of Interest
None declared.

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