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Early-onset fulminant sepsis in a preterm neonate due to Streptococcus gallolyticus: A case report and literature review

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

Key Words:
Neonatal sepsis; Streptococcus bovis; streptococcus gallolyticus; streptococcus pasteurianus; neonatal meningitis; chorioamnionitis; preterm

Introduction:

Streptococcus (S.) gallolyticus is a group of bacteria that belong to the non-enterococcal group D Streptococci previously known as S. bovis/S. equinus complex (SBSEC)\(^1\). S. 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 seven days of latency antibiotics (48 hours of intravenous (IV) ampicillin followed by five days of oral amoxicillin and a single dose of azithromycin), that was completed five 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 labs including group B streptococcal (GBS) culture were negative. The infant was born via spontaneous vaginal delivery with a birth weight of 950 grams. 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 pCO2 of 76 mm Hg and a base excess of -15.9 mmol/L. His venous cord blood gas pH was 7.17 with a pCO2 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 lab, 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. *S. 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 non-fermenting 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*\(^1,3-5\).

Figure 1 shows a simplified taxonomical classification of *S. bovis*.

*S. 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\(^1-3\). *S. 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. *S. gallolyticus subsp. macedonicus* has not been associated with infections in humans.

*S. infantarius* has been associated with non-colonic 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 (≤ 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 to 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)\(^2,8-21\). Of the 30 cases reported in literature, only 10 cases were reported from the United States\(^7,11,14,15\).
Fifty-eight percent of the patients presented during the first week of life. There was a slightly higher incidence of early-onset (≤6 days) (n=17; 55%) and late-onset infections (>6 days) (n=14; 45%) due to *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.\textsuperscript{14} hypothesized that *S. gallolyticus* infection in neonates follows the pattern of early and late-onset GBS disease. 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 to late-onset infection (76% vs 43%).\textsuperscript{22} Meningitis was more commonly reported in term neonates (16 of 18; 89%) compared to preterm neonates (2 of 12; 17%).

In one patient, bacteremia was associated with infective endocarditis, and in another patient with liver abscess.\textsuperscript{2,19} Park et al.\textsuperscript{16} 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 3\textsuperscript{rd} 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 re-hospitalized 2 weeks post-discharge due to partially treated meningitis but had no long-term neurological
sequalese. Only one patient with meningitis was reported to have long-term neurological deficits.

This is the first reported case of fulminant lethal sepsis due to \textit{S. galloyticus}. 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 \textit{S. galloyticus} infection in neonates remains uncertain. It is presumed that like GBS, \textit{S. galloyticus} infection occurs either vertically via transvaginal transmission or postnatal horizontal transmission. Fikar and Levy\textsuperscript{23} reported positive rectal and vaginal cultures from the patient’s mother two weeks following the onset of symptoms in a neonate with \textit{S. bovis} meningitis. In another report, mother of the infant with \textit{S. pasteurianus} meningitis grew \textit{Escherichia coli} and Group D streptococcus in the urine culture collected on 4\textsuperscript{th} postpartum day.\textsuperscript{13} A case of intrapartum infection and post-partum bacteremia without neonatal infection has also been reported\textsuperscript{24}. Floret et al.\textsuperscript{10} and Saegeman et al.\textsuperscript{17} reported clusters of neonatal infections due to \textit{S. pasteurianus} in their respective NICUs, likely due to horizontal transmission from healthcare workers. In one case series, one of the four patients had history of maternal contact with chicken that died one week prior to patient’s birth, however postmortem testing of chickens was not performed\textsuperscript{11}.

Similar to GBS, \textit{S. galloyticus} is often sensitive to penicillin, however, cases with reduced susceptibility to penicillin have been reported including two cases of neonatal meningitis due to \textit{S. pasteurianus}\textsuperscript{3,9,11}. This organism is also susceptible to aminoglycosides, cephalosporin, and vancomycin, and high rates of resistance to quinolones, macrolides, and tetracyclines have been reported\textsuperscript{3}. 

\textsuperscript{7}
S. 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 is 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.

Conflict of Interest:

None declared.

References:


**Figure 1: Taxonomical classification of S. bovis:** This figure shows the correlation between the previously used biochemical/phenotypic classification and the new genetic classification of non-enterococcal group D streptococcus.

Reconstructed based on the description by Dekker et al.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 sequencing¹,⁵.

*S. equinus* and *S. macedonicus* likely belong to biotype II/1 based on phenotypic data⁵.

** Phenotypic data for *S. alactolyticus* is variable and hence biotypic classification is not possible⁵.

Abbreviations: *SG*: Streptococcus gallolyticus; *SBSEC*: Streptococcus bovis/Streptococcus equinus complex; *subps*: subspecies; *BE*: bile-esculin.

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients reported</th>
<th>Birthweight (kg)</th>
<th>GA (weeks)</th>
<th>Delivery Type</th>
<th>Age of presentation</th>
<th>Organism</th>
<th>Clinical Symptoms</th>
<th>Sites organism isolated from</th>
<th>Diagnosis</th>
<th>Final Antibiotic therapy course</th>
<th>Final Disposition</th>
</tr>
</thead>
</table>

12
<table>
<thead>
<tr>
<th>Study</th>
<th>Case</th>
<th>Term</th>
<th>Vaginal</th>
<th>Days</th>
<th>SG Subsp Pasteuri</th>
<th>Symptoms</th>
<th>Blood</th>
<th>Bacteremia</th>
<th>Penicillin</th>
<th>Days</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gavin et al. (2003)</td>
<td>1</td>
<td>Term</td>
<td>Vaginal</td>
<td>3 days</td>
<td>SG Subsp Pasteuri</td>
<td>Fever, seizures</td>
<td>Blood + CSF</td>
<td>Bacteremia, Meningitis</td>
<td>Penicillin G x 14 days</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>Onoyma et al. (2009)</td>
<td>1</td>
<td>Term</td>
<td>Vaginal</td>
<td>4 days</td>
<td>SG Subsp Pasteuri</td>
<td>Fever, decreased activity</td>
<td>Blood + CSF</td>
<td>Bacteremia, Meningitis</td>
<td>Cefotaxime x 14 days</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>Khan (2009)</td>
<td>1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>3 days</td>
<td>SG Subsp Pasteuri</td>
<td>Apnea, lethargy</td>
<td>Blood + CSF</td>
<td>Bacteremia, Meningitis</td>
<td>Penicillin and Gentamicin x 14 days</td>
<td>Survived</td>
</tr>
<tr>
<td>Floret et al. (2010)</td>
<td>5</td>
<td>Not reported</td>
<td>Pre-term</td>
<td>Not reported</td>
<td>13-56 days</td>
<td>SG Subsp Pasteuri</td>
<td>Gastrointestinal symptoms in all pts including abdominal distension and diarrhea</td>
<td>Blood</td>
<td>Bacteremia</td>
<td>Cefotaxime x 10 days</td>
<td>Survived</td>
</tr>
<tr>
<td>Klatte et al. (2011)</td>
<td>4</td>
<td>Not reported</td>
<td>Term</td>
<td>Vaginal</td>
<td>2-13 days</td>
<td>SG Subsp Pasteuri</td>
<td>Pt 1: Congestion, respiratory distress, increased sleepiness; Pt 2: Fever, seizures; Pt 3: Lethargy, seizures; Pt 4: Fever, congestion, lethargy</td>
<td>CSF in all pts; Blood in pts 2,3,4</td>
<td>Meningitis in All pts; Bacteremia in Pts 2,3,4</td>
<td>Pts 1,4: Cefotaxime x 14-16 days; Pts 2,3: Ampicillin 14-16 days</td>
<td>Survived</td>
</tr>
<tr>
<td>Nagama et al. (2012)</td>
<td>1</td>
<td>3.092</td>
<td>40</td>
<td>Vaginal</td>
<td>8 days</td>
<td>SG Subsp Pasteuri</td>
<td>Seizures, fever, inconsolability, decreased oral intake</td>
<td>CSF</td>
<td>Meningitis</td>
<td>Ampicillin, Panipenem/betamipron x 20 days</td>
<td>Survived</td>
</tr>
<tr>
<td>Thatrimontricha et al. (2012)</td>
<td>1</td>
<td>3.188</td>
<td>39</td>
<td>Vaginal</td>
<td>3 days</td>
<td>SG Subsp Pasteuri</td>
<td>Fever, lethargy, poor oral intake, bulging fontanelle</td>
<td>CSF</td>
<td>Meningitis</td>
<td>Cefotaxime x 14 days</td>
<td>Survived</td>
</tr>
<tr>
<td>Hede et al. (2015)</td>
<td>2</td>
<td>(twins)</td>
<td>C-section</td>
<td>3 weeks</td>
<td>SG Subsp Pasteuri</td>
<td>Pt 1: Lethargy, irritability, respiratory distress, poor feeding, loose stools, seizures; Pt 2: Respiratory distress</td>
<td>Pt 1: Blood + CSF, Pt 2: Blood</td>
<td>Meningitis in both pts; Sepsis in Pt 1; Bacteremia in Pt 2</td>
<td>Ampicillin x 10-20 days</td>
<td>Both patients survived; but Pt I was reported to have long term neurologic deficits</td>
<td></td>
</tr>
<tr>
<td>Kennedy et al. (2015)</td>
<td>1</td>
<td>3.05</td>
<td>37</td>
<td>Vaginal</td>
<td>4 days</td>
<td>SG Subsp Gallolyticus</td>
<td>Fever, lethargy, irritability.</td>
<td>Blood + CSF</td>
<td>Bacteremia and Meningitis</td>
<td>Ampicillin x 14 days</td>
<td>Survived</td>
</tr>
<tr>
<td>Park et al. (2015)</td>
<td>1</td>
<td>3.6</td>
<td>38</td>
<td>Vaginal</td>
<td>28 days</td>
<td>SG Subsp Pasteuri</td>
<td>Fever, lethargy</td>
<td>CSF + Blood + Urine</td>
<td>Meningitis, UTI, Bacteremia</td>
<td>Ampicillin + Cefotaxime x 21 days</td>
<td>Survived, but rehospitalized 2 weeks later due to fever and seizures, requiring 31 additional days of</td>
</tr>
<tr>
<td>Author(s) and Year</td>
<td>Case Number</td>
<td>GA (wks)</td>
<td>Gestational Age</td>
<td>Birth Weight (g)</td>
<td>Sex</td>
<td>GA (days)</td>
<td>Isolated Pathogen(s)</td>
<td>Symptoms</td>
<td>Laboratory Results</td>
<td>Outcome</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>Saegema et al. (2016)</td>
<td>1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>7 days</td>
<td>SG subsp. pasteurianus</td>
<td>Sepsis</td>
<td>Blood</td>
<td>Sepsis</td>
<td>Penicillin, duration unknown</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>Yamamura et al. (2018)</td>
<td>1</td>
<td>3.68</td>
<td>Term</td>
<td>Vaginal</td>
<td>SG subsp. pasteurianus</td>
<td>Fever, lethargy, irritability, cold extremities</td>
<td>Blood + CSF</td>
<td>Sepsis, Meningitis</td>
<td>Ampicillin n x 22 days</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>Geetha et al. (2021)</td>
<td>1</td>
<td>3.77</td>
<td>36</td>
<td>Vaginal</td>
<td>&lt;24 hours</td>
<td>SG subsp. pasteurianus</td>
<td>Respiratory distress, sepsis</td>
<td>Blood</td>
<td>Liver abscess, Sepsis</td>
<td>Cefotaxime x 5 weeks, co-amoxiclay for 3 weeks</td>
<td>Survived</td>
</tr>
<tr>
<td>Sim et al. (2021)</td>
<td>4</td>
<td>1.81-3.37</td>
<td>Ps 1-3: Term; Pt 4: 34</td>
<td>Ps 1-3: Vaginal; Pt 4: C-section</td>
<td>1-23 days</td>
<td>SG</td>
<td>Pt 1: Respiratory distress; Pt 2-4: fever; Pt 3: Lethargy/poor feeding</td>
<td>Blood</td>
<td>Ps 1-4: Blood; Ps 1:2: CSF</td>
<td>Sepsis: All pts; Meningitis: Ps 1,2</td>
<td>Amoxicillin n, Clindamycin or Vancomycin x 7-14 days</td>
</tr>
<tr>
<td>This case</td>
<td>1</td>
<td>0.95</td>
<td>26</td>
<td>Vaginal</td>
<td>&lt;24 hours</td>
<td>SG</td>
<td>Respiratory distress, sepsis</td>
<td>Blood</td>
<td>Sepsis</td>
<td>n/a</td>
<td>Died at 5 hours</td>
</tr>
</tbody>
</table>

Abbreviations: GA: gestational age; GBS: group B streptococcus; S. Streptococcus; SG:

Streptococcus gallolyticus; CSF: cerebrospinal fluid; pt: patient; UTI: Urinary tract infection

* Exact number of neonates (≤28 days) unknown.