

## Neonatal Sepsis Caused by *Streptococcus bovis* Variant (Biotype II/2): Report of a Case and Review

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***Streptococcus bovis* is an uncommon cause of infection in neonates. However, *S. bovis* is capable of causing fulminant neonatal sepsis or meningitis that is indistinguishable clinically from that caused by group B streptococcus. *S. bovis* and *S. bovis* variant (sometimes referred to as *S. bovis* biotypes I and II, respectively) are phenotypically similar but may be differentiated by expanded testing. In adults, specific associations between disease states and different biotypes of *S. bovis* are apparent. No data exist on possible differences or clinical relevance of neonatal infection caused by different biotypes or newer species of *S. bovis*. We report a 3-day-old neonate with bacteremia and meningitis caused by *S. bovis* variant (*S. bovis* biotype II/2) and review the literature.**

### CASE REPORT

A 3-day-old baby boy presented with fever, inconsolable irritability, and decreased oral intake and urine output. He was born at term, weighing 3,925 g, to a 41-year-old primigravida mother. Maternal prenatal culture was negative for group B streptococcus. Pregnancy was complicated by preeclampsia, but labor was uneventful, without prolonged rupture of membranes or maternal fever. At birth, the baby was cyanotic with a pulse of 100/min but responded quickly to suctioning and bag and mask ventilation (Apgar scores, 3<sup>1</sup>, 8<sup>5</sup>, and 9<sup>10</sup>). The initial blood glucose level of 17 mg/dl responded to intravenous glucose infusion. No antibiotics were given. Thereafter, blood glucose measurements remained normal. He was changed to bottle feeding after 6 h and discharged home after 48 h of observation.

Examination on readmission, 8 h later, revealed a fever of 103°C, heart rate of 198/min, respiration rate of 60/min, and a tense anterior fontanelle. Seizure-like episodes consisting of stiffening, crying, and staring were noted. The remainder of the examination was normal, without evidence of congenital anatomic anomaly. Specimens for laboratory studies and blood cultures were collected, and therapy with intravenous ampicillin (50 mg/kg of body weight every 6 h) and ceftriaxone (50 mg/kg every 12 h) was started. The baby's condition improved, and 1.5 h later cerebrospinal fluid (CSF) was obtained by lumbar spinal tap and additional blood was collected for culture.

Laboratory studies showed the following: hemoglobin, 13.2 g/dl; white blood cells, 3,400/ $\mu$ l (neutrophils, 21%; bands, 41%; lymphocytes, 36%); platelets, 201,000/ $\mu$ l; and blood glucose, 67 mg/dl. CSF was turbid with white blood cells at 2,100/ $\mu$ l (neutrophils, 80%; bands, 10%; lymphocytes, 10%), red blood cells at 3,150/ $\mu$ l, glucose at 4 mg/dl, and protein at 600 mg/dl. Gram staining of CSF revealed gram-positive cocci in pairs and

short chains. Ceftriaxone was discontinued, and intravenous gentamicin (2.5 mg/kg every 12 h) was added (ampicillin was continued). Initial blood and CSF cultures were positive for alpha-hemolytic streptococci, identified tentatively as viridans streptococcus group. Isolates from blood and CSF cultures were susceptible to penicillin (MIC, <0.06  $\mu$ g/ml). Gentamicin and ampicillin were discontinued, and treatment was continued with intravenous penicillin G (50,000 U/kg every 8 h). The second blood culture, performed at the time of the spinal tap and after the first dose of antibiotics, was negative. The baby defervesced after 24 h and remained seizure-free thereafter. He continued to improve throughout his hospital stay and was discharged home after completing a 14-day course of intravenous penicillin G.

The first blood culture demonstrated gram-positive cocci in pairs and short chains after 12 h of incubation in broth at 37°C (Bactec 9240; Becton Dickinson, Baltimore, Md.). Subsequent subculture on 5% sheep blood and chocolate agars incubated at 35°C demonstrated alpha-hemolytic colonies with a distinct caramel-like odor. Culture of CSF was similarly positive after 36 h of incubation. The isolates were negative for catalase and pyrrolidonyl arylaminidase; showed no zone of inhibition around a 5- $\mu$ g-optochin disk; did not produce acid from sorbitol, arabinose, or sorbose; were unable to hydrolyze arginine; failed to grow in heart infusion broth containing 6.5% NaCl; and were weakly bile esculin positive (darkening of slant only, not butt of medium) after overnight incubation. A tentative identification of viridans group streptococcus was made.

Subsequently, blood and CSF isolates were identified as *Streptococcus bovis* variant (biotype II) by RapID STR system (Remel, Lenexa, Kans.) (code number 22321) and Vitek 2 (bioMérieux Vitek, Inc., Hazelwood, Mo.) and as biotype II/2 by API 20 Strep (bioMérieux SA, Marcy l'Etoile, France) (code number 5650450). Cellular fatty acid analysis (MIDI Inc., Newark, Del.) provided additional confirmation of the identification as *S. bovis* variant (21). Subsequently, expanded biochemical testing was also indicative of *S. bovis* variant. Spe-

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TABLE 1. Cases of neonatal infection caused by *S. bovis*<sup>a</sup>

Yr (reference)	Age at onset	Sex	Site	<i>S. bovis</i> biotype	Treatment	Outcome
1977 (19)	6 infants <6 wk	NR	Blood	Biotype II	NR	NR
1978 (15)	At birth <24 h	F	Blood	NR	Ampicillin, gentamicin, methicillin	D
		M	Blood			S, poor prognosis
1978 (24)	4 infants <5 d 1 infant <5 d 2 infants <5 d	NR	Blood	NR	Penicillin	NR
		NR	CSF			
		NR	Urine			
1978 (1)	<24 h	NR	Blood-CSF	NR	Ampicillin, gentamicin Penicillin	S
		NR	Blood-CSF			D
		NR	Blood-urine			D
		NR	Blood			S
1979 (4)	9 d 19 d 4 d 21 d	NR	CSF	NR	Penicillin, gentamicin	S
		NR	CSF	NR		S
		NR	Blood			S
		NR	Blood			S
1979 (12)	<3 d	M	Blood-CSF	NR	Ampicillin plus kanamycin or gentamicin	S
1979 (3)	40 d 24 h	M	Blood	NR	Ampicillin plus kanamycin or gentamicin	S
		M	Blood			D
1981 (17)	7 wk	F	CSF	NR	Ampicillin	S
1982 (11)	24 h	M	Blood-CSF	NR	Ampicillin plus chloramphenicol	S
2000 (13)	5 wk	F	CSF	Biotype II	Ampicillin	S
2000 (5)	4 wk	M	Blood-CSF	Biotype II/2	Penicillin	S
Present case	3 d	M	Blood-CSF	Biotype II/2	Penicillin	S

<sup>a</sup> Abbreviations: d, days; NR, not recorded; F, female; M, male; S, survived; D, died.

cifically, blood and CSF isolates failed to hydrolyze starch or produce acid from mannitol (9, 21).

Antimicrobial susceptibility testing was performed by a broth microdilution method (NCCLS standard M7-A5, 35°C). The 24-h MICs were as follows: penicillin, 0.06 µg/ml; ceftriaxone, 0.12 µg/ml; clindamycin, 0.06 µg/ml; erythromycin, >1 µg/ml; and vancomycin, 0.5 µg/ml.

**Review.** Among group D streptococci, enterococci are well recognized as causes of neonatal sepsis and meningitis (24). In contrast, *S. bovis* is considered an uncommon cause of neonatal infection (14, 24). However, the frequency of infection may be an underestimate because many clinical *S. bovis* isolates may have been misidentified previously as enterococci or viridans group streptococci (9). Definitive identification of these streptococci requires an expanded battery of physiological tests (8, 9, 21). In addition, *S. bovis* (biotype I) is differentiated physiologically from *S. bovis* variant (biotype II) by the ability of the former to hydrolyze starch and ferment mannitol (9, 21). *S. bovis* variant (biotype II) is further divided into type II/1 and type II/2 by the API 20 Strep system (bioMérieux SA).

Reports of neonatal infection caused by *S. bovis* group strains are summarized in Table 1. Full- and preterm neonates were equally represented among the cases. Neonatal *S. bovis* infection demonstrates a clinical presentation similar to that of neonatal group B streptococcus infection. In cases of early-onset (within the first week of life) *S. bovis* infection in neo-

nates, bacteremia is the most common clinical manifestation (18 of 25 cases, 72%), whereas meningitis is less common (5 of 25 cases, 20%) and of late onset. Specifically, the majority of neonates (15 of 18, 83%) with bacteremia caused by *S. bovis* presented with acute onset of respiratory distress and/or sepsis within the first 5 days of life. In contrast, four of five neonates (80%) with meningitis presented beyond the first week of life (mean, 28 days; range, 9 to 49 days). Two additional cases of apparent urinary sepsis caused by *S. bovis* presented early (24). *S. bovis* neonatal infection appears to be associated with a relatively good prognosis: 14 of the 18 (78%) patients for which prognosis is recorded survived (one of whom had "a severely complicated course and a very poor prognosis").

Enterococcal group D streptococci and viridans group streptococci, such as *S. milleri* group and nonhemolytic strains of *S. salivarius*, may have similar phenotypic characteristics as do strains of *S. bovis* (8, 21, 22). Accurate identification of *S. bovis* as a cause of neonatal infection has important implications for treatment. Penicillin G alone is considered sufficient treatment for neonatal infections caused by *S. bovis*, whereas vancomycin or the addition of an aminoglycoside may be necessary for neonatal infections caused by enterococcal and some viridans streptococcal species (2). Although rare isolates of *S. bovis* have demonstrated resistance to penicillin, the vast majority of clinical isolates remain exquisitely sensitive (23).

New molecular techniques have clarified taxonomy of what

was termed *S. bovis*, separating it into five different species (*S. bovis*-*S. equinus*, *S. gallolyticus*, *S. infantarius*, *S. pasteurianus*, and *S. lutetiensis*) (7). However, most clinical laboratories do not accurately identify members of the *S. bovis* group and have yet to adopt the new nomenclature, which is confusing and still subject to debate. As a result, most clinicians remain unfamiliar with biotypes or newer *S. bovis* species, and clinical correlates are uncommon. According to current terminology, strains formerly termed *S. bovis* (biotype I) and *S. bovis* variant (biotype II/2) are now named *S. gallolyticus* and *S. pasteurianus*, respectively, while the former *S. bovis* variant (biotype II/1) is now named *S. infantarius* (7). The *S. bovis* variant (biotype II/2) isolates from the present case translate into correct terminology as *S. pasteurianus*.

In adults, the association of *S. bovis* bacteremia with malignancies of the gastrointestinal tract is well documented (18). More recently, clinically relevant differences were demonstrated in the association of specific biotypes of *S. bovis* with colonic neoplasia and bacterial endocarditis (16, 22). Specifically, 71 and 94% of adults with bacteremia caused by *S. bovis* (biotype I) had underlying colonic neoplasia or bacterial endocarditis, respectively (22). In contrast, only 17 and 18% of patients with bacteremia caused by *S. bovis* variant (biotype II) had these diseases, respectively (22). In addition, of the two biotypes, *S. bovis* (biotype I) was found in 11 of 12 (92%) cases of *S. bovis* endocarditis (16). Ruoff et al. proposed that the striking association of *S. bovis* (biotype I) with both underlying colonic neoplasia and bacterial endocarditis compared with *S. bovis* variant (biotype II) suggests different specific bacterium-host cell interactions between biotypes (22).

In the majority of reports of *S. bovis* infection in neonates, detailed identification and biotyping of clinical isolates were not reported. However, in the nine cases of neonatal *S. bovis* infection that reported biotyping, all were caused by *S. bovis* biotype II (5, 13, 19; this work) (Table 1).

Similarly, where further biotyping was performed for two neonates with meningitis, both were caused by *S. bovis* variant (biotype II/2) (5; this work). In addition, in adults with meningitis caused by *S. bovis*, where biotyping was recorded, three of four were caused by *S. bovis* variant (biotype II/2) (6, 10). Thus, just as differentiation of *S. bovis* from other streptococci is of therapeutic importance, more accurate differentiation of *S. bovis* biotypes may be clinically relevant. Specifically, whereas *S. bovis* (biotype I) bacteremia, in adults, is more closely associated with endocarditis or colonic neoplasia, it appears that *S. bovis* variant (particularly biotype II/2) may be more closely associated with meningitis or neonatal infection. Potential mechanisms may include a specific virulence trait of the organism, increased host susceptibility, and differences in portal of entry or maternal colonization. Further studies are required to verify this apparent association.

*S. bovis* (biotype I) is differentiated physiologically from *S. bovis* variant (biotype II) by its ability to hydrolyze starch and ferment mannitol (9, 20, 21). *S. bovis* variant (biotype II) is further divided into type II/1 and type II/2 based on phenotypic testing in the Rapid Strep system. Increased use of extended physiologic testing or automated bacterial identification sys-

tems and kits by the clinical laboratory results in improved diagnostic certainty and may provide useful clinical correlation and a better understanding of pathogenicity. We speculate that, as in adult infections, isolation of specific biotypes or newer species of *S. bovis* may be of clinical and pathophysiologic relevance in neonatal infections. We conclude that more accurate identification and differentiation of biotypes or newer species of *S. bovis* should be more widely applied.

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