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Probiotic-Associated Bacillus subtilis subsp. subtilis Catheter-Related Bloodstream Infection in a Preterm Infant: A Safety Warning for Neonatal Intensive Care Units

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Short Report

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Abstract

We report the case of catheter-related bloodstream infection (CRBSI) caused by *Bacillus subtilis* subsp.*subtilis* associated with probiotic administration. A 32^{+5}-week preterm infant developed systemic inflammation during oral probiotic therapy. CRBSI was definitively diagnosed via differential time to positivity between peripheral and catheter-drawn blood cultures. Microbiological analysis confirmed that clinical isolates and the probiotic strain shared identical antimicrobial susceptibility profiles. This novel case identifies a specific infectious risk for *B. subtilis* in neonates with central venous access and underscores the necessity of considering probiotics as a potential source of catheter-related sepsis.

Introduction

Central venous catheters are integral to neonatal intensive care; however, catheter-related bloodstream infections (CRBSIs) continue to contribute substantially to morbidity and mortality despite preventive strategies[1]. Preterm infants are particularly susceptible, owing to prolonged parenteral nutrition, immunologic immaturity, and frequent catheter manipulation[2]. While probiotics are commonly used to prevent necrotizing enterocolitis, they have emerged as potential opportunistic pathogens in high-risk neonates[3]. Most probiotic-associated sepsis involves *Lactobacillus* or *Saccharomyces*; neonatal infections caused by *Bacillus subtilis* subsp. *subtilis* are exceedingly rare and have historically been attributed to environmental contamination[4–6]. Recent safety alerts have highlighted rare but severe cases of probiotic-associated sepsis, particularly among extremely preterm infants and those with indwelling central venous catheters[5, 7]. We describe a preterm infant who developed catheter-related bloodstream infection (CRBSI) caused by *B. subtilis* subsp. *subtilis*, which was associated with the administration of a probiotic containing *B. subtilis*. This is the first report of neonatal catheter-related infection caused by *B. subtilis* subsp. *subtilis*.

Case

A female preterm infant was delivered at 32^{+5} weeks' gestation via cesarean section as part of a twin pregnancy conceived through assisted reproductive technology. Birth weight was 2000 g, and Apgar scores were 10 at 1, 5, and 10 minutes. The mother received antenatal dexamethasone and clindamycin prior to delivery. The infant was admitted to the neonatal intensive care unit (NICU) for management of prematurity.

On day of life (DOL) 6, a peripherally inserted central catheter (PICC) was placed via the right femoral vein to facilitate parenteral nutrition and intravenous therapy. Correct catheter tip position was radiographically confirmed, and no immediate complications occurred. On DOL 7, a dual-strain oral probiotic preparation containing *Bacillus subtilis* was initiated because of feeding intolerance manifested by recurrent emesis.

On DOL 15, after eight days of probiotic exposure, the infant developed acute clinical deterioration characterized by recurrent vomiting, progressive abdominal distension, bradycardia, and oxygen

desaturation episodes. Laboratory evaluation demonstrated elevated C-reactive protein (CRP, 25.72 mg/L) and leukocytosis with neutrophil predominance. In view of suspected CRBSI, paired blood cultures were obtained simultaneously from a peripheral vein and the PICC lumen. Empirical intravenous piperacillin–tazobactam was initiated immediately after specimen collection.

On DOL 17, both peripheral and catheter-drawn blood cultures yielded *B. subtilis* subsp. *subtilis*. The time to positivity was shorter in the catheter-drawn sample (4 h 17 min) than in the peripheral sample (8 h 27 min), and the differential time to positivity supported a catheter-related source. Antimicrobial susceptibility testing demonstrated susceptibility to penicillin, levofloxacin, meropenem, and vancomycin. Given that the patient had received probiotics containing *B. subtilis* since DOL7, a probiotic-associated source was considered highly likely. Subsequently, the same organism was recovered from the administered probiotic product; the antimicrobial susceptibility profile is summarized in Table 1.

Table 1
Antimicrobial susceptibility profiles of *Bacillus subtilis* subsp. *subtilis* isolates from peripheral blood, catheter-drawn blood, and administered probiotic product

Antibiotic	**Breakpoint** [i] **(μg/mL)**	**MIC (μg/mL) / Susceptibility** [ii]		
		peripheral blood	**Catheter-drawn blood**	**Probiotic product**
Penicillin	0.12	≤ 0.06(S)	≤ 0.06(S)	0.012(S)
Levofloxacin	2	0.12(S)	0.12(S)	0.12(S)
Meropenem	4	≤ 0.06(S)	≤ 0.06(S)	0.03(S)
Vancomycin	4	0.5(S)	0.5(S)	0.5(S)
[i] Breakpoints for susceptibility are based on Clinical and Laboratory Standards Institute (CLSI) guidelines for Bacillus spp. (M45, 3rd ed., 2015)				
[ii] Susceptibility interpretation: S, susceptible.				
Abbreviations: CRP, C-reactive protein; DOL, day of life; PICC, peripherally inserted central catheter; Pip/Tazo, piperacillin/tazobactam				

The PICC was promptly removed, and antimicrobial therapy was de-escalated to penicillin G according to susceptibility results. Inflammatory markers declined progressively, with CRP returning to the normal range. Follow-up blood cultures remained sterile. The infant completed an eight-day course of targeted therapy and achieved full clinical recovery. The temporal relationship among probiotic exposure, catheter removal, antimicrobial therapy, and inflammatory markers is shown in Fig. 1.

Discussion

This case underscores a potential association between probiotic exposure and CRBSI in a preterm infant. Although probiotics are routinely administered in neonatal intensive care units to prevent

necrotizing enterocolitis and late-onset sepsis, safety concerns remain in high-risk subgroups. Systematic reviews suggest that probiotic-associated invasive infections in children are uncommon but occur predominantly in preterm infants and those with central venous catheters. In a review of 49 pediatric cases, prematurity (55%) and intravenous catheter use (51%) were the most frequently identified predisposing factors, with sepsis representing the most common clinical presentation.[8].

The present case extends prior observations to *B. subtilis* subsp. *subtilis*, an organism traditionally regarded as minimally pathogenic[9]. Although serious neonatal infections due to *B. subtilis* are uncommon, they have been reported, particularly in immunologically immature hosts[6]. Given that *B. subtilis* is a ubiquitous environmental organism, distinguishing true bacteremia from contamination is critical. In this case, several microbiologic and clinical features support a diagnosis of genuine catheter-related bloodstream infection. Paired blood cultures obtained simultaneously from a peripheral vein and the peripherally inserted central catheter yielded *B. subtilis* subsp. *subtilis*, with a shorter time to positivity in the catheter-drawn sample, fulfilling accepted criteria for differential time to positivity consistent with CRBSI. The microbiologic findings coincided with acute clinical deterioration and objective evidence of systemic inflammation, including markedly elevated C-reactive protein and neutrophil-predominant leukocytosis. Clinical status and inflammatory markers normalized following catheter removal and targeted antimicrobial therapy. Taken together, these findings strongly support a clinically significant catheter-related infection rather than incidental contamination.

Multiple mechanisms may account for probiotic-associated CRBSI, as conceptualized in Fig. 2. First, bacterial translocation across an immature intestinal barrier may permit systemic dissemination, particularly in preterm infants with impaired mucosal integrity[8, 10]. Second, contamination of catheter hubs or lumens during probiotic preparation or administration could facilitate direct device colonization. Once introduced into the bloodstream, biofilm formation on catheter surfaces may promote persistent bacteremia, especially in the presence of glucose-containing parenteral nutrition[10]. *B. subtilis* subsp. *subtilis* is well recognized for its capacity to form robust biofilms mediated by extracellular matrix components that enhance surface adherence and persistence[9], a property that may contribute to catheter colonization. In the present case, the anatomical proximity of the femoral PICC insertion site to the perineal area likely facilitated this infection. We hypothesize that oral *B. subtilis* colonized the gastrointestinal tract and was subsequently shed in the stool. This proximity created a localized reservoir, promoting external contamination of the catheter and subsequent biofilm formation. Consequently, the choice of venous access site may be a critical, underrecognized risk factor for probiotic-associated CRBSI in neonates.

This case highlights the importance of careful consideration when administering probiotics to preterm infants with indwelling central venous catheters. Strict handling procedures, appropriate patient selection, and prompt evaluation of unusual bloodstream isolates may help reduce the risk of device-associated infection.

Conclusion

This report documents catheter-related bloodstream infection due to *B. subtilis* subsp. *subtilis* in a preterm infant exposed to probiotic therapy, who recovered fully following treatment with penicillin G. While probiotic-associated invasive infections remain rare, clinicians should remain aware of this risk in preterm infants with central venous catheters and implement strict infection-control and handling measures in this setting.

Declarations

Ethical approval

Written informed consent was obtained from the infant's parents for publication of this case report. Institutional ethical approval was not required for a single retrospective case report at our institution.

Declaration of competing interest

The authors have no competing interests to declare.

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Author Contribution

J.C. wrote the main manuscript text; X.L. and X.H. collected clinical data and performed microbiological analysis; M.H. prepared Figure 1 and Table 1. All authors reviewed and approved the final manuscript.

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Data Availability

All data supporting the findings of this study are included within the paper. Specifically, the clinical progression, diagnostic time to positivity values, and comparative antimicrobial susceptibility profiles are presented in the main text, Figure 1, and Table 1.

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Figures

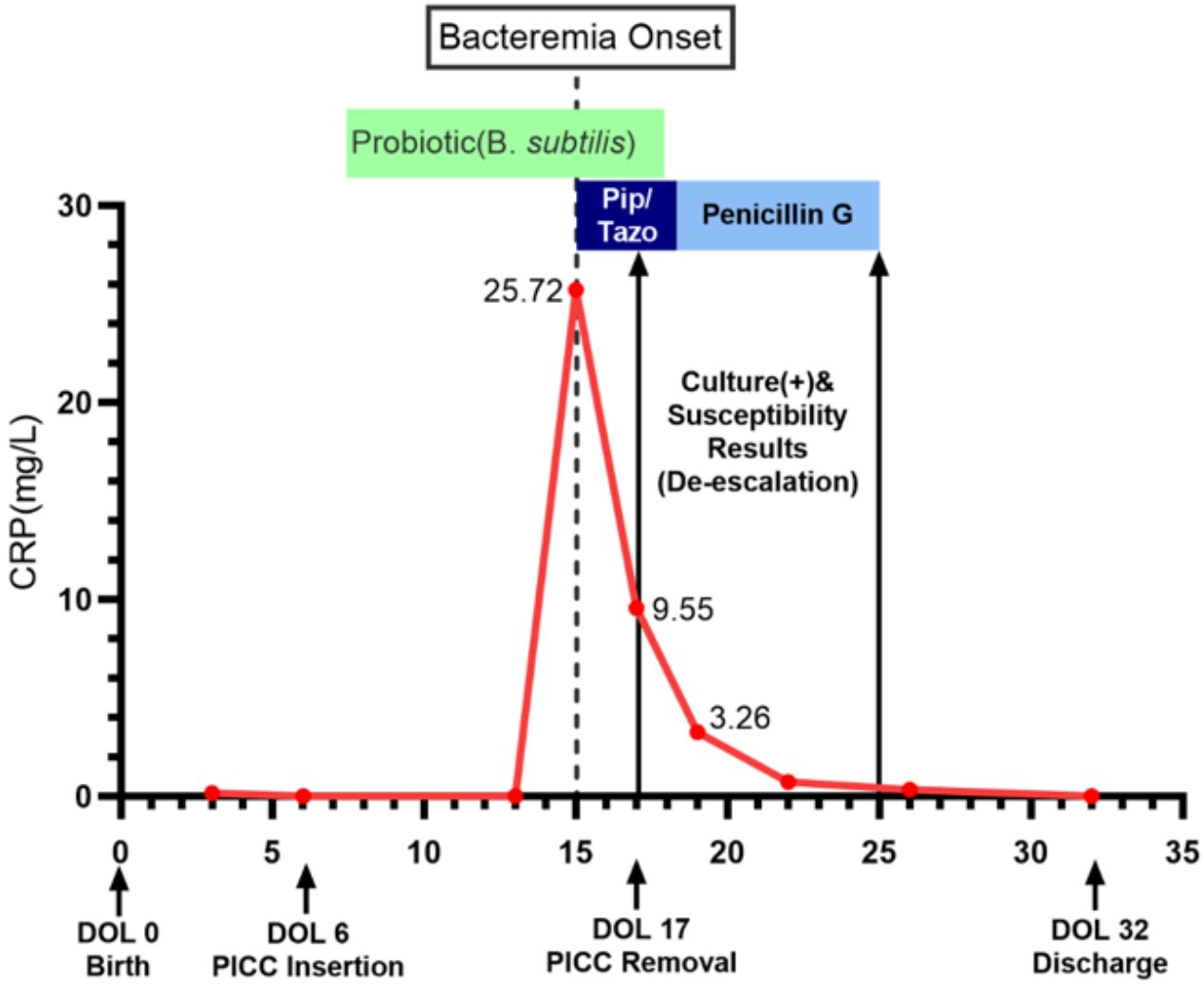


Figure 1

Timeline of clinical events and C-reactive protein levels.

Caption: CRP levels from birth to discharge are shown. Bacteremia onset occurred on DOL 15, with peak CRP of 25.72 mg/L. Empirical piperacillin–tazobactam was initiated, followed by de-escalation to penicillin G after culture results. The PICC was removed on DOL 17, after which inflammatory markers declined and clinical recovery ensued

Abbreviations: CRP, C-reactive protein; DOL, day of life; PICC, peripherally inserted central catheter; Pip/Tazo, piperacillin/tazobactam

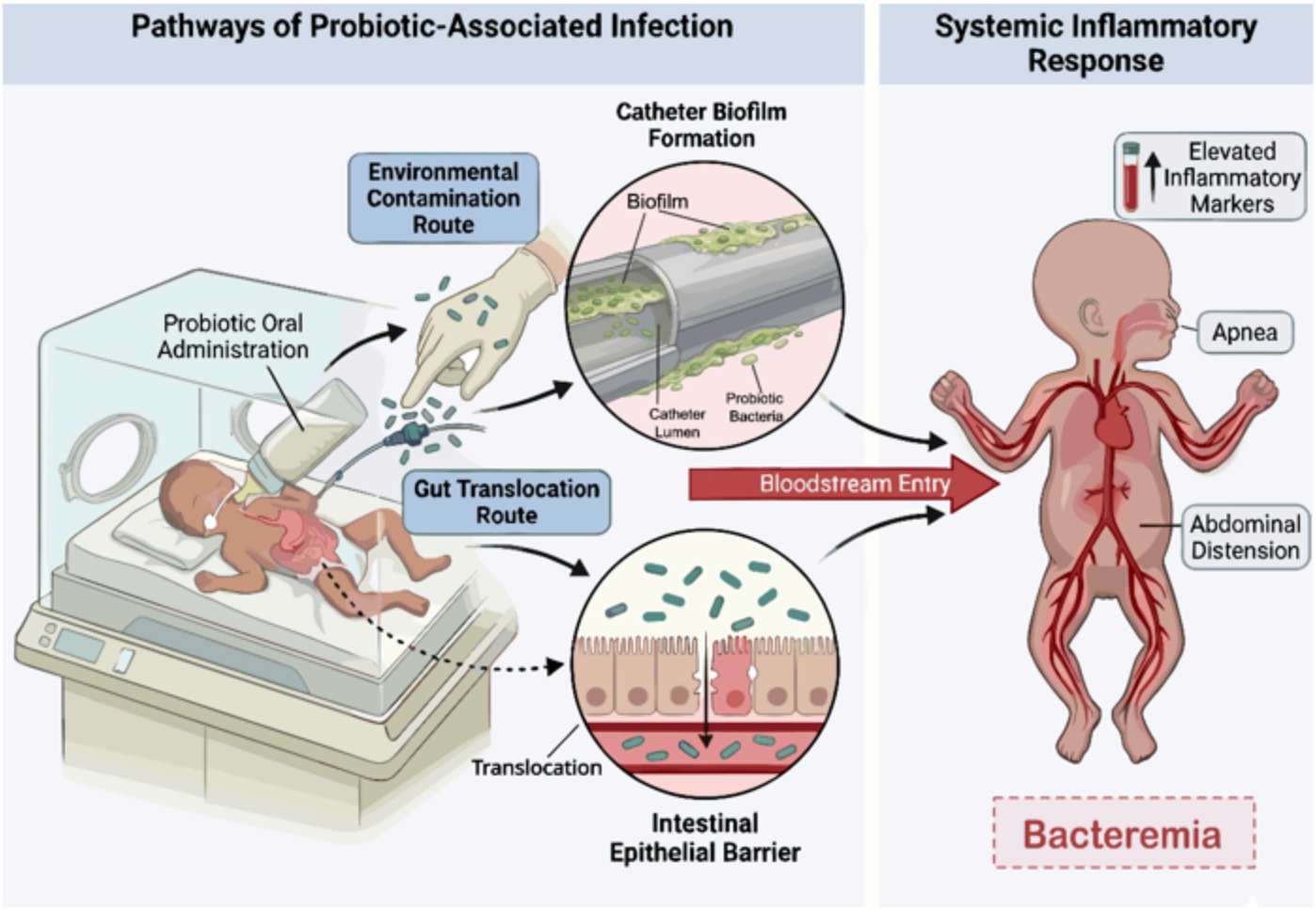


Figure 2

Mechanistic pathways of probiotic-associated systemic sepsis and catheter-related infection in neonates.

Caption: The illustration delineates two primary routes of infection: (1) the Gut Translocation Route, where bacteria traverse the immature intestinal epithelial barrier; and (2) the Environmental Contamination Route, where handling during administration leads to catheter hub colonization and subsequent biofilm formation. Both pathways facilitate Bloodstream Entry, culminating in a systemic inflammatory response characterized by apnea, abdominal distension, and elevated inflammatory markers