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Title: Recurrent Late-Onset Group B Streptococcal Infection: Successful Prevention of Further Recurrence with Prolonged Hospitalization and Family Oral Ampicillin Prophylaxis

Running Title: Recurrent Late-Onset Group B Streptococcal Invasive Infection

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Clinical Question Box

Which preventive approaches should be considered for neonates experiencing recurrent invasive group B Streptococcal infection?

Screening for immunological function and potential infectious sources is important, followed by group B *streptococcus* screening of the mother and other family members. When no abnormalities are found, or when it is difficult to perform family screening, preventive strategies against horizontal transmission may include prolonged hospitalization for close monitoring, extended oral antibiotic therapy for the infant after discharge, and administration of oral antibiotics to family members.

Abstract

Background: Group B *streptococcus* (GBS) is a major cause of neonatal invasive infection. Recurrent invasive GBS infection occurs in 1.4–3.7 % of infant invasive GBS cases; however, its risk factors and preventive strategies remain poorly understood. **Case Presentation:** A term female infant was born to a GBS-positive mother who received intrapartum antibiotic prophylaxis. She developed fever, lethargy, and poor feeding on day 16 of life, and blood cultures were positive for GBS. She received 10 days of intravenous ampicillin followed by four days of observation before discharge. She was readmitted four days later with recurrent GBS bacteremia and meningitis, progressing to a preshock condition. The infant underwent antimicrobial treatment and prolonged hospitalization. GBS isolates from both episodes were identified as serotype III, sequence type 17. Maternal and breast milk cultures were negative, and no immunological abnormalities were detected. Considering the risk of horizontal transmission, oral amoxicillin was administered to family members before the infant's final discharge, and no further recurrence occurred. **Conclusion:** Recurrent late-onset invasive GBS infection can be life-threatening condition and impose a significant medical and societal burden. Preventive measures—including immunological and imaging screening, maternal and family GBS screening, family-targeted oral antibiotic therapy, and prolonged hospitalization for close monitoring—may be considered.

Keywords: group B *streptococcus*, recurrence, prevention, case report

Introduction

Group B *streptococcus* (GBS) is a major cause of neonatal invasive infections, including sepsis and meningitis.[1] Early-onset disease, occurring within the first 6 days of life, is usually acquired through vertical transmission from mother colonized with GBS, and can be largely prevented by intrapartum antibiotic prophylaxis (IAP).[2] However, late-onset disease (LOD), developing between 7 and 89 days of age, is less well understood. LOD may result from vertical or horizontal transmission, but in many cases the source of infection remains unclear, and importantly it is not prevented by IAP. [3,4]

Recurrent invasive GBS infection has been reported in approximately 1.4–3.7% of infant invasive GBS cases and remains a substantial medical and societal burden.[4-6] Suggested risk factors include prematurity, breast milk contamination, and persistent mucosal colonization, although in many instances the underlying cause is unknown. To date, there are very few studies addressing prophylactic strategies for recurrent late-onset GBS invasive infection, highlighting the importance of further investigation in this area.

Here, we report a case of an otherwise healthy and immunocompetent infant, born to a mother in whom GBS colonization was not detected, who nevertheless developed recurrent late-onset invasive GBS disease. We further discuss a prophylactic approach that successfully prevented subsequent recurrence.

Case Presentation

A female infant was born at 40 weeks and 4 days of gestation with a birth weight of 2,488 g. Vaginal and rectal screening for GBS at 35 weeks of gestation was positive, and the mother received IAP. The infant showed no abnormalities at delivery and remained well until day 16 of life, when she developed a high fever of 40.5 °C accompanied by lethargy and poor feeding. On admission, her heart rate was 200 beats/min and her respiratory rate was 56 breaths/ min. The anterior fontanelle was normal, and no other remarkable findings were noted on physical examination. Laboratory tests showed a white blood cell count of 3,500/μL (neutrophils 64.2%) and a C-reactive protein level of 0.59 mg/dL. Urinalysis and cerebrospinal fluid (CSF) studies revealed no abnormalities. Empirical intravenous antimicrobial therapy was initiated with ampicillin (ABPC, 200 mg/kg/day) and cefotaxime (CTX, 200 mg/kg/day), and her clinical condition improved rapidly. On hospital day 2, blood culture grew GBS, but no bacteria detected in the CSF or urine cultures. As the isolate was highly susceptible to ABPC, CTX was discontinued, and intravenous ABPC was continued at 300 mg/kg/day for 10 days. She was discharged in good condition on hospital day 15 (Figure 1A).

Four days after discharge, the infant again developed a fever of 39.5 °C. On admission, she presented in a pre-shock state, with a heart rate of 198 beats/min, lethargic with pallor, a capillary refill time of 3 seconds, and a bulging anterior fontanelle. She received supportive treatment for shock and was started on intravenous ABPC and CTX once again. Both blood and CSF cultures yielded GBS this time. On the following day, she experienced three seizures, which were controlled with phenobarbital (Figure 1B). An infection work-up, including contrast-enhanced MRI of the entire spine, contrast-enhanced brain MRI, and contrast-enhanced CT from the neck to the pelvis, revealed no significant abnormalities. Immunological studies demonstrated normal

lymphocyte proliferative responses to phytohemagglutinin (stimulation index = 28.6) and concanavalin A (stimulation index = 44.7). Flow cytometric analysis revealed T cells 57.1%, B cells 23.0%, and NK cells 19.1%. $CD4^+$ and $CD8^+$ subsets accounted for 36.8% and 18.2%, respectively, with a CD4/CD8 ratio of 2.02. Serum IgG was 356 mg/dL. No abnormalities were detected, and no *Toll-like receptor*–related gene variants were identified.

GBS isolates from blood cultures in both episodes and from the CSF culture of the second episode were analyzed for serotype and sequence type. All three isolates were identified as serotype III. Multilocus sequence typing revealed sequence type 17. Antimicrobial susceptibility testing showed susceptibility to penicillin G, ABPC, CTX, vancomycin, and ciprofloxacin, but resistance to erythromycin and clindamycin. One week after treatment initiation, the CSF culture became negative. She ultimately received a total of 39 days of intravenous ABPC therapy and remained hospitalized. After completion of antibacterial therapy, repeat CSF cultures remained negative, and the CRP levels stayed within the normal range.

Maternal cultures for GBS were negative in breast milk, throat, rectum, and vagina (tested twice). As transmission from within the household was suspected, both parents and two siblings received a 10-day course of oral amoxicillin. Following this intervention, the patient was discharged in good condition, with no recurrence of invasive GBS disease. She received all immunizations according to the national schedule without any adverse reactions. An adequate antibody response was confirmed after hepatitis B vaccination. Follow-up brain MRI at 6 and 18 months of age showed no abnormalities. The patient demonstrated normal developmental milestones, having rolled over at 5 months, sat without support at 8 months, walked independently at 11 months, and spoken her first words at 15 months.

Discussion

This case demonstrated recurrent late-onset invasive GBS infection that led the term infant to a life-threatening condition and highlighted the considerable medical and societal burden of recurrent GBS disease. Several studies have examined the risk factors for recurrent invasive GBS disease. A large cohort study from Japan identified prematurity and maternal colonization as significant contributors, while a recent French nationwide study similarly reported that preterm birth or very low birth weight was frequently associated with recurrence.[4,6] Other proposed risk factors include multiple birth, immunodeficiency, HIV exposure, and insufficient duration of antibiotic therapy.[7,8] However, our patient exhibited none of these conditions, suggesting that even healthy term infants may be vulnerable to severe recurrent invasive GBS disease.

GBS serotype III and clonal complex 17 have been reported significantly more frequently in recurrent cases, consistent with our patient's presentation.[4,9,10] Empirical antibiotic therapy generally includes amoxicillin or cefotaxime in combination with amikacin or gentamicin, administered for approximately 10 days in line with current recommendations.[11] Although clonal complex 17 has been suggested to be hypervirulent and associated with late-onset disease and recurrence, its antimicrobial susceptibility is not different from that of other sequence types, and a recent retrospective observational study reported no β-lactam–tolerant strains, supporting the effectiveness of standard antibiotic therapy.[4] In many infants, recurrence is thought to result from reinvasion of persistently colonized mucosal sites or re-exposure to a household carrier. Reports indicate that breast milk accounts for nearly half of recurrent GBS disease cases, and in some infants, sibling-to-sibling transmission has been documented. Furthermore, studies have shown that recurrence often involves the same strain as the initial infection, supporting the hypothesis of persistent colonization rather than reinfection with a new strain.[5,12] However, data on family

colonization sources are often insufficient, making precise identification of the pathogen source difficult. Similar to our case, although maternal breast milk and body sites were screened and found to be negative for GBS, transmission from another family member or transient colonization could not be excluded.

Therefore, preventive strategies against recurrence are necessary, even in term and immunocompetent infants. There is few study foucing on the preventing recurrent GBS disease. To gather insights into possible approaches, we reviewed case reports relevant to rerecurrent GBS disease and assessed the preventive measures described (Table 1).[13-17] Initial steps often include immunological and imaging evaluations to exclude underlying abnormalities that might predispose to reinfection. Maternal bacterial screening is frequently performed to help identify the source of infection. Considering that breast milk has been reported as a frequent source of late-onset infection, interruption of breastfeeding or pasteurization may be effective, as illustrated in Case 1. When GBS is detected in maternal cultures, oral antibiotic therapy for the mother has also been suggested, as in Case 4. Prolonged or repeated antibiotic therapy for the infant after hospitalization may also contribute to preventing recurrence (Case 2, 3, 5). Although paternal cultures were examined only in Case 4 and were negative, the possibility of household transmission should not be overlooked. In our case, although we were unable to perform comprehensive family cultures, prophylactic oral antibiotics administered to both parents and siblings successfully prevented further recurrence. This emphasizes the potential role of household-targeted interventions, although ideally GBS screening should be performed prior to prophylaxis. In addition, as observed in Case 2 and in our patient, extended hospitalization after completion of antibiotic therapy allowed for close monitoring and temporary separation from potential household sources of infection. Furthermore, intravenous immunoglobulin (IVIG) administration has been reported to increase

anti-GBS type III antibody levels and may serve as immunoprophylaxis against horizontal transmission in very low birth weight infants. This approach could also be considered in recurrent cases.[18]

There are several limitations to this case report. Although horizontal transmission was suspected, institutional regulations prevented GBS screening of other family members, including the father and two siblings, making it impossible to confirm the source of the GBS isolates. In addition, the single-case nature of this report limits the generalizability of the preventive strategies proposed. Nevertheless, the optimal preventive strategies remain uncertain, and evidence-based guidelines are lacking. Large-scale studies are required to clarify the most effective approaches. Until maternal GBS vaccines become widely available, heightened surveillance, early recognition of recurrence, and consideration of preventive measures remain essential in clinical practice. [19]

Conclusion

This case highlights that recurrent invasive GBS infection can occur even in term, immunocompetent infants. Although infectious colonization was not detected by maternal screening, prolonged hospitalization for close monitoring and prophylactic oral antibiotic therapy for family members successfully prevented further recurrence.

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Data Availability Statement: The datasets used in the current study are available from the corresponding author upon reasonable request.

Ethical Statement: The article does not involve the participation of any animals. The patient have written informed consent to the publication of this report and accompanying images.

Conflict of Interest: The authors report no conflicts of interest in this work.

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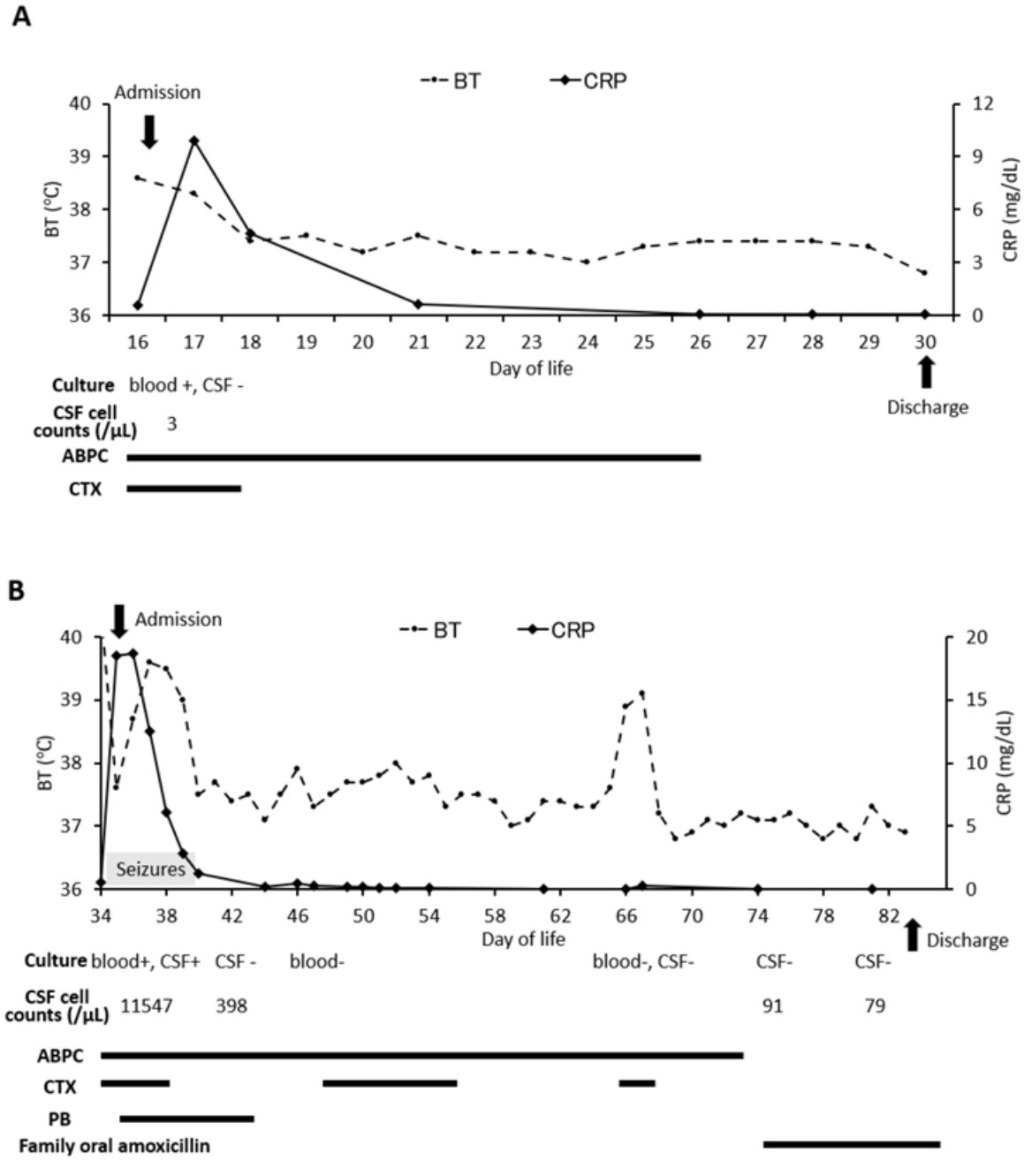
Table 1: Review of the Literature on Rerecurrent Invasive GBS Disease

Characteristics	**Case 1** *Hanna 2010* [13]	**Case 2** *Dietra 1985* [14]	**Case 3** *Jane 1998* [15]	**Case 4** *J.H. 1978* [16]	**Case 5** *Shouda 2012* [17]
Gestational age / Birth weight / Sex	38 weeks / ND / M	28 weeks / 920 g / M	27 weeks / ND / F	29 weeks / 1134 g / F	39 weeks / 3112 g / M
Delivery	Vaginal delivery	Cesarean section	Cesarean section	Vaginal delivery	Cesarean section
Nutrition	Breast milk	ND	Breast milk	ND	ND
Day of first onset	0	0	48	7	43
Infection focus	Bacteremia	Bacteremia, pneumonia	Bacteremia	Bacteremia	Bacteremia
Treatment	PCG 10 days, GM 5 days	ABPC+GM	ABPC, PCG 14days, GM 7 days	PCG 14days, GM 7 days	CTX 2 days, ABPC 10 days
Second onset / Therapy interval	Age 14 days / 4 days	Age 6 weeks / 22 days	Age 75 days / 14 days	Age 35 days / 14 days	Age 58 days / 5days
Infection focus	Bacteremia	Bacteremia	Bacteremia, cellulitis	Bacteremia, meningitis	Bacteremia
Treatement	PCG 10 days, GM 5 days	PCG 14 days	Antibiotics 21 days	PCG + AMK 21 days	ABPC + CTX 14 days
Third onset / Therapy interval	Age 28 days / 4 days	Age 10 weeks / 2 weeks	Age 4 months / 24 days	Age 60 days / 4 days	Age 74 days / days
Infection focus	Bacteremia	Bacteremia, pneumonia	Bacteremia	Bacteremia, pneumonia	Bacteremia
Treatement	PCG 14 days, RFP 6 days oral	PCG 3 weeks + IVIG	CTRX, PCG + IVIG	PCG, AMK + IVIG	ABPC, CTX 14 days + IVIG
GBS serotype	ND	III (1-3 episodes)	Ia / Ic (1st episode)	Ib (3rd episode)	III (1-3 episodes)
Maternal bacterial culture	Breast milk GBS (+)	Not perfomed	Rectovaginal and breast milk GBS (+)	Vaginal (+), skin, rectum, pharynx (-)	negative
Family member screening	Not perfomed	Not perfomed	Not performed	Father: skin, rectum, pharynx, urethra (-)	Not performed
Imaging studies	wholebody MRI, Echo	Gallium scan	Head/neck, abdominal CT, Bone scan, Echo	Head CT: hydrocephalus	Gallium scan, Echo, contrast CT
Immunological assessment	Immunoglobulin, complement	Immunoglobulin	HIV(-)	Not performed	Not performed
Preventive intervention	Breastfeeding stopped, Cephalexin PO 1 month	Hospitalization, RFP PO 7 days	RFP PO 7 days (mother and infant)	Mother PCG PO 10 days; vaginal culture (-)	PCG PO

M: Male; F: Female; ND: Not described; PCG: Penicillin G; GM: Gentamicin; ABPC: Ampicillin; AMK: Amikacin; CTX: Cefotaxime; IVIG: Intravenous Immunoglobulin; RFP: Rifampin; Echo: Echocardiography; CT: Computed Tomography

Figure 1: Clinical Course of the Patient



A: the first episode of hospitalization; B: the second episode of hospitalization

BT: Body Temperature; CRP: C-Reactive Protein; CSF: cerebrospinal fluid; ABPC: Ampicillin; CTX: Cefotaxime, PB: phenobarbital