Enhanced Postnatal Acquisition of Hypervirulent Group B *Streptococcus*

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(See the Major article by Tazi et al on pages 1740–8.)

At the time of Lancefield's original differentiation of the hemolytic streptococci on the basis of carbohydrate antigens, "group B" *Streptococcus* was described as a common etiologic agent of bovine mastitis and occasional commensal in the human gastrointestinal and genitourinary tracts [1, 2]. Subsequent reports demonstrated that group B *Streptococcus* (GBS) could cause disease in humans, with a predilection for peripartum women and neonates [3–6]. In ensuing decades, the rate of GBS neonatal sepsis increased substantially, and by the 1970s, GBS had emerged as a leading cause of both early-onset (days 0–6 of life) disease (EOD) and late-onset (days 7–89) disease (LOD). Seminal studies from the 1970s and 1980s identified maternal rectovaginal GBS carriage, which occurs in approximately 25% of pregnant women, as a primary risk factor for neonatal GBS sepsis and demonstrated the efficacy of intrapartum antibiotic prophylaxis (IAP) for prevention of EOD [7–9]. Currently, the Centers for Disease Control and Prevention guidelines advise routine screening of pregnant women for GBS colonization in late pregnancy and provision of IAP to carriers

[10]. This strategy has led to a significant decrease in EOD rates in the United States, from approximately 1.8/1000 live births in the pre-IAP time period to 0.22/1000 in 2016 [10, 11]. Unfortunately, LOD rates have not decreased over the same period, and LOD now represents the most common presentation of neonatal GBS disease, occurring in 0.25/1000 live births [11]. Worldwide, the burden of GBS disease remains high, with recent estimates of 320 000 cases of neonatal sepsis and 90 000 infant deaths annually [12].

This discrepancy in the effect of culture-based screening and IAP guidelines on early- vs late-onset GBS sepsis suggests key differences in mechanisms of pathogenesis between the 2 clinical entities. In contrast to EOD, which most commonly presents as isolated GBS bacteremia and sepsis, meningitis is a frequent component of LOD, leading to neurodevelopmental impairment in >30% of cases [13]. Premature birth and maternal rectovaginal GBS colonization are important risk factors for LOD [14]. There are 10 known GBS capsular serotypes (Ia, Ib, II–IX). The distribution of serotypes that cause EOD approximates that detected in maternal vaginorectal colonization, though most studies find more serotype III among EOD than colonization isolates [15–17]. In contrast, LOD is characterized by a marked overrepresentation of serotype III strains, particularly those belonging to clonal complex (CC) 17 [16, 17]. The emergence of human pathogenic GBS clones, including this "hypervirulent" CC17

lineage, has been linked to population-level use of tetracycline antibiotics starting in the late 1940s [18], but we still do not understand what accounts for the remarkable success of CC17, serotype III GBS as a LOD pathogen.

A detailed understanding of LOD pathogenesis remains elusive, but the most frequently postulated mechanism involves asymptomatic colonization of the infant gastrointestinal tract followed by delayed invasion through tight junctions of the gastrointestinal epithelium, with subsequent seeding of the bloodstream and penetration of the blood–brain barrier [19–21]. Important questions regarding LOD pathogenesis remain unanswered.

Why are premature infants disproportionately affected by LOD? While most cases of LOD occur in term infants, the attack rate is substantially increased in the setting of prematurity due to incompletely characterized host factors [14, 22].

Why are CC17 strains vastly overrepresented in LOD? Studies based on in vitro and animal model data suggest that the presence of the hypervirulent GBS adhesin (HvgA) may be a major factor in translocation across the gut mucosa and invasion of the blood–brain barrier, though other CC17 surface proteins and mutations in regulatory pathways may also be relevant to pathogenesis [21, 23, 24].

What are the relative contributions of perinatal and postnatal GBS exposure, including breast milk, to LOD pathogenesis? Nursery and neonatal intensive care unit outbreaks of GBS sepsis as well as synchronous recurrence cases suggest

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that postnatal exposure is sufficient to trigger LOD, but the majority of cases are sporadic [25–28]. In addition, robust longitudinal sampling studies are rare, making specific conclusions regarding the timing of exposure and disease onset difficult.

What is the role of anticapsular antibody in protection against LOD? A role for protein-polysaccharide conjugate GBS vaccines in prevention of both EOD and LOD has been proposed, and such vaccines are in clinical trials [29, 30]. Serologic correlates of protection against EOD caused by some GBS serotypes (including III) have been described [15, 31]. However, it remains unknown whether vaccine-induced anticapsular antibodies can either provide protection against LOD or significantly impact maternal GBS carriage, though a recent publication suggests that conjugate vaccines may delay new acquisition of serotype III GBS colonization [32]. In addition, capsular switching by CC17 GBS due to acquisition of a chromosomal region, including the *cps* operon from nonserotype III strains, has been described and may pose challenges to real-world effectiveness of conjugate vaccines that target a limited number of serotypes [33–35]. The clinical importance of such capsule switch strains has not been fully defined and may depend on the specific role of the type III capsule in the hypervirulent phenotype of CC17 GBS.

In this issue of *Clinical Infectious Diseases*, Tazi and colleagues present data from a longitudinal, multicenter, cohort study in which they examined predictors of GBS colonization in infants born to GBS-colonized women in France.[36] The cohort was large compared to many prior studies of GBS acquisition (890 mother–baby dyads), and longitudinal sampling of both mothers and infants is a major strength of the study design. Consistent with findings from prior studies, the investigators found that receipt of adequate (>4 hours) IAP was associated with lower rates of GBS colonization of the infant in the peripartum period [37–39]. Notably,

CC17 GBS strains were no more likely than other GBS to transmit at the time of delivery. Although only 7% of infants were colonized at delivery, delayed GBS colonization was common in the cohort, with 32% of infants demonstrating colonization at either the early (day 21) or late (day 60) follow-up time point. New detection of GBS colonization following initial negative testing may involve peripartum transmission at initial bacterial densities too low to be reliably detected in the setting of IAP, which the majority of the cohort received, or postnatal acquisition from maternal or nonmaternal sources. At later time points, such horizontal transmission may be the more important mechanism. New acquisition at day 60 was significantly more common for CC17 GBS than for non-CC17 strains, consistent with the hypothesis that CC17 isolates may have an enhanced ability to establish and maintain colonization in older infants following nonperinatal exposure. This observation suggests another potential factor that may contribute to the overrepresentation of CC17 strains in LOD.

Constraints of the study design, many of which are pointed out by the authors in their discussion, limit the conclusions that can be drawn based on these data alone. The cohort was made up nearly exclusively of women who delivered at or near term, with a mean gestational age of 40 weeks and approximately 1% of deliveries occurring prior to 37 weeks. This factor is particularly notable because of the increased relevance of LOD in the preterm population. However, as a study of colonization and transmission dynamics rather than LOD pathogenesis, the data remain applicable. As might be expected from the cohort size and the use of IAP, no enrolled infants developed neonatal sepsis due to GBS. Consistent with clinical practice at the centers where patients were enrolled, only vaginal (rather than rectovaginal) colonization was assessed, likely leading to failure to identify some colonized women [40]. Some factors, such as breast milk colonization with GBS, are

difficult to interpret in the context of the study, as milk may be seeded as the result of contact with the infant's colonized oral mucosa or (as has been hypothesized by several groups) the breast milk itself may act as a vehicle of transmission to the infant [37, 41]. Likewise, the involvement of GBS transmission from nonmaternal contacts was not assessed and may be particularly relevant to new acquisition of colonization at later time points. Despite these limitations, this work provides a major extension of available knowledge by identifying enhanced postnatal transmission as a candidate mechanism for CC17 pathogenesis, opening new areas of investigation to better understand and prevent LOD.

Notes

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References

1. Lancefield RC. A serological differentiation of human and other groups of hemolytic streptococci. *J Exp Med* 1933; 57:571–95.
2. Lancefield RC, Hare R. The serological differentiation of pathogenic and non-pathogenic strains of hemolytic streptococci from parturient women. *J Exp Med* 1935; 61:335–49.
3. Eickhoff TC, Klein JO, Daly AK, Ingall D, Finland M. Neonatal sepsis and other infections due to group B beta-hemolytic streptococci. *N Engl J Med* 1964; 271:1221–8.
4. Hood M, Janney A, Dameron G. Beta hemolytic streptococcus group B associated with problems of the perinatal period. *Am J Obstet Gynecol* 1961; 82:809–18.
5. Nyhan WL, Fousek MD. Septicemia of the newborn. *Pediatrics* 1958; 22:268–78.
6. Fry RM. Fatal infections by haemolytic streptococcus group B. *Lancet* 1938; 231:199–201.
7. Allardice JG, Baskett TE, Seshia MM, Bowman N, Malazdrewicz R. Perinatal group B streptococcal colonization and infection. *Am J Obstet Gynecol* 1982; 142:617–20.
8. Baker CJ, Barrett FF. Transmission of group B streptococci among parturient women and their neonates. *J Pediatr* 1973; 83:919–25.
9. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. *N Engl J Med* 1986; 314:1665–9.

10. Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep* **2010**; 59:1–36.
11. Centers for Disease Control and Prevention. Active bacterial core surveillance report, emerging infections program network, group B streptococcus, 2016. Available at: <https://www.cdc.gov/abcs/reports-findings/surveports/gbs16.html>. Accessed 01 January 2019.
12. Seale AC, Bianchi-Jassir F, Russell NJ, et al. Estimates of the burden of group B streptococcal disease worldwide for pregnant women, stillbirths, and children. *Clin Infect Dis* **2017**; 65:200–19.
13. Kohli-Lynch M, Russell NJ, Seale AC, et al. Neurodevelopmental impairment in children after group B streptococcal disease worldwide: systematic review and meta-analyses. *Clin Infect Dis* **2017**; 65:190–9.
14. Lin FY, Weisman LE, Troendle J, Adams K. Prematurity is the major risk factor for late-onset group B streptococcus disease. *J Infect Dis* **2003**; 188:267–71.
15. Fabbrini M, Rigat F, Rinaudo CD, et al. The protective value of maternal group B streptococcus antibodies: quantitative and functional analysis of naturally acquired responses to capsular polysaccharides and pilus proteins in European maternal sera. *Clin Infect Dis* **2016**; 63:746–53.
16. Madzivhandila M, Adrian PV, Cutland CL, Kuwanda L, Schrag SJ, Madhi SA. Serotype distribution and invasive potential of group B streptococcus isolates causing disease in infants and colonizing maternal-newborn dyads. *PLoS One* **2011**; 6:e17861.
17. Seale AC, Koech AC, Sheppard AE, et al. Maternal colonization with *Streptococcus agalactiae* and associated stillbirth and neonatal disease in coastal Kenya. *Nat Microbiol* **2016**; 1:16067.
18. Da Cunha V, Davies MR, Douarre PE, et al; DEVANI Consortium. *Streptococcus agalactiae* clones infecting humans were selected and fixed through the extensive use of tetracycline. *Nat Commun* **2014**; 5:4544.
19. Carl MA, Ndao IM, Springman AC, et al. Sepsis from the gut: the enteric habitat of bacteria that cause late-onset neonatal bloodstream infections. *Clin Infect Dis* **2014**; 58:1211–8.
20. Doran KS, Engelson EJ, Khosravi A, et al. Blood-brain barrier invasion by group B streptococcus depends upon proper cell-surface anchoring of lipoteichoic acid. *J Clin Invest* **2005**; 115:2499–507.
21. Tazi A, Disson O, Bellais S, et al. The surface protein HvgA mediates group B streptococcus hypervirulence and meningeal tropism in neonates. *J Exp Med* **2010**; 207:2313–22.
22. Korir ML, Manning SD, Davies HD. Intrinsic maturational neonatal immune deficiencies and susceptibility to group B streptococcus infection. *Clin Microbiol Rev* **2017**; 30:973–89.
23. Almeida A, Rosinski-Chupin I, Plainvert C, et al. Parallel evolution of group B streptococcus hypervirulent clonal complex 17 unveils new pathoadaptive mutations. *mSystems* **2017**; 2:e00074–17.
24. Lentini G, Midiri A, Firon A, et al. The plasminogen binding protein PbsP is required for brain invasion by hypervirulent CC17 group B streptococci. *Sci Rep* **2018**; 8:14322.
25. Berardi A, Guidotti I, Creti R, et al. Two overlapping clusters of group B streptococcus late-onset disease in a neonatal intensive care unit. *Pediatr Infect Dis J* **2018**; 37:1160–4.
26. Berardi A, Rossi C, Lugli L, et al. Group B streptococcus late-onset disease: 2003–2010. *Pediatrics* **2013**; 131:e361–8.
27. Elling R, Hufnagel M, de Zoysa A, et al. Synchronous recurrence of group B streptococcal late-onset sepsis in twins. *Pediatrics* **2014**; 133:e1388–91.
28. Jauneikaite E, Kapatai G, Davies F, et al. Serial clustering of late-onset group B streptococcal infections in the neonatal unit: a genomic re-evaluation of causality. *Clin Infect Dis* **2018**; 67:854–60.
29. Kobayashi M, Vekemans J, Baker CJ, Ratner AJ, Le Doare K, Schrag SJ. Group B streptococcus vaccine development: present status and future considerations, with emphasis on perspectives for low and middle income countries. *F1000Res* **2016**; 5:2355.
30. A phase 1/2, randomized, placebo-controlled, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of a multivalent group B streptococcus vaccine in healthy nonpregnant women and pregnant women 18 to 40 years of age and their infants. Available at: <https://clinicaltrials.gov/ct2/show/NCT03765073>. Accessed 1 Jan 2019.
31. Baker CJ, Carey VJ, Rensch MA, et al. Maternal antibody at delivery protects neonates from early onset group B streptococcal disease. *J Infect Dis* **2014**; 209:781–8.
32. Hillier SL, Ferrieri P, Edwards MS, et al. A phase II randomized, control trial of group B streptococcus (GBS) type III capsular polysaccharide-tetanus toxoid (GBS III-TT) vaccine to prevent vaginal colonization with GBS III. *Clin Infect Dis* **2018**. doi: 10.1093/cid/ciy838.
33. Bellais S, Six A, Fouet A, et al. Capsular switching in group B streptococcus CC17 hypervirulent clone: a future challenge for polysaccharide vaccine development. *J Infect Dis* **2012**; 206:1745–52.
34. Luan SL, Granlund M, Sellin M, Lagergård T, Spratt BG, Norgren M. Multilocus sequence typing of Swedish invasive group B streptococcus isolates indicates a neonatally associated genetic lineage and capsule switching. *J Clin Microbiol* **2005**; 43:3727–33.
35. Teatero S, McGeer A, Low DE, et al. Characterization of invasive group B streptococcus strains from the greater Toronto area, Canada. *J Clin Microbiol* **2014**; 52:1441–7.
36. Tazi A, Plainvert C, Anselem O, et al. Risk factors for infant colonization by hypervirulent CC17 group B streptococcus: toward the understanding of late-onset disease. *Clin Infect Dis* **2019**; 68:2079–86.
37. Berardi A, Rossi C, Creti R, et al. Group B streptococcal colonization in 160 mother-baby pairs: a prospective cohort study. *J Pediatr* **2013**; 163:1099–104.e1.
38. Berardi A, Rossi C, Guidotti I, et al. Factors associated with intrapartum transmission of group B streptococcus. *Pediatr Infect Dis J* **2014**; 33:1211–5.
39. Toyofuku M, Morozumi M, Hida M, et al. Effects of intrapartum antibiotic prophylaxis on neonatal acquisition of group B streptococci. *J Pediatr* **2017**; 190:169–73.e1.
40. Russell NJ, Seale AC, O'Driscoll M, et al; GBS Maternal Colonization Investigator Group. Maternal colonization with group B streptococcus and serotype distribution worldwide: systematic review and meta-analyses. *Clin Infect Dis* **2017**; 65:100–11.
41. Filleron A, Lombard F, Jacquot A, et al. Group B streptococci in milk and late neonatal infections: an analysis of cases in the literature. *Arch Dis Child Fetal Neonatal Ed* **2014**; 99:F41–7.