Group B *Streptococcus* Late-onset Neonatal Disease

An Update in Management and Prevention

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Group B *Streptococcus* (GBS), also known as *Streptococcus agalactiae*, colonizes the vagina or vaginal/rectal (VR) sites of 10%–30% of pregnant women. GBS is a major cause of neonatal and infant infections with high mortality and morbidity rates, including late-onset neonatal disease (LOGBS), the disease occurring at 7 to 89 days after birth.[1,2] Based on capsular polysaccharides, 10 GBS serotypes are identified (Ia, Ib II–IX). Serotypes Ia, Ib, II, III, IV and V are the most prevalent, with serotype III accounting for most cases (56%) of LOGBS.[3] LOGBS incidence is currently estimated at 0.28 to 0.31 per 1000 infants in the United States, unaffected by the widespread use of intrapartum antibiotic prophylaxis (IAP) to prevent early-onset sepsis.[1,2]

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MODES OF TRANSMISSION AND RISK FACTORS

The incubation period in LOGBS is unknown and transmission routes are poorly understood.[2]

GBS can be acquired from the mother, both perinatally and postnatally, and maternal colonization is a major risk factor (RF).[4] LOGBS can result from neonatal colonization acquired during passage through the birth canal and colonization can be confirmed up to one year of age.[5] A seminal study showed that 48% of infants were colonized at birth with the same GBS serotype that subsequently caused LOGBS.[6] In a case-control study, infants of mothers with a GBS positive screening had an odds ratio of 4.15 (95% CI, 1.27–13.60) for LOGBS.[7] However, vertical transmission presumably does not account for all cases of LOGBS, since IAP (which is known to prevent early colonization at birth) had no effects on incidence rates of LOGBS.[2] IAP may delay LOGBS onset or perhaps reduce its severity, probably by preventing early neonatal colonization at birth and shifting the mode of acquisition of GBS from vertical to horizontal[8]: IAP does not eradicate colonization in the mother, who may therefore remain a postnatal source of GBS.[9]

Although still under debate, GBS-contaminated breast milk (with or without mastitis) has been associated with heavy neonatal colonization[9] and LOGBS.[10] However, most breast-fed infants do not develop LOGBS, since up to 3.5% of breast-feeding mothers carry GBS in their milk.[11] Indeed, human milk oligosaccharides show antimicrobial and antibiofilm activity against GBS, and GBS-specific IgA in milk and colostrum are associated with both increased GBS clearance[12] and reduced risk of LOGBS.[12,13] However, in some cases, no source of LOGBS other than breast milk can be identified.[10,14] Furthermore, compared with the overall risk, higher recurrence rates of LOGBS are reported in infants fed with GBS-contaminated breast milk (25% vs. 0.5%–4.5%).[10,14] Progression to infection after ingestion of GBS-contaminated breast milk has been related to prematurity, high bacterial inoculum and persistent gut colonization.[14]

Approximately in 1/3 of cases, LOGBS is acquired from nonmaternal sources (such as caregivers and healthcare workers). Compared with term neonates, nosocomial transmission of GBS (from nonmaternal sources) is more common in preterm infants who have prolonged hospital stay.[4] Hospital clusters of LOGBS have been associated with crowding, high patient-to-nurse ratio and inadequate disinfection practices.[15] Notably, identification of GBS hospital clusters can be challenging, since long intervals (up to 50 days) between consecutive cases have been reported; hospital stay of affected infants may even not overlap, raising suspicion of

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a potential point source.[15] Indeed, GBS carriage of neonatal intensive care unit staff has also been reported[15]: whether staff carriage could represent a potential source of infection is a highly sensitive topic, which warrants further investigation.

Similar to transmission routes, RFs for LOGBS remain poorly understood. In addition to the aforementioned maternal GBS colonization, established RFs include African race, young maternal age, maternal HIV infection and prematurity.[4] In fact, ≈40% of all LOGBS now affect preterm infants under 37 weeks' gestation, who have case fatality rates roughly twice than full-term infants (7.8% vs. 3.4%).[3]

PREVENTION

Mode of transmission, RFs and prevention strategies are summarized in Table 1.

Vaccination

A promising strategy to reduce antibiotic use and to prevent both early- and late-onset GBS infections is the vaccination of pregnant women in the second or third trimester. By means of transplacental transfer of IgG antibodies, the vaccination would confer a passive immunity protecting infants up to three months of life. Vaccination could be effective also in preventing maternal VR colonization, which is a main RF for LOGBS. However, a vaccination strategy may be less effective in protecting very preterm neonates from LOGBS because the transplacental transfer of antibodies mainly occurs after 34 weeks' gestation.[4]

Trivalent (targeting serotypes Ia, Ib and III) and hexavalent (targeting serotypes Ia, Ib, II, III, IV and V) protein-polysaccharide conjugate vaccine have reached phase 2 clinical trials. Vaccines targeting antigenic surface proteins and pili subunits (highly conserved structures across all GBS serotypes) are in study as an alternative to capsular polysaccharide vaccines. These vaccines may overcome the limited serotype coverage and ideally provide universal protection against GBS.

Table 1. Late-Onset GBS Disease: Routes of Transmission, Risk Factors and Potential Strategies for Prevention

Transmission	Routes and Risk Factors	Supporting (+) and Opposing (–) Data From Previous Studies	Prevention Strategies
Maternal			
Perinatal	Maternal GBS colonization at birth	(+) Case-control study. GBS maternal VR colonization at screening was more common among mothers of LOGBS cases (38% vs. 17%), OR for LOGBS, 4.15 (95% CI, 1.27–13.60).[7]	Maternal vaccination
		(+) Prospective cohort study. Ten of 21 infants with LOGBS were colonized at birth with the same maternal serotype that subsequently caused the neonatal disease.[6]	Probiotic supplementation in pregnant women (*Lactobacillus salivarius*)
		(+) GBS gut colonization in infants can be detected up to 1 yr.[5]	
		(–) LOGBS incidence has been unaffected by the use of IAP.[1]	
Postnatal	Maternal GBS colonization after birth	(+) Prospective cohort study. At the time of LOGBS diagnosis, maternal VR colonization is confirmed in 64% of cases (30 of 47). Mothers of neonates with LOGBS are more likely to be carrying GBS at the time of LOGBS diagnosis than at the time of antenatal screening (n = 13, $p < 0.01$).[8]	Hygiene measures
		(+) Prospective cohort study. IAP does not eradicate GBS colonization in the mother, who remains a source of GBS after delivery: among 70 women exposed to IAP because of GBS positive screening, 54 (77.1%) were confirmed positive at hospital discharge.[9]	Hand washing
		(+) Prospective cohort study. Neonates born to GBS colonized IAP-exposed mothers are less likely to be colonized during hospital stay (5.3% exposed neonates vs. 53.8% unexposed neonates, $p < 0.01$). However, IAP administration is associated with a trend toward delayed neonatal colonization with the same maternal serotype, suggesting a maternal postnatal transmission.[9]	Maternal vaccination
	Breast milk	(+) Review regarding 59 case reports of LOGBS associated with contaminated breast milk: GBS strain isolated in breast milk commonly matches the serotype isolated from the infant. Mastitis was reported in 24 mothers (41%).[10]	Maternal vaccination
		(+) In some LOGBS, no source of GBS other than breast milk can be identified (negative maternal VR swabs, low risk of colonization in the setting of a cesarean section with intact membranes, no nosocomial sources).[10,14]	Breast-feeding whenever possible
		(+) When breast milk is regarded as the cause of LOGBS, recurrence rate is much higher (25%–35%) than overall risk of recurrence (0.5%–4.5%).[10,14]	Screen breast milk for GBS in case of mastitis, premature infants, after a single/recurrent LOGBS (debated)
		(–) Prospective cohort study. GBS yields from breastmilk of 40 (3.5%) of 1132 breast-feeding mothers. The health state of these 40 infants did not deviate from total mean morbidity among other infants.[11]	Stop breast milk temporarily or pasteurize when GBS is contaminated. Attempt to eradicate the breast colonization with rifampicin (7 d) or amoxicillin (7–10 d) (debated)
		(–) Prospective cohort study. Follow-up of 750 mother/infant pairs; noncolonized infants born to colonized mothers and infants who cleared colonization after birth received colostrum with significantly higher GBS-specific IgA ($p < 0.0001$) compared to persistently colonized infants.[12]	Attempt to eradicate the persistent neonatal colonization with rifampicin (7 d) if LOGBS is recurrent (debated)
		(–) Matched case-control study. Among 241 infants, high GBS-specific IgA concentrations in milk reduce by 90% the risk of LOGBS due to serotype Ia and III (≥0.14 and ≥0.32 μg/mL respectively).[13]	

(Continued)

Table 1. (*Continued*.)

Transmission	Routes and Risk Factors	Supporting (+) and Opposing (–) Data From Previous Studies	Prevention Strategies
Nonmaternal			
Community-based	Caregivers		Hygiene measures. Hand washing
	Twins	(+) Increased risk of infection has been reported in the birth mates of a multiple-birth index case.[1]	Close clinical observation of one twin if the other is affected by LOGBS
		(+) Twins share exposition to maternal colonization, community and hospital environment and genetic predisposition. The shared susceptibility to late-onset sepsis in 170 monozygotic and 665 dizygotic twin pairs can be attributed to both genetic factors (49.0%) and residual environmental factors (51%).[4]	Do not give prophylactic antibiotics
Nosocomial	Other patients	(+) Hospital clusters of late-onset sepsis have been associated with crowding, high patient-to-nurse ratio and inadequate disinfection practices.[15]	Standard precautions Prospective surveillance of LOGBS Surveillance of neonatal colonization. Cohort colonized and infected infants with dedicated staff (debated)
	Healthcare workers	(+) In some outbreaks, hospital stay of infants with LOGBS does not overlap, raising suspicion of a potential point source.[15]	Hand hygiene and infection control practices. Sterilization, decontamination and cleaning techniques. Aseptic techniques for invasive procedures
		(+) Evidence of staff GBS carriage (anogenital and throat) as a potential reservoir has been identified in two studies. One study reports that 41% (11/27) of staff members who had direct contact with cases of a cluster were GBS positive, of whom 4 had the same cluster GBS serotype. Another study reported an overall GBS carriage of 34% (18/53) among nursery staff; one month later 4 of 15 infants were colonized with the same GBS bacteriophage type carried by 3 staff members.[15]	Staff colonization surveillance and decolonization (debated)
	Antibiotic exposure and dysbiosis	(+) Case-control study including 122 case patients with LOGBS and 122 controls: with respect to controls, cases were more likely to have been treated with antibiotics after birth (p <.001), prior to LOGBS.[7]	Judicious use of antibiotics Supplement with probiotics (combining *Lactobacillus spp* and *Bifidobacterium spp*)
	Prematurity	(+) GBS disease is more common in preterm infants compared to full- or late-preterm neonates because of the immature immune system and risks of nosocomial transmission.[4] (+) 42% of all LOGBS affect preterm infants <37 wk.[3] (+) Case-control study. The above-mentioned study[7] reports that for each week of decreasing gestation the risk of LOGBS increases by a factor of 1.34 (95% CI, 1.15–1.56).	I.v. GBS-specific hyperimmune Ig (debated)

i.v. indicates intravenous; OR, odds ratio.

Prevention in Twins

Twin pregnancies are associated with higher preterm delivery rates, and prematurity is an important RF for LOGBS. Moreover, twins are exposed to the same maternal genital bacteria, breast milk, nursing care, hospital environments and share genetic susceptibility to infections.[4] Because of increased risks, siblings of a multiple-birth index case with LOGBS should be observed carefully and treated empirically for suspected invasive infection if signs of illness occur.[1] No prophylactic antibiotic treatment is recommended in such cases.

Prevention of Nosocomial Infections

Efforts should focus on developing practices for infection prevention and control, including catheter care, hand hygiene, breast-feeding care and keeping antibiotic usage to a minimum, given their known impact on neonatal gut microbiome. Indeed, early antibiotics are associated with increased risks of sepsis and LOGBS both in term and preterm infants.[7] Although enteric colonization with pathogens causing late-onset sepsis (including GBS) may appear a few days prior to the sepsis and help to predict a subsequent bloodstream infection, routine cultures to detect GBS in patients' stools and surfaces or rifampicin treatment to eradicate mucosal colonization are currently not recommended.[1] Breast-feeding should be encouraged because it promotes the development of a protective gut microbiota against infections. Finally, oral probiotics (namely combinations of *Lactobacillus spp* and *Bifidobacteria*) appear to be a promising strategy for decreasing the risk of late-onset sepsis in preterm infants. Interestingly, oral *Lactobacillus salivarius* seems effective in eradicating GBS VR colonization in pregnant women.

Breast Milk

There is no consensus for the prevention and management of LOGBS associated with contaminated breast milk. Routine screening of breast milk for GBS is not recommended, even when mastitis is present. Some authors do recommend testing breast milk in case of mastitis, in premature infants, after a first episode of LOGBS or in recurrent LOGBS.[10,14] Temporarily ceasing breast-feeding or pasteurization is frequently recommended when breast milk is GBS contaminated.[10] Although not always successful, amoxicillin (for 7–10 days) or rifampicin (for 7 days) has also been given to eradicate maternal breast colonization.[10]

MANAGEMENT

Most LOGBS present with bacteremia without a focus, but meningitis is frequent (≈30% of cases).[3] More rarely, LOGBS affects bones, joints, soft tissues or the urinary tract.[1,2] Notably, some presenting signs (apnea, tachycardia, poor feeding) are common in younger preterm infants and overlap with other disorders. For in-hospital neonates, even a single case should be considered secondary to potential nosocomial transmission: retrospective and prospective surveillance should be enhanced to identify a possible cluster. Blood and cerebrospinal

fluid cultures should be obtained if symptoms develop, and a strict adherence to cardiopulmonary resuscitation guidelines is recommended. First-line interventions for severe sepsis and septic shock include prompt fluid administration; if there is no response to volume filling, inotropes (dopamine, dobutamine, adrenaline) must be infused within 1 hour of onset.

Life-threatening infections require immediate and aggressive use of antimicrobials. For empiric therapy of late-onset sepsis in infants 8 to 28 days of age, ampicillin plus gentamicin is recommended. In case of suspected meningitis, ampicillin plus cefotaxime should be used and recommended dosing of ampicillin is higher.[1] When GBS infection is confirmed, penicillin G (or ampicillin, as an acceptable alternative) is recommended. Despite anecdotal reports of penicillin nonsusceptible GBS strains, beta-lactams remain the antibiotic of choice. Based on expert opinion, 10–14 days of intravenous antibiotics are suggested for sepsis without a focus and uncomplicated meningitis respectively, but longer courses may be required if meningitis complicates (ie, 4 weeks in ventriculitis). Three to 4 weeks are recommended in septic arthritis or osteomyelitis.[1]

Routine administration of polyvalent intravenous immunoglobulin (IVIG) in suspected or proven neonatal infection is not recommended because they have no impact on mortality, death or major disability. In contrast, GBS-specific hyperimmune IVIG could improve the outcome of LOGBS. In animal studies, they enhanced survival even in case of overwhelming neonatal GBS sepsis. In neonates, GBS hyperimmune IVIG (500 mg/kg) increases serum levels of GBS-specific IgG and opsonic activity of sera. However, their effectiveness in preventing LOGBS or improving the neonatal outcome must be confirmed in large trials because currently, firm evidence is lacking. Hyperimmune IVIG would be particularly helpful in early preterm neonates, who could not benefit from maternal vaccination.

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