REVIEW ARTICLE

Group B Streptococcal Infections in Neonates

Kirtikumar Upadhyay[1], Ajay Talati[2]

Abstract

Despite significant advances in preventive and therapeutic approaches, Group B streptococcus (GBS) still remains one of the most common causes of sepsis and meningitis in neonates. There is considerable variability in the immune responses that is related to microbial virulence, bacterial load, and immaturity of immune response system of the host. In this review, the mechanisms of GBS invasion and host–pathogen interactions are described. Understanding the host immune response to various bacterial components of GBS could help in refining our future strategies to mitigate the immune response and improve neonatal outcomes due to GBS sepsis.

Keywords: Antibiotics, Bacterial components, Group B streptococcus, Group B streptococcus immune response, Group B streptococcus vaccine, Host–pathogen, Inflammation.

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Introduction

Group B streptococci (GBS, *Streptococcus agalactiae*) were first reported as a disease-causing pathogen in humans in 1935.[1] These have been identified as a leading cause of early and late sepsis in neonates across the world (Fig. 1).[2–4] GBS are encapsulated Gram-positive bacteria that can colonize the genitourinary and gastrointestinal tracts of 10–30% of healthy women.[5–7] During pregnancy, these bacteria have been implicated as a primary/contributing cause in preterm labor, urinary tract infections, chorioamnionitis, endometritis, pelvic thrombophlebitis, and endocarditis.[8] Data from the Center for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance System, a network of 10 sites across the United States that conducts active, population-based surveillance, show GBS to cause about 1,000 cases of neonatal sepsis/invasive disease per year. About 70% of these cases are full-term infants born at ≥37 weeks' gestation.[9] These microorganisms may sometimes cause serious invasive infections in non-pregnant adults, who are often immunocompromised or elderly with multiple associated morbidities. The total burden of invasive GBS disease in the population is approximately 9.9 per 100,000 with a mortality rate of 0.55 per 100,0000 population.[10]

Maternal colonization with GBS is an important risk factors for neonatal sepsis.[11] The risk of vaginal GBS colonization in women is known to increase in several biological and socioeconomic conditions. The biological risk factors include premature rupture of membranes (PROM), gastrointestinal GBS colonization, and increased maternal age.[12–15] High rates of vaginal carriage have also been associated with specific ethnic groups, obesity, low vitamin D intake, hygiene, sexual activity, specific healthcare occupations, and illiteracy.[13,16–18] The identification of GBS colonization prior to the onset of labor and intrapartum antibiotic prophylaxis is an important preventive strategy for early-onset GBS sepsis.[19] The implementation of these strategies by both the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP)[20] has helped in reducing the incidence of early-onset GBS disease, although the frequency of late-onset GBS disease has not changed. The most recent CDC active bacterial surveillance data show the incidence of late-onset GBS sepsis in the United States to be approximately 0.28 per 1,000 live births. Following widespread implementation of intrapartum antibiotic prophylaxis in 1999, early-onset GBS infections decreased to 0.25/1,000 live births, but mortality continues to be high in premature infants.[20]

In GBS-colonized mothers, bacterial carriage >10 colony-forming units per milliliter have been associated with increased risk of vertical transmission to infants. Vertical transmission from

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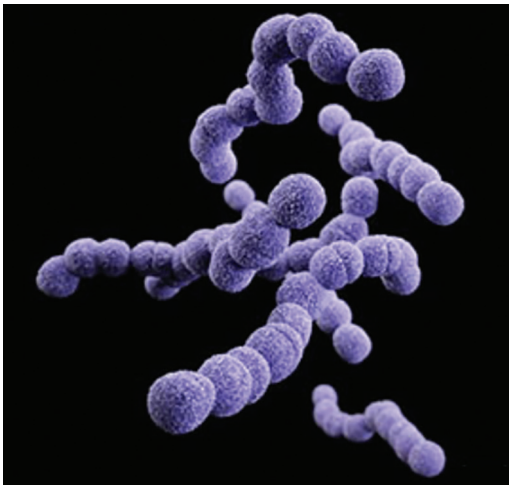


Fig. 1: Group B streptococci

colonized mothers to their neonates is seen in 41–72% of cases (mean 50%). About 1–12% of colonized infants (mean, 5%) are born to non-colonized mothers. The severity of colonization in infants can increase the risk of early- or late-onset GBS disease,[21] which typically presents with pneumonia, bacteremia, meningitis, and sometimes, septic arthritis and osteomyelitis.[7]

Since Austrian and Gold first demonstrated the therapeutic efficacy of penicillin in adults with streptococcal infections more than 50 years ago, GBS still remains the drug of choice for these infections.[22] However, even though timely and successful treatment of maternal GBS infection using ampicillin or penicillin may correct maternal colonization and reduce the risk of neonatal infections, it may not always alter medium/long-term neonatal outcomes.[23,24] These infants need close clinical follow-up after discharge.[25]

GBS Infection

Invasive fetal/neonatal GBS disease begins with the migration of these bacteria across the epithelial barrier in the mucus membranes or the skin. Most infants can successfully control GBS invasion, but some aspirate maternal secretions containing GBS into the lungs. These bacteria can proliferate to enormous densities (10^9–10^{11} colony-forming units per gram lung tissue).[26]

Doran and Nizet[27] have described four stages of fetal GBS infection: (a) adherence of bacteria to the lung mucosa followed by transepithelial migration; (b) proliferation in lung tissue and evasion of local innate immune defenses; (c) migration into the bloodstream, where these circulating bacteria escape elimination by mononuclear phagocytes; and finally (d) widespread dissemination to cause a systemic inflammatory response syndrome.

From the host's perspective, the phagocytic efficiency of innate immune cells such as neutrophils and monocyte/macrophages are important.[28] The ability of these cells to eliminate bacteria without an unduly intense/dysregulated inflammatory response is a key determinant of outcome. These defenses can be studied as host recognition of the pathogens, directed cellular movements (chemotaxis), engulfment (phagocytosis), and finally, the destruction of the microorganism.

Types of GBS and its Disease-causing Components

GBS normally resides as a commensal in maternal genital and lower gastrointestinal tracts but can acquire pathogenic characteristics and infiltrate many tissues following changes in the variable fraction of the genome. The Lancefield classification of GBS is based on the cell wall polysaccharides and describes nine serotypes, including Ia, Ib, and II–VIII.[28] More recently, a serotype IX was added. Type III is frequently seen in GBS meningitis, whereas serotype V is a leading cause of invasive disease in adults.[29,30] Overall, 96% of the invasive GBS infections are caused by serotypes Ia, Ib, and III. The maternal isolates included the serotype variant I (35%), III (21%), Ib (13%), and Ia (11%). Frequent sequence types were ST1 (32%), ST12 (22%), and ST23 (15%).[31] A surface antigen, the C protein with its α and β components, is seen in all Ib, 30% of type Ia, 60% of type II, and in some type IV, V, and VI strains.

Genome analysis of the five major disease-causing capsular serotypes (Ia, Ib, II, III, and V) indicates that there is a "core" genome comprised of nearly 80% of all genes.[32] The remaining 20% of the genome is relatively variable and contains many virulence factors such as pore-forming toxins and the sialic acid–rich capsular polysaccharides, which are involved in adherence and invasion of host cells and evasion of host immunity.[33]

The GBS cell wall is a network of cross-linked peptidoglycans, surface proteins, polyanionic teichoic acid, and lipoteichoic acid. The best-characterized proteins in the cell wall are shown clockwise in Figure 2 and the characterized are summarized in the following.[34] We have also provided brief descriptions of carbohydrates and lipids known to be present in the GBS cell wall.

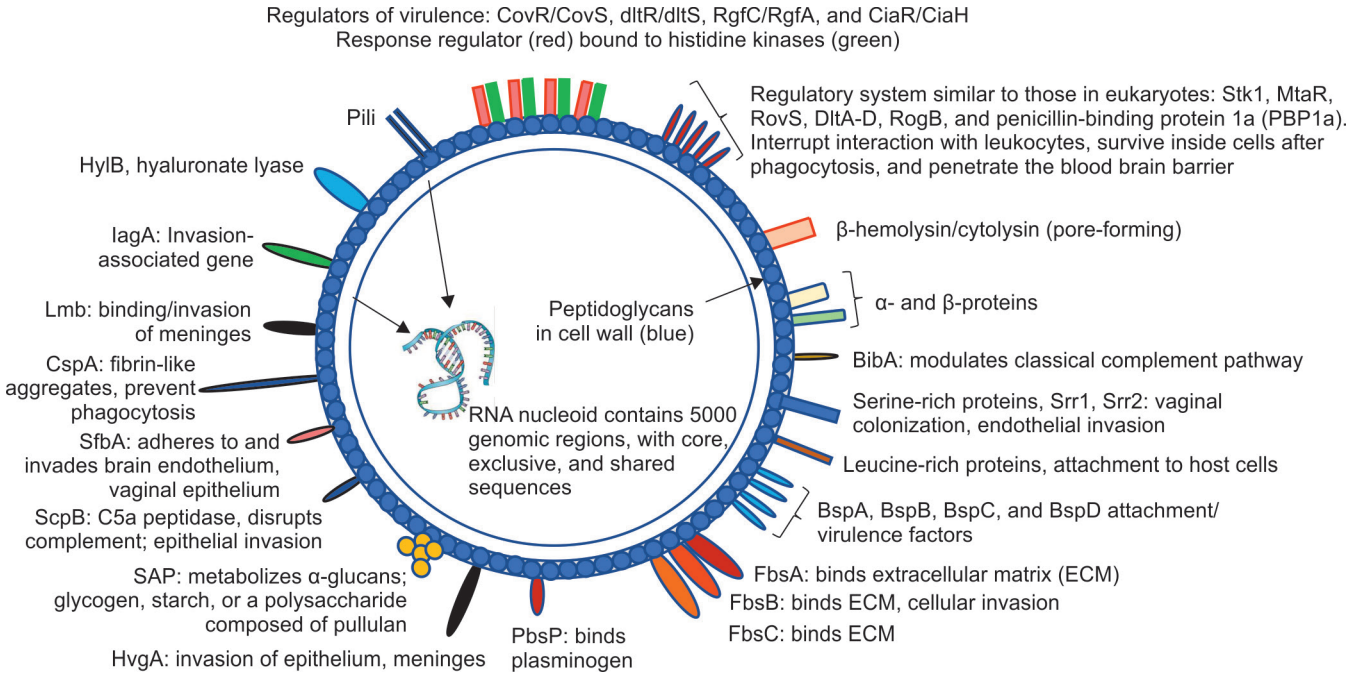


Fig. 2: Best-characterized GBS cell wall proteins involved in its pathogenic effects

Regulatory Signaling Systems

GBS are known to contain up to 107 regulatory signaling systems, 17–20 have been associated with pathogenicity and 4 have been studied closely.[35] These four response regulators CovR, dltR, RgfC, and CiaR stay bound to specific histidine kinases: CovR/CovS, dltR/dltS, RgfC/RgfA, and CiaR/CiaH.[35] Upon exposure to an external signal, the kinases phosphorylate conserved aspartate residue(s) in target proteins to alter the function.

GBS encodes for several regulatory enzymes that resemble those in eukaryotes. One example is the serine-threonine kinase Stk1 and its cognate phosphatase Stp1; the pair regulates the expression of pore-forming toxins.[36] Three other regulators, MtaR, RovS, and RogB have also been identified.[37] MtaR, methionine transport regulator regulates methionine transport/uptake and seems to be critical for GBS survival.[38,39] Another tyrosine kinase, CpsD and its cognate phosphatase, CpsB, are also being investigated; these proteins may be immunization targets.[40]

RovS (regulator of virulence in *S. agalactiae*) can activate superoxide dismutase and detoxify reactive oxygen species (ROS).[37] It is important for the adhesion of GBS to eukaryotic cells and increases the expression of other known and putative virulence genes and of hemolysin.

DltA-D proteins, the RogB protein, penicillin-binding protein 1a (PBP1a), and pilus island proteins PI-2a and PI-2b can modify reactions to other antimicrobial peptides.[37] The fibronectin-binding proteins, (FBP)-A and FBP-B, can also alter GBS adherence to host cells.[41]

Pore-forming toxins such as β-hemolysin/cytolysin (β-H/C, CylE) may trigger host-cell lysis.[42] The toxins are activated by the serine/threonine protein kinase Stk1 through CovR, or directly by CovS. The Christie Atkins Munch Peterson (CAMP) factor Cfb also forms pores in host cell membranes and is activated by CovR/CovS.[43]

Alpha-like proteins (alps) expressed on the bacterial surface bind glycosaminoglycans on epithelial cells and facilitate entry into the host epithelial cells.[44] Alp1 is expressed on serotypes Ia, Ib, and II; alp2 on serotypes Ia, III, and V; and Alp 3 on V and VIII. The Alp family also includes the Rib proteins expressed in type III, several type II, and some type V strains.

Beta proteins on the surface of serotypes Ia, Ib, II, and V can bind (a) the Fc moiety of human IgA and inhibit its function; (b) the complement inhibitor factor H and block phagocytosis; and (c) human Siglec-5, a leukocyte cell-surface receptor, to inhibit phagocytosis, oxidative burst, and extracellular trap production, promoting bacterial survival in the host.[45]

BibA, GBS immunogenic bacterial adhesion protein is a cell wall protein that binds human C4-binding protein (C4BP), a modulator of the complement classical pathway.[46]

Serine-rich repeat (Srr) proteins are a group of cell wall–anchored proteins; the best characterized members are Srr1 and Srr2.[47] Srr1 gets glycosylated and is then displayed on the cell wall in a configuration resistant to proteolysis. Srr1 glycosylation alters binding to epithelium; binding to cytokeratin 4 and keratin promotes attachment to vaginal epithelial cells.

Leucine-rich repeat (LRR) proteins contain leucine-rich repeats and are involved in enzyme inhibition, cell adhesion, trafficking, and signal transduction.[46] These are virulence factors; a leucine-rich repeat protein of GBS (LrrG) promotes attachment of bacterium to host cells.

BspA, BspB, BspC, and BspD, Group B Streptococcus surface proteins encode for four GBS attachment/virulence factors that bind host proteins or other surface components.[46]

FbsA, FbsB, and FbsC, Fibronectin-binding surface proteins are seen in nearly all serotypes with variable number of repeats.[41] These adhesins promote attachment to epithelial cells and protect against opsonophagocytosis. There may be a variable degree of binding to fibrinogen and platelets. FbsA may activate TLR2. FbsC contains immunoglobulin-like tandem repeats, which might promote attachment to epithelial cells.[48]

PbsP, plasminogen-binding surface protein is a cell wall–anchored serotype III protein expressed in some concentrations by almost all clinical GBS isolates. It binds/activates plasminogen.[49]

HvgA, hypervirulent GBS adhesin is seen in the hypervirulent GBS clone ST-17 associated with severe late-onset disease.[50] GBS strains expressing HvgA adhere avidly to epithelial and blood-brain barrier endothelial cells.

SAP, S. agalactiae pullulanase: SAP metabolizes α-glucans.[51] It can degrade glycogen, starch, or a α-glucan polysaccharide composed of repeating maltotriosyl units known as pullulan.[52] Sap is a conserved protein comprised of five conserved domains: (a) an N1 unit encoding two carbohydrate-binding motifs; (b) N2 pullunase unit; (c) N3 isoamylase; (d) a glycoside hydrolase; and (e) a C-terminal β-sandwich domain.

ScpB, Streptococcal C5a peptidase B is expressed in all GBS serotypes and functions as a surface protease and adhesin/invasin.[53] Some naturally occurring variants maintain the ability to interact with fibronectin by inhibiting C5 peptidase function.

SfbA, Streptococcal fibronectin binding adhesin binds and invades the microvascular endothelial cells in the brain. It also contributes to GBS invasion of vaginal and cervical epithelium and hence may take part in GBS niche establishment in the vagina.

CspA, cell surface-associated protein A is expressed in highly virulent type III GBS isolates.[54] It promotes the formation of fibrin-like aggregates and protects these bacteria from phagocytosis by neutrophils. It can also inactivate CXC chemokines to block leukocyte chemotaxis.

Lmb, laminin-binding protein promotes GBS adherence to host cells.[55] It binds the extracellular matrix and is an important determinant of pathogenicity.

Invasion-associated gene (*iagA*) contributes to GBS meningeal infection and virulence by facilitating invasion of blood-brain barrier and other host cells. The gene product is a glycolipid anchor for lipoteichoic acid and interacts directly with host cells.[56]

HylB, hyaluronate lyase cleaves hyaluronan and promotes spread of GBS during infection.[57] Both bacterial hyaluronan and hyaluronan lyases play a role.

Pilus island proteins (PI-2a and PI-2b): These proteins can alter the reaction to other antimicrobial peptides.[58,59]

Capsular Polysaccharides

Capsular polysaccharides contribute to GBS virulence by interfering with C3 opsonization through inhibition of the alternative complement pathway in the absence of type-specific capsule antibodies.[60,61] Group-specific GBS polysaccharides seem to be more potent inflammatory stimuli than the type-specific ones.[27,62] Both categories are covalently linked to peptidoglycans and, possibly, to other cell wall components of GBS. Sialylation of these polysaccharides can help immune evasion through molecular mimicry of glycoconjugates on the host cell surface.[63] Sialylation can also prevent opsonophagocytosis through inhibition of alternative complement pathway activation.

Capsular Lipids: GBS produce a pigmented, cytotoxic lipid, known as granadaene (ornithine *rhamnopolyene)*, which confers

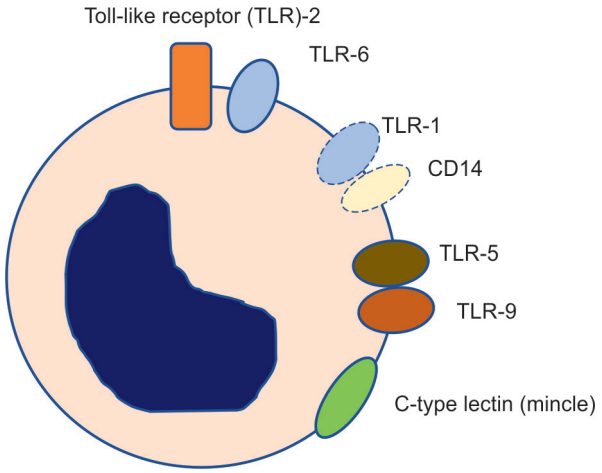


Fig. 3: Cell surface receptors that may play a role in recognition of GBS and induction of downstream signaling

pigmentation and hemolytic activity, and is a major contributor to most of the inflammatory manifestations of GBS disease. Hemolytic and hyper-hemolytic GBS strains are associated with increased virulence.[64]

Host Recognition of GBS

The innate immune system may utilize several receptor systems in timely recognition of GBS and the induction of appropriate local/systemic defense responses (Fig. 3). Toll-like receptors 2 (TLR2) are the primary pattern-recognition receptors (PRRs).[65,66] GBS shows sialic acid O-acetylation, and therefore, C-type lectin receptors (mincle) also merit investigation. However, nucleotide-binding oligomerization domain-containing receptors (NLRs) may not play a major role in GBS immunity. At the cellular level, the innate immune system is comprised of monocytes, granulocytes, macrophages, and the complement system. In a healthy host, targeted local immune responses destroy invading bacteria without undue inflammation. However, if the local immunity is inadequate, a systemic inflammatory response syndrome may be seen.[67]

TLR-2 and its analogues are membrane-spanning, non-catalytic PRRs that are most highly expressed in sentinel cells, such as macrophages and dendritic cells.[68] These receptors, in conjunction with TLR6, bind GBS peptidoglycans and lipoteichoic acid. The binding may be stronger to secreted components of GBS components than to those present in the bacterial cell wall.[69] There may also be some species differences. In human cells, but not in mice, lipoteichoic acid–mediated TLR2 activation may involve CD14 and TLR1.[70,71] In conjunction with TLR6 or TLR1, TLR2 can recognize bacterial products, such as peptidoglycan, lipoproteins, capsular polysaccharide, and glycolipids.[72] TLR5 and TLR9 can bind bacterial flagellin and bacterial DNA, respectively.[73]

TLRs typically contain an extracellular leucine-rich repeat domain that binds specific pathogen-associated molecular patterns, and adaptors containing an intracellular Toll/IL-1R (TIR) domain that can activate downstream signaling. MyD88 is one of the best known of these adaptors; it recruits IL-1R-associated kinase (IRAK), followed by the tumor necrosis factor (TNF) receptor–associated factor 6 (TRAF6). The activation of TGF-β-activated kinase (TAK1) and downstream signaling stimulates mitogen-activated protein kinases (MAPKs) and the nuclear factor-kappa B (NF-κB). These events stimulate the expression of inflammatory cytokines/chemokines.[74]

TLR2 and MyD88 play a synergistic defense role against GBS.[75] TLR2 can activate cytokine responses to extracellular products of GBS, although this does not happen upon exposure to whole bacteria. MyD88 can activate inflammation upon exposure to both types of stimuli.[76] MyD88 and downstream IRAK1 stimulate the protein kinase D1 (PKD1) and related inflammatory mediators, such as the mitogen-activated protein (MAP) kinases, p38 and c-Jun kinase (JNK), and the transcription factors NF-κB and activator protein 1.[77] Kenzel et al.[65] showed that JNK evokes cytokine expression by activating AP-1 and NF-κB. Human studies have confirmed elevated plasma interleukin (IL)-1 and CXC ligand/IL-8 concentrations (57). GBS-infected neonates develop systemic inflammation with increased TNF and IL-1.[75] In contrast, for unclear reasons, purified TLR2 and -4 do not consistently activate cord blood mononuclear cells to the same extent.[78–81]

TLR8, an endosomal sensor of RNA degradation products, can sense GBS and activate the interferon regulatory factor 5 (IRF5) to increase the expression of interferon-β, IL-12p70, TNF, and IL-12. TLR8 activates IRAK-1, by forming a Myddosome, filamentous structures composed of MyD88 oligomers.[82] TLR9 binds CpG DNA and can play an important role in macrophage expression of TNF, IL-6, and IL-12 upon exposure to GBS. This pathway may not be so important to upregulate NO, iNOS, or IFN-β production.[83]

To summarize, TLR-2 is the key receptor for detecting GBS. TLR6 and TLR1 can assist in detecting bacterial products, such as peptidoglycan, lipoproteins, capsular polysaccharide, and glycolipids.[72] TLR5 can bind bacterial flagellin. TLR8 and TLR9 might play important roles in the detection of bacterial RNA and DNA, respectively.

Fetal/Neonatal Adaptive Immune System

The fetal adaptive immune system is relatively immature due to the limited exposure to antigens *in utero*.[84,85] Transplacentally acquired maternal anti-GBS antibodies provide some protection prior to and after birth. *In vitro*, maternal anti-capsular IgG concentrations >1 μg/mL mediated GBS killing and were predicted to reduce the risk of early-onset GBS Ia and III disease by 81% [95% confidence interval (CI): 40–100%] and 78% (95% CI: 45–100%), respectively.[86] In other studies, infants born to mothers with anti-GBS type III IgG antibody ≥10 μg/mL has a 91% lower risk for early-onset disease than those born to mothers with levels <2 μg/mL.[87] Infants with GBS sepsis had lower levels of antibodies against the capsular polysaccharide than those who were recently colonized with these bacteria, suggesting that these antibodies are rapidly consumed.[88] The neonatal adaptive immune system took a few weeks to start functioning with synthesis of immunoglobulin G and expansion of the appropriate V_H gene repertoire.[89] GBS rapidly activated NK cells in the innate immune response to encapsulated bacterial infection by inducing the release of IFN-γ.[90]

Both the maternal and fetal immune systems show a bias toward producing T helper-2 (T_H2)-cell-polarizing cytokines.[91] After birth, the neonatal immune responses can rapidly shift toward a T_H1 prominent proinflammatory cytokine response following exposure to certain antigens,[67,92] although there is some evidence that infections such as those with GBS can overwhelm these changes and suppress such rise in T_H1-polarizing cytokines.[93] GBS infections can bias the Th differentiation program of neonatal $CD4^+$ T cells and promote proinflammatory Th1 and Th17 phenotypes in Tregs. GBS-stimulated neonatal neutrophils may drive proinflammatory T-helper (Th) cell programming. GBS-stimulated neonatal

neutrophils can also induce the expression of the canonical nuclear transcription factors for Th1 (Tbet) and Th17 (IL-17) cells in $CD4^+$ T cells. These activated neutrophils and neutrophil-derived mediators can also alter the Tregs to acquire Th1 and Th17 characteristics.[94]

Immunity or Inflammation: Host Responses to GBS

The elimination of GBS from tissues and the bloodstream involves a sequence of events, where resident macrophages, monocytes, and circulating neutrophils recognize the pathogen, release cytokines to activate peers in the vicinity, chemokines to recruit other circulating phagocytes, and finally, to promote phagocytosis and killing of the pathogens that have been internalized or are in close vicinity.[82] Many of these events are not fully matured in newborn infants.

Chemotaxis is focused leukocyte movement that is directed toward pathogens or their components. It is often still immature in preterm and term neonates; possible reasons may involve lower total neutrophil cell mass and sFcRIII concentration;[34] poor rolling and adhesion to endothelium due to less L-selectin expression,[60,61] inefficient formation of lamellipodia, and/or reduced movement toward stimulus.[62] Neutrophils exposed to GBS recruit peer phagocytes by releasing/expressing chemokines, such as CXC ligand 8/interleukin-8 and its analogues, leukotriene B4, and complement factors C3b and C5a.[69] To counteract the concentration gradients of these factors, GBS express a C5a peptidase on its surface that contributes to immune evasion by reducing chemoattractant C5a.[70]

Phagocytosis involves recognition of the pathogen by cell surface receptors, actin polymerization under the membrane at the site of contact, and the formation of actin-rich membrane extensions to engulf the pathogen. The phagosome matures via a series of membrane fusion and fission events and eventually fuses with a proximate lysosome to become a phagolysosome. This phagolysosome is an acidic, hydrolytic compartment in which the pathogen is killed and digested in preparation for antigen presentation.[95]

In the lungs, resident macrophages are the first to encounter newly aspirated GBS, and neutrophils are recruited to enhance the protective responses. Unfortunately, both macrophages and neutrophils in neonates seem to be less efficient in killing GBS. The TLR2 receptors are not particularly important because wild-type and genetically altered macrophages lacking TLRs or MyD88 internalize GBS at similar speeds.[95] The chronological age is important; the efficiency of phagocytosis is low in preterm infants and increases with development (64). These findings may be explained by the requirement for the CD11b/CD18 (Mac-1) receptor and opsonization with complement.[96,97] Neonatal neutrophils also contain less lysozyme.[98] Reactive oxygen species are critical for killing of GBS;[99] neutrophils from very-low-birth weight (VLBW) infants show a less-intense intracellular oxidative burst than in those from older subjects.[100] GBS possess a Mn-cofactored superoxide dismutase that serves as a virulence factor by counteracting intracellular killing in macrophages.[101]

Animal models of GBS sepsis and meningitis show an intense, dysregulated inflammatory response. There is excessive production of inflammatory mediators, especially TNF and nitric oxide (NO), which have been associated with more severe disease and increased mortality.[102–104] Excessive NO during sepsis appears to be largely responsible for the refractory hypotension that is seen in septic shock.[102] Indeed, the clinical symptoms of GBS sepsis are related to the host–pathogen interaction and cytokine production during the process.

Early- and Late-onset GBS

Early-onset disease begins within the first 6 days after birth.[105] However, most infants (61–95%) become symptomatic within the first 24 hours (median, 1 hour). The most frequent presentation is with respiratory distress, apnea, tachypnea, grunting respirations, and cyanosis. Many patients may show lethargy, poor feeding, abdominal distention, pallor, jaundice, tachycardia, and hypotension. Term infants may be febrile, although preterm infants may be hypothermic.

Bacteremia is the most common form of early-onset GBS disease, accounting for approximately 80% of cases. Pneumonia and meningitis, although not uncommon, are less likely presentations in early-onset disease, accounting for 15% and 5–10%, respectively.

Late-onset disease is defined as GBS infections manifesting between postnatal days 7–89 (median 37 days). The clinical presentation resembles early-onset disease.[105] Bloodstream infections remain the most common presentation of the late-onset disease. However, meningitis occurs in about 30% of cases, as opposed to 5% in early-onset disease.

Late-onset disease may also present with focal diseases, such as osteomyelitis, pyogenic arthritis, and cellulitis-adenitis syndrome.[106] The proximal humerus is frequently affected in infants with osteomyelitis, whereas pyogenic arthritis typically affects the hip and/or knee joints. GBS cellulitis-adenitis syndrome is generally unilateral, involving facial or submandibular sites. It can also involve inguinal, scrotal, and prepatellar regions. The cellulitis-adenitis syndrome presents with swelling of the affected area and local lymphadenopathy. Aspiration of the affected area of cellulitis can yield GBS. Blood cultures can be positive.

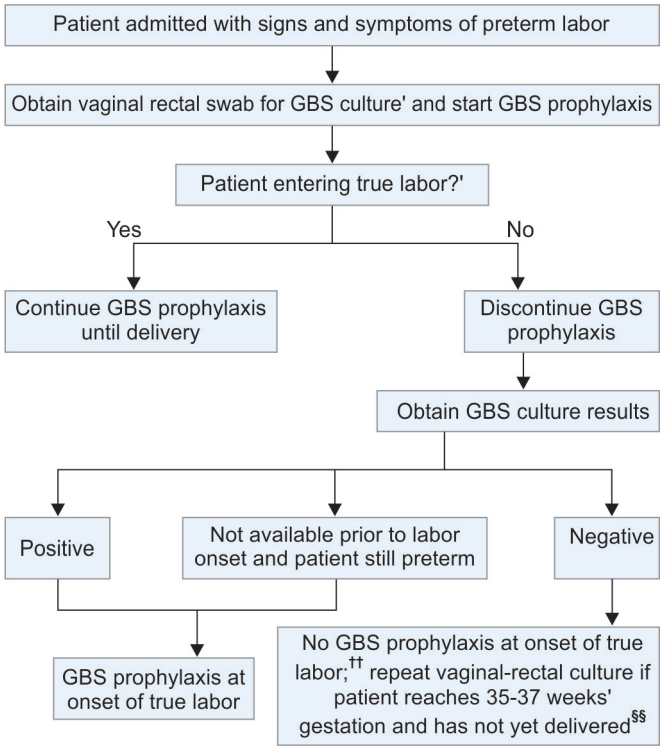
Delayed late-onset GBS disease manifests after 3 months following birth. Most cases occur in premature/VLBW infants. In term infants, delayed late-onset GBS disease can be associated with HIV infection or immunodeficiency. The clinical manifestations are similar to those in patients with typical late-onset infections; bacteremia without a focus and meningitis are the most common clinical features.[21]

Intrapartum Antibiotic Prophylaxis

The US CDC recommend universal screening of pregnant women for vaginorectal colonization in weeks 35–37 of gestation and intrapartum (intravenous) antibiotic prophylaxis (IAP) to GBS-positive mothers (Flowcharts 1 and 2). IAP can reduce vaginal colonization with GBS to 47% within 2 hours of administration and 12% after 4 hours of administration.[107] It also reduces the likelihood of neonatal colonization.[107–109] Importantly, the maternal vaginal flora, including GBS, does not appear to develop selective antibiotic resistance after IAP.[110]

IAP has lowered the incidence of early-onset neonatal GBS sepsis. The possibility of negative effects of IAP including increased infections with Gram-negative bacteria, such as ampicillin-resistant *Escherichia coli* remains unclear.[104,111] A recent epidemiological study found increased late-onset GBS disease during the periods 1997–2001 and 2002–2010, but we do not know if these shifts reflected changes GBS pathogenicity, increased survival of preterm infants, or delay in disease onset from IAP.[112] Some data suggest that maternal vaginal flora may be altered due to IAP with increased susceptibility of both the mother and the child to fungal infections during the postpartum period. Infants born to women treated with antibiotics for spontaneous preterm labor showed increased

Flowchart 1: Algorithm for GBS intrapartum prophylaxis for women with preterm labor



*At <37 weeks and 0 days' gestation; †If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative; Patient should be regularly assessed for progression to true labor; if the patient is considered not to be in true labor, discontinue GBS prophylaxis; **If GBS culture results become available prior to delivery and are negative, then discontinue GBS prophylaxis; ††Unless subsequent GBS culture prior to delivery is positive; §§A negative GBS screen is considered valid for 5 weeks. If a patient with a history of PTL is re-admitted with signs and symptoms of PTL and had a negative GBS screen >5 weeks prior, she should be rescreened and managed according to this algorithm at that time (From: 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(RR-10):22. PMID: 21088663.)

risk of cerebral palsy.[113] Exposure to antibiotics prior to, or during early infancy, is associated with increased risk of childhood obesity, asthma, and thicker aortic intima-media layer on echocardiography, an early marker for risk of cardiovascular disease.[114–116]

Alternative Therapies Against GBS

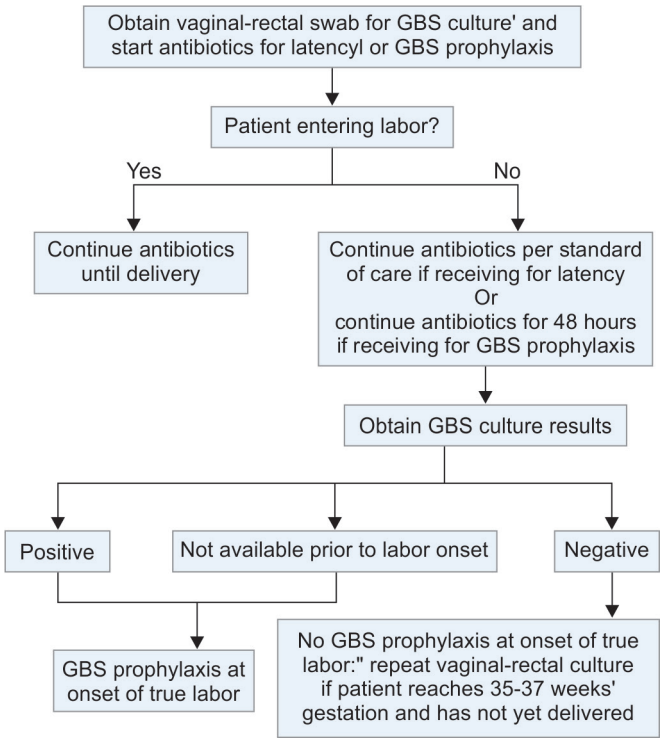
Since Austrian and Gold[22] showed that penicillin was an effective treatment for adults with streptococcal infections, and penicillin or other β-lactam agents have been considered to be the treatment of choice for most GBS-infected infants.[117] Currently used bactericidal antibiotics may cause a rapid release of bacterial components in infants with high bacterial loads and induce a SIRS with morbidity and mortality.[118]

There is a need for alternative therapies with immunomodulatory and bacteriostatic effects, such as macrolides such as azithromycin. These antibiotics show a ribosomal-targeted mechanism to inhibit the expression of production of inflammatory toxins and other virulence factors. There have been encouraging results in pneumococcal infections.[23,24,119] The combination of a β-lactam with a macrolide may have benefits. Some *in vitro* and animal models have been used to compare antibiotics, such as rifampin, clindamycin, ampicillin, azithromycin, and cefotaxime, in various combinations.[77,120,121] The role of various inflammatory molecular pathways involving TLR2, MyD88, IRAK, and PKD1 also needs attention.[77]

GBS Vaccine

Vaccination may be a useful strategy to stimulate the production of active antibodies that could cross the placenta and prevent GBS disease. Humans generate serotype-specific IgG antibodies against the GBS capsular polysaccharides,[122] which show a concentration-dependent protective effect.[87,123] The first human clinical trials were conducted with purified native type Ia, II, or III polysaccharides injected in healthy adult volunteers, including pregnant women.[122] These vaccines were safe but were not adequately immunogenic.[124] Conjugation with protein carriers enhanced the immunogenicity of polysaccharide vaccines.[125,126] A second generation of GBS vaccines was developed using glycoconjugates. A trial showed the conjugates of serotype III with tetanus toxoid in pregnant women showed increased titers of protective IgG to type III CPS. After glycoconjugate vaccination, the titers were also increased.[127,128] Monovalent conjugate vaccines representing the disease-causing serotypes Ia, Ib, II, III, and V are being tested in phase I and phase II trials.[129] Multivalent capsular conjugate vaccines are also being developed.[130] There may be promising vaccine candidates in the core genome but there is a risk of losing proteins that are not

Flowchart 2: Algorithm for screening for group B streptococcal colonization and use of intrapartum prophylaxis for women with preterm premature rupture of membranes



*At <37 weeks and 0 days' gestation; †If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative; §Antibiotics given for latency in the setting of pROM that include ampicillin 2 g intravenously (IV) once, followed by 1 g IV every 6 hours for at least 48 hours are adequate for GBS prophylaxis. If other regimens are used, GBS prophylaxis should be initiated in addition; **GBS prophylaxis should be discontinued at 48 hours for women with pROM who are not in labor. If results from a GBS screen performed on admission become available during the 48-hour period and are negative, GBS prophylaxis should be discontinued at that time; ††Unless subsequent GBS culture prior to delivery is positive; §§A negative GBS screen is considered valid for 5 weeks. If a patient with pROM is entering labor and had a negative GBS screen >5 weeks prior, she should be rescreened and managed according to this algorithm at that time (From: 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(RR-10):22. PMID: 21088663.)

essential for bacterial growth but may be important virulence factors. Hence, the glycoconjugate generation vaccine remains the best hope.

There are challenges in conducting efficacy clinical trials due to the low incidence of neonatal diseases. The establishment of maternal CPS-specific antibody levels at the time of delivery above a quantified threshold, which can be predicted to confer high level of protection against early-onset GBS disease.[87,131,132]

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