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Neonatal group B streptococcal disease: from pathogenesis to preventive strategies

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Abstract

Streptococcus agalactiae, or group B streptococcus (GBS), remains the leading cause of neonatal sepsis and meningitis, as early-onset or late-onset diseases (EOD, LOD). Where consensus guidelines to detect and treat intrapartum women with GBS colonization have been widely adopted, incidence of neonatal EOD has dramatically declined. In response to both successful impacts on the incidence of GBS-EOD and analyses of missed opportunities, the first American guidelines for prevention issued in the 1990s have since been adapted in several stages to improve their efficacy. In some countries in Europe, nationwide guidelines, whether screening-based or risk-based, for the prevention of neonatal GBS diseases have also been issued and adopted, with the expected impact on incidence of GBS-EOD. In spite of universal screening, in spite of the great progress that has been made, GBS-EOD continues to occur and the GBS burden remains a significant public health issue. Continuous efforts to improve screening for GBS status continue to be important and may be able to take advantage of new rapid diagnostic technologies. The current screening-based strategy for prevention is highly effective but imperfect. Given the challenges, limitations and potential complications of maternal intrapartum prophylaxis, a new approach is still needed. Maternal immunization against GBS is an attractive alternative for the prevention of not only neonatal diseases but also still-births and maternal diseases. Vaccines against GBS may become the most effective and sustainable long-term preventive strategy.

Keywords: Epidemiology, group B streptococci, meningitis, neonatal infection, prevention, screening, sepsis, *Streptococcus agalactiae*, vaccine

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Introduction

In the 1970s, *Streptococcus agalactiae*, also referred to as Lancefield group B streptococcus (GBS), emerged abruptly as an important pathogen causing invasive bacterial infections, sepsis, pneumonia and meningitis in human neonates during the first week of life [1]. Since that time, GBS has remained the leading infectious cause of neonatal morbidity and mortality in industrialized countries, affecting 0.5–3 newborns in every 1000 live births [2–8]. In less-developed countries, the incidence of GBS neonatal disease also varies widely: 0.17 per 1000 live births in India to three per 1000 live births in sub-Saharan Africa [9–12].

Two distinct clinical syndromes among infants became apparent: early-onset disease (EOD) presenting within the first week of life, and late-onset disease (LOD) affecting infants between 1 week and 3 months old [1–4,13,14].

Because many babies with GBS-EOD disease are already septicaemic at birth, limiting the opportunity for timely interventions, disease prevention rather than treatment is the focus of attempts to reduce neonatal GBS infections and the burden of the disease. Today, with the implementation of specific policies, the overall incidence of GBS-EOD has progressively declined [3,8,15–17]. However, prevention of EOD is still the subject of controversy, and despite considerable efforts and economic resources spent on prevention of GBS-EOD, cases continue to occur [2,4,5,13,15,18–20].

Group B streptococcal diseases are not restricted to newborns. They are also common in pregnant women and have been recognized as an ever-growing cause of severe invasive infections in non-pregnant adults, particularly older adults and immunocompromised patients [1,3,7,13,21]. In women during pregnancy or the postpartum period, genital tract colonization with GBS is usually asymptomatic, but GBS clinical manifestations include urinary tract infections, chorioamnionitis, endometritis, wound infections associated with caesarean delivery or episiotomy, puerperal sepsis and, occasionally, meningitis, septic thrombophlebitis, or other serious complications [13]. Infections with GBS probably cause 15–25% of puerperal fever with or without bacteraemia [1,3]. Women colonized with GBS during pregnancy are at increased risk of stillbirths and premature delivery [13].

GBS, the Bacteria and Colonization

Group B streptococci are Gram-positive encapsulated bacteria usually subdivided according to their type specific capsular polysaccharides (CPS) into ten antigenically unique serotypes (Ia, Ib, II–IX) [1]. This capsule represents one of the major virulence factors [14]. Among GBS, serotype III strains are responsible for a considerable percentage of EOD and for the majority of LOD [20,22]. Furthermore, a highly virulent clone of GBS serotype III, GBS ST-17, is reported in several studies as the main sequence type causing neonatal invasive disease and as being responsible for almost all cases of meningitis [20].

Group B streptococci remain fully susceptible to penicillin as well as to most β-lactams, and penicillin remains the first-choice antibiotic to prevent GBS-EOD and to treat GBS disease. However, recently identified very rare isolates with decreased susceptibility to penicillin have been reported in Japan and the USA [23]. A point mutation in the GBS *pbp*2x gene conferring this decrease in susceptibility was identified [23]. Their clinical significance is unclear, and clinicians can confidently continue to use penicillin and other β-lactams for intrapartum antibioprophylaxis (IAP) and treatment of GBS infections. Of more concern is the finding that, over the last two decades, resistance to macrolides and clindamycin among invasive isolates of GBS has increased from <5% to common resistance of 20–30% [17,24,25]. Different known mechanisms account for acquired resistance to macrolides. The most prevalent of these is based on the alteration of the target-binding site, a ribosomal modification mediated by erythromycin ribosome methylase encoded by *erm* genes. The presence of an Erm methylase confers resistance to erythromycin and inducible or constitutive resistance to lincosamides and streptogramin B, the so-called MLS_B phenotype. Another mechanism, involving increased drug efflux, is conferred by the *mef* gene; the presence of a Mef pump only affects 14-membered and 15-membered macrolides, the M phenotype. These resistances are worrying, and continuing surveillance of susceptibility patterns is therefore warranted.

The gastrointestinal tract is the natural reservoir for GBS and is likely the source for vaginal colonization [1,3]. Many adults, up to 30%, are commonly colonized with GBS in the gastrointestinal and genital tract but remain asymptomatic. Vaginal colonization is unusual in childhood but becomes more common in late adolescence [2]. Among pregnant women, GBS carriage rate in the vaginal and rectal microbiota ranges from 10% to 37% and is similar in developing and developed countries [16,18,22,26]. Large variations in colonization rates can be observed and correlated with body sites sampled, microbiological procedures performed and populations studied. The site chosen for culture is critical [1]: the distal vagina yields GBS more frequently than the cervix, and collecting both vaginal and rectal swabs results in optimal detection of carriers. Colonization with GBS can be transient, intermittent or persistent [3,16] and, as it is commonly asymptomatic, bacteriological screening must be performed to identify carriers. Irrespective of preventive strategy for GBS-EOD, the GBS colonization rate among pregnant women has remained steady over time, and no marked change has been observed in the distribution of serotypes [16].

GBS Neonatal Disease

Early and late onset diseases

Among cases of GBS-EOD, which typically occur within the first 6 days of life, the greatest number present with signs of systemic infection at birth or within the first 24 h: fulminant pneumonia or sepsis or, less commonly, meningitis [1,3,14,27]. Without prompt therapy, rapid clinical deterioration typically characterizes EOD. Despite intensive supportive care and diagnostic and therapeutic advances, these infections remain associated with high mortality and morbidity. GBS early-onset infection is vertically transmitted and is characteristically related to maternal carriage of GBS in the genital tract, with vertical transmission occurring immediately before or during labour and delivery. About 30–70% of neonates born to GBS-colonized mothers become transiently colonized by their mother's organism. Most of them remain asymptomatic, but among these infants 1–3% develop a severe disease [1,3,7,16,19,27]. They can become colonized or infected *in utero* or contaminated with GBS upon passage