Clinical and microbiological aspects of perinatal group B streptococcal disease.

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Abstract

Group B Streptococci (GBS) continues to be a universal agent that causes early onset sepsis in newborns. Universal maternal screening for recto-vaginal GBS carriage at 35-37 weeks' gestation, combined with intra-partum antibiotic prophylaxis for colonized mothers, is currently the most effective strategy to reduce early-onset neonatal GBS disease. This strategy has not reduced the incidence of late or late late-onset GBS infection, for which environment is the typical source of GBS infection. It remains unclear whether greater antibiotic use in the peripartum period affects the incidence and antibiotic resistance profiles of GBS and other perinatally acquired bacterial infections. Vaccines against GBS may become the most effective and sustainable long-term preventive strategy.

Keywords: GBS, *Streptococcus agalactiae*, Neonates, Pregnancy, Intra-partum, Antibiotic prophylaxis vaccine.

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Introduction

Group B *Streptococcus* (*Streptococcus agalactiae*; GBS) is a leading cause of neonatal disease. Here we provide a brief review of GBS perinatal disease, including its biology, epidemiology, clinical features and outcomes, and prevention methods.

Epidemiology

Group B *Streptococcus* has been the leading cause of early onset neonatal sepsis globally since 1970 [1]. Before the era of maternal prophylaxis, the reported US incidence of 2/1,000 live births were associated with a 50% mortality rate [2]. The approaches to maternal prophylaxis have resulted in a remarkable decrease in the incidence of early-onset GBS disease (EOD), defined by disease present in the first week of life. The current incidence of EOD in industrialized countries is 0.34-0.37/1000 [2]. In less-developed geographic areas, the highest incidence per 1,000 births is seen in Africa (0.53,95% CI 0.15-0.92), followed by the Americas (0.50, CI 0.143-0.57). The lowest incidence is in Southeast Asia (0.11, 95% CI 0.012-0.220) [3].

Literature Review

Infant GBS cases have decreased among all races with maternal prophylaxis; however, racial disparities remain with the African American community most at risk [2]. GBS carriage status, an important risk factor for neonatal GBS infection, is higher among black women [4]. In a recent study, black women were significantly less likely to be screened for GBS than were white women [4].

In another study, Hispanic women were less likely than non-Hispanic women to be screened for GBS [5], suggesting that race might be a surrogate for social determinants of health that contribute more broadly to disease disparities [6].

Nearly 80% of all invasive GBS infections occur in the first few days of life. Most cases are caused by bacteremia, with 10% of those cases being associated meningitis [7].

The GBS infection recurrence rate is approximately 1% for newborns treated appropriately [7]. Around 50% of newborns with recurrent GBS infection have a new site of involvement with the second episode [8].

In 1996 guidelines were published for intrapartum antibiotic prophylaxis (IAP) for pregnant women at risk of transmitting GBS to their newborns [9]. At that time, the average incidence of EOD was 1.8/1,000 live births. By 1998, the incidence of EOD had decreased to 0.6/1,000 live births. It further decreased to 0.25 per 1,000 live births in 2010 [2]. The incidence of late-onset disease (LOD) affecting infants between 1 week and 3 months old, remained unchanged at 0.26 per 1,000 [2].

The group B streptococci

GBS is a gram-positive diplococcal facultative encapsulated bacterium, which is found in chains or pairs. *S. agalactiae* belongs to the family *Streptococcaceae* and is characterized by the Lancefield group B antigen. After incubation for 24 hours, pearly grey mucoid and soft colonies appear measuring 0.1 mm in diameter. Most human strains produce a narrow zone of β-haemolysis, although this may appear hazy (Figure 1) [10].

GBS are subdivided into ten antigenically unique serotypes (Ia, Ib, II-IX) by their type-specific capsular polysaccharides (CPS); CPS is one of the major virulence factors of the bacteria [10]. The most common serotypes causing EOD are Ia, III and V. Type III strains dominate in LOD [11].

GBS colonization

The gastrointestinal tract is likely the source for genital colonization [11]. About 10-30% of women are colonized with GBS during pregnancy; those women are 25 times more likely to pass GBS infection to their infants during labor and delivery than those who are not colonized [11,12]. Approximately 40-50% of infants born to colonized mothers will become colonized with GBS, with only 1-2% developing EOD [8].

Women colonized with GBS during pregnancy are at increased

risk of stillbirth and premature delivery, GBS urinary tract infection, chorioamnionitis, endometritis, wound infection associated with cesarean delivery or episiotomy, puerperal sepsis and, occasionally, meningitis and septic thrombophlebitis [8,13].

Neonatal infection

Early–Onset Disease (EOD): EOD is related to maternal carriage of GBS in the genital tract, with transmission occurring immediately before or during labor and delivery [8].

The classical four factors for EOD are:

1. Premature labor and delivery (before 37 weeks), which are related to an incomplete transfer of maternal antibodies [7,9].
2. GBS bacteriuria at any time during the current pregnancy [2].
3. Intrapartum maternal fever, a marker of chorioamnionitis and [4], prolonged rupture of membranes (more than 18 hours before delivery) [7].

Other risk factors include: Black race [2], young maternal age [7], maternal HIV infection [14] and certain obstetric procedures (e.g., use of intrauterine fetal monitoring devices or performing five or more vaginal examinations during labor) [13].

Most EOD presents in the first 24 hours of life, and often as early as the first hour [14]. Symptoms of infection may be non-specific (e.g., temperature instability, poor feeding, excessive crying or irritability, and respiratory distress). EOD usually presents as septicemia without a focus (~80%), pneumonia (~7%), and/or meningitis (~6%) [11].

EOD has been associated with developmental disabilities (mental retardation, visual and hearing loss) and increased incidence of bronchopulmonary dysplasia, intraventricular hemorrhage, and periventricular leukomalacia [7,8] The mortality rate has been estimated at 4.5% to 15%. Mortality rate in premature newborns is approximately 30%, 10% and 2% for infants born at ≤ 33, 34 to 36, and ≥ 37 weeks' gestational age, respectively [8,15].

Late–Onset Disease (LOD): LOD, or onset between 7-89 days of life appears to have a different pathophysiology from EOD [11,16] Postnatal passage of the bacteria to the infant through the environment is the most common source of GBS LOD acquisition. The organisms are acquired from GBS carriers who have contact with the infant, e.g., nursing staff in hospital and, perhaps, colonized infants sharing the same ward, or from community sources [11].

Breast milk has been reported as a source of LOD via feeding by breast or other means due to infected breast milk [17,18]. Breast milk may become infected through transmission by an already infected infant, through translocation from the maternal gastrointestinal tract to the mammary glands by the lymphatic system or colonization of the maternal skin [18]. Breast milk can be infected with GBS during breast expression, by a contaminated breast pump, or the milk container bottle [19]. Recently, a case in which a newborn infant developed recurrent neonatal group B *Streptococcus sepsis* after the mother ingested contaminated placenta capsules containing *Streptococcus agalactiae* was published [20].

LOD usually presents with bacteremia, with associated meningitis in approximately 25% of cases. The mortality rate is 10-20% [11]. Less common clinical presentations of LOD are osteomyelitis, arthritis, cellulitis or adenitis (facial, submandibular, scrotal or prepatellar infections) [11].

Late Late–Onset Disease (LLOD): LLOD occurs in infants older than 89 days and is the most infrequent type of GBS infection [8,11,16]. Very low birth weight infants with prolonged hospital stay and more invasive intervention in the NICUs are at increased risk for LLOD. GBS is acquired through nosocomial routes, for example, through the hands of health care workers [21].

Diagnosis

Evaluation for neonatal sepsis includes blood, CSF and urine cultures. There has been debate regarding the need for a lumbar puncture in newborns being evaluated for EOD. Some advocated that a lumbar puncture should be performed in the first weeks of life if the newborn has positive blood cultures [8]. However, 15 to 38% of newborns with meningitis will have negative blood cultures, thus examination of the CSF is the only way to determine the presence of meningitis [22].

The use of intrapartum antibiotic prophylaxis and empirical antibiotic therapy for presumed sepsis might result in a "culture negative" infection [3]. In this situation, PCR testing of the CSF specimen, for example, is useful specially when there is a high CSF white cell count [23]. However, PCR may miss 35% of positive blood culture cases [24]. In addition, PCR is unable to provide information about antibiotic susceptibility and should not replace blood cultures for diagnosis of neonatal sepsis [23].

Studies have shown that a single white blood cell (WBC) screen is a poor predictor of infection in neonates [25,26]. However, serial normal values may confirm noninfection. Murphy and Weiner showed that 2 normal WBC screens separated by 8 to 12 hours and a negative blood culture in the first 24 hours of life had a negative predictive value and sensitivity of 100% (95% CI: 99.905%-100%), but the specificity and positive predictive value were 51% and 8.8% respectively [27].

In neonates, serial measurements of the CRP in the first 24-48 hours of symptoms increases the sensitivity of the test, with data suggesting that normal values during this period have a 99% negative predictive value for determination of infection [28]. Procalcitonin (PCT) levels increase more rapidly than CRP levels. In a multicenter study of 762 neonates, the median value of PCT was significantly higher in neonates with versus without sepsis (3.58 vs 0.49 ng/ml; $p<0.001$). Also, a cut-off value of 2.4 ng/ml was suggested as the most accurate level for differentiation of sepsis in neonates, with a sensitivity of 62% and a specificity of 84% [29]. Further studies are needed to clarify the use of PCT in neonatal sepsis.

Treatment

For empirical suspected GBS infection, ampicillin plus an aminoglycoside is the recommended treatment, unless local antibiotic-resistance patterns suggest the need for another combination [8,11,22]. Once GBS meningitis is confirmed, the drug of choice is penicillin G (250,000 to 450,000 U/kg/day, intravenously, in 3 divided doses; for infants older than 7

days, 450,000 to 500,000 U/Kg/day, intravenously, in 4 divided doses is recommended) or ampicillin (200 to 300 mg/kg/day, intravenously, in 3 divided doses for infants 7 days or younger; and 300 mg/kg/day, intravenously, in 4 divided doses for infants older than 7 days) [30]. For empirical therapy of late-onset meningitis, ampicillin and an aminoglycoside or cefotaxime are recommended [16].

For meningitis, some experts believe that a second lumbar puncture approximately 24 to 48 hours after initiation of therapy assists in management and determining prognosis. If CSF sterility is not achieved, a complicated course (e.g., cerebral infarcts) can be expected. Increased protein concentration also suggests an intracranial complication (e.g., infarction, ventricular obstruction) [16].

Isolated bacteremia should be treated for 10 days, and uncomplicated meningitis for 14 days, but longer periods of treatment may be necessary for infants with prolonged or complicated courses. Endocarditis or ventriculitis require treatment for at least 4 weeks; septic arthritis or osteomyelitis should be treated for 3-4 weeks [16].

Due to the increased risk of infection, the birth mates of a multiple birth index case with EOD or LOD should be observed carefully and evaluated and treated empirically for suspected systemic infection if signs of illness occur [16].

Prevention

Guidelines for prevention of GBS early-onset disease: In the late 1980s, clinical trials demonstrated that GBS EOD could be prevented by administering antibacterial prophylaxis during labor and delivery to women who were colonized by GBS [7]. Two approaches, either based on the presence of risk factors associated with increased risk of GBS EOD (see above) or on GBS-positive late antenatal cultures obtained between 35 and 37 weeks' gestation, were then recommended to identify women at risk of delivering a GBS-infected infant [31].

In 2000, the results of a large retrospective cohort study comparing the effectiveness of both approaches were published demonstrating that, universal GBS antenatal screening at 35-37 weeks' of gestation was 65% more effective than the risk-based approach in prevent GBS EOD [13].

As a result, the CDC recommended late-antenatal GBS screening at 35-37 weeks' of gestation for all women and intrapartum antibiotic prophylaxis (IAP) for: 1. Women with GBS colonization or with GBS bacteriuria during pregnancy (≥ 104 colony-forming units/mL) or 2. Unknown maternal GBS status at the onset of labor and any of the following: delivery at <37 weeks' gestation, PROM ≥ 18 hours, an intrapartum fever ≥ 100.4°F (≥ 38.0°C) or an intrapartum nucleic acid amplification test (NAAT) positive for GBS. Women who have a caesarean section with intact membranes before labor begins do not require prophylaxis. Women who had GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease should receive intra-partum antibiotic prophylaxis (IAP) without the need to perform vaginal and rectal cultures [2].

Prophylactic treatment is not recommended for any asymptomatic newborn born at >35 weeks' gestation whose mother had at least one dose of intrapartum antibiotics at least 4 hours prior to delivery. These newborns should be evaluated for signs of infection and have a limited evaluation (blood culture at birth and CBC with differential and platelets at birth and/or at 6-12 hours of life), and not be treated with antibiotics. They need to be observed in the hospital for at least 48 hours [2].

Well-appearing infants with chorioamnionitis should also have a limited evaluation (CBC with differential and blood culture) and antibiotic therapy. Well-appearing infants born at 35-36 weeks' gestation whose mothers received adequate intrapartum antibiotic prophylaxis do not require a diagnostic evaluation [2].

Well-appearing term infants born to women with inadequate or no IAP may be managed with observation unless membranes have been ruptured ≥18 hours, in which case a limited evaluation is indicated. All infants born at <37 weeks' gestation whose mothers had inadequate or no IAP should undergo a limited evaluation and observation for at least 48 hours [2].

Screening – specimen collection and processing: Critical factors that influence the accurate detection of GBS maternal colonization include sampled anatomic sites, timing in pregnancy, transport condition of swabs and culture procedures [9]. The 2010 CDC guidelines provides directions for collecting and processing these specimens [2].

Intrapartum use of nucleic acid amplification tests (NAAT) should reduce the number of women unnecessarily given IAP [1]. However, the sensitivity of NAAT is suboptimal compared with standard culture unless an enrichment step is included prior to specimen analysis. This enrichment step significantly increases turnaround time and therefore limits the feasibility of this technique in women who present in active labor [2].

NAAT is best used in full term pregnancies, with unknown colonization and no prementioned risk factors [1]. Also, PCR can detect GBS in women who did not receive prenatal care or have an antenatal culture collected, and in cases where cultures are negative in the presence of risk factors. The major advantage of cultures is the ability to test for antibiotic susceptibility and it should not be replaced by PCR [1].

Intrapartum antibiotic prophylaxis: Penicillin G (5 million units for the first dose and then 2.5-3 million units every 4 hours) remains the agent of choice for GBS prophylaxis, with ampicillin as an alternative [1]. Penicillin G should be administered intravenously at 4-hours intervals from the onset of labor until delivery. A woman is considered to have received adequate GBS prophylaxis if she has received at least one dose of penicillin ≥ 4 hours before delivery. The use of an antibiotic other than penicillin, ampicillin or cefazolin should be considered inadequate prophylaxis because of a lack of proven efficacy [1].

Women who are sensitive to β-lactam antibiotics should receive cefazolin, while those at high risk of anaphylaxis should receive clindamycin (if GBS is susceptible) or vancomycin [1].

Persistence of GBS disease despite universal screening: A significant number of infants develop GBS disease annually despite adequate prophylaxis, particularly VLBW infants [32]. Of concern are reports that many of these infants developed EOS without evidence of maternal colonization.

Possible explanations for these findings are: acquisition of colonization following a negative screen, effects of undocumented use of outpatient antibiotics, and inconsistent techniques in the acquisition and/or processing of specimens for culture. False-negative rates from 4-8% have been reported, mostly secondary to inappropriate collection or processing of specimens [33]. Late gestational acquisition of GBS likely accounts for a small proportion of the negative tests [33].

Unintended consequences of intrapartum antibiotic prophylaxis: There are three major concerns about widespread IAP:

1. Other pathogens might replace GBS as a cause of neonatal sepsis.
2. There may be increased antibiotic resistance to neonatal pathogens.
3. Adverse effect on the development of the neonatal intestinal microbiome with unknown long-term impacts upon immunological and metabolic programming.

A 10 year-period surveillance representing ~5% of US live births, showed that the overall incidence rates of all-cause and *E. coli* invasive early-onset sepsis were stable, whereas the incidence of GBS slightly decreased [34]. In this study, the vast majority of infants exposed to intrapartum antibiotics were exposed to a β-lactam or cefazolin, suggesting that exposure to those antibiotics for GBS prophylaxis has not resulted in an increase in Gram-negative sepsis. Other studies showed similar results [35,36].

A major concern is the rising incidence of antibiotic resistance in gram-negative organisms, particularly *E. coli*. In a study analyzing the antimicrobial susceptibility profile of the positive neonatal cultures from the above study, clonal changes in *E. coli* associated with early-onset sepsis, in particular emerging ampicillin resistance, were documented in two-thirds of the cases [37]. This finding suggest that ongoing surveillance of antibiotic resistance among EOS isolates is warranted, to ensure that standard empiric regimens remain effective.

Few studies have focused on the effects of maternal IAP on the infant fecal microbiota. Mazzola et al. demonstrated an inverse relationship between *Enterobacteriacea* family and *Bifidobacterium spp*. counts following maternal IAP during the first week of life. At 30 days of life, the bifidobacteria population appears to have recovered in exclusively breast-fed infants whose mothers received IAP, although *Enterobacteriacea* remained highest in comparison to exclusively breast fed infants not exposed to IAP [38]. Other studies showed that those changes in microbiota development would persist during the first year of life and, as a result, disrupting proper development of the gut, immune, metabolic and brain systems [39].

Figure 1. *Colonies of S. agalactiae growing on blood agar plate: Creamy texture, grey color with a diffuse zone of β – hemolysis (arrow). Courtesy: Monica Rogers.*

Maternal GBS immunization

Active immunization of women against GBS is considered the ideal preventive strategy. It would provide protections against early- and late-onset infections and should avoid the adverse effects of IAP. In addition, vaccination might also prevent some of the adverse effects of GBS during the pregnancy such as preterm labor, stillbirth, or intrauterine death.

A multivalent (serotypes Ia, Ib and III) GBS polysaccharide-protein conjugate vaccine has completed phase II evaluation in HIV-infected and HIV-uninfected women [14].

It is necessary to determine if vaccination eliminates genital colonization in addition to preventing disease. If colonization remains, IAP will be needed to prevent disease in those most susceptible, such as preterm and VLBW infants and in cases of vaccine non-responders.

Discussion and Conclusion

Although the incidence of invasive GBS disease has decreased in high income countries with the use of intrapartum antibiotic prophylaxis, through universal or risk based screening, GBS remains a leading cause of sepsis and meningitis in young infants in both high-income and low-income countries.

Prevention strategies are required, and the current strategies are based around intrapartum antibiotic prophylaxis. Women at risk are identified either based on clinical risk factors or on positive lower vaginal/rectal swabs obtained late in pregnancy. Penicillin is administered intravenously at the onset of labour, with other agents available for women who are allergic to penicillin. Concerns exist about unintended consequences of the IAP, specifically the development of antibiotic resistance.

GBS vaccines hold great promise for disease prevention as they may prevent all GBS- associated disease and avoid the issues around screening and antibiotic use; furthermore, they are likely to be the most cost-effective approach of all.

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References

1. Randis T, Polin R. Early-onset group B Streptococcal sepsis: New recommendations from the centres for disease control and prevention. Arch Dis Child Fetal Neonatal. 2012;97(4):F291-9.
2. Verani JR, McGee L, Schrag SJ. Division of bacterial diseases, National Center for immunization and respiratory diseases, Centers for Disease Control and Prevention (CDC). Prevention of Perinatal Group B Streptococcal Disease: Revised Guidelines from CDC, 2010. Morbidity and Mortality Weekly Report. Recommendations and Reports/ Centers for Disease Control. 2010;59(RR10):1-36.
3. Edmond KM, Kortsalioudaki C, Scott S, et al. Group B streptococcal disease in infants aged younger than 3 months: Systematic review and meta-analysis. Lancet. 2012;379:547-56.
4. https://doi-org.ezproxy.hsc.usf.edu/10.1007/s10995-010-0682-8.
5. Avery M, Brown HW, Schrag S. Disparities in universal prenatal screening for group B *Streptococcus*-North Carolina, 2002–2003. Morbidity and Mortality Weekly Report. 2005;54(28):700-3.
6. Weston-Emily J, Tracy P, Melissa ML, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. The Pediatric Infectious Disease Journal. 2011;11:937-41.
7. Schuchat A. Group B *Streptococcus*. Lancet. 1999;353(9146):51-6.
8. Edwards MS, Nizet V, Baker CJ. Group B streptococcal infections. Infectious diseases of the fetus and newborn infant. Philadelphia: Elsevier Saunders. 2011;pp:419-69.
9. Schrag S, Gorwitz R, Fultz-Butts K, et al. Prevention of perinatal group B streptococcal disease. MMWR Recomm Rep. 2002;51:1-22.
10. Melin P. Neonatal group B streptococcal disease: From pathogenesis to preventive strategies. Clin Microbiol Infect. 2011;17(1):1294-303.
11. Petterson K. Perinatal infection with group B *Streptococci*. Seminars in Fetal and Neonatal Medicine. 2007;12(3):193-7.
12. Gilbert R. Prenatal screening for group B streptococcal infection: Gaps in the evidence. Int J Epidemiol. 2003;33:2-8.
13. Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med. 2000;342:15-20.
14. Cutland CL, Schrag SJ, Thigpen MC, et al. Increased risk for group B streptococcus sepsis in young infants exposed to HIV, Soweto, South Africa, 2004-2008. Emerg Infect Dis. 2015;21(4):638-45.
15. Madoff LC, Michel JL, Gong Ew, et al. Protection of neonatal mice from group B streptococcal infection by maternal immunization with beta C protein. Infect Immun. 1992;60(12):4989-94.
16. American Academy of Pediatrics. Group A streptococcal infections. In: Pickering LK, ed. 2015 Red Book Report of the Committee on Infectious Diseases. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics. 2015;pp:745-50.
17. Gagneur G. Infected breast milk associated with late-onset and recurrent group B streptococcal infection in neonatal twins: A genetic analysis. Eur J Pediatr. 2009;168(9):1155-8.
18. Zimmermann P, Gwee A, Curtis N. The controversial role of breast milk in GBS late-onset disease. Journal of Infection. 2017;74(1):S34-40.
19. Boo NY, Nordiah AJ, Alfizah H, et al. Contamination of breast milk obtained by manual expression and breast pumps in mothers of very low birth weight infants. J Hosp Infect. 2001;49:274-81.
20. Buser GL, Mato S, Zhang AY, et al. Notes from the field: late-onset infant group B *Streptococcus* infection associated with maternal consumption of capsules containing dehydrated placenta—Oregon, 2016. MMWR Morb Mortal Wkly Rep. 2017;66:677-8.
21. Paredes A, Wong P, Mason EO Jr, et al. Nosocomial transmission of group B *Streptococci* in a newborn nursery. Pediatrics. 1977;59:679-82.
22. American Academy of Pediatrics. Recommendations for the prevention of perinatal Group B Streptococcal (GBS) disease. American Academy of Pediatrics. 2011;128(3):611-6.
23. Meehan M, Cafferkey M, Corcoran S, et al. Real-time polymerase chain reaction and culture in the diagnosis of invasive group B streptococcal disease in infants: A retrospective study. Eur J Clin Microbiol Infect Dis. 2015;34(12):2413-20.
24. Morrissey SM, Nielsen M, Ryan L, et al. Group B streptococcal PCR testing in comparison to culture for diagnosis of late onset bacteremia and meningitis in infants aged 7-90 days: A multi-centre diagnostic accuracy study. Eur J Clin Microbiol Infect Dis. 2017;36(7):1317-24.
25. Ottolini MC, Lundgren K, Mirkinson LJ. Streptococcal diseases. Pediatr Infect Dis J. 1987;6:440-442.
26. Rozcki HJ, Stahl GE, Baumgart S. Impaired sensitivity of a single early leukocyte count in screening for neonatal sepsis. Pediatric Infect Dis J. 1987;6:440-442.
27. Murphy K, Weiner J. Use of leukocyte counts in evaluation of early – onset neonatal sepsis. Pediatr Infect Dis J. 2012;31(1):16-9.
28. Hengst JM. The role of C-reactive protein in the evaluation and management of infants with suspected sepsis. Adv Neonatal Care. 2003;3:3-13.

29. Auriti C, Fiscarelli E, Ronchetti MP, et al. Procalcitonin in detecting neonatal nosocomial sepsis. Arch Dis Child Fetal Neonatal Ed. 2012;97:F3:68-70.

30. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. N Engl J Med. 2011;364:2016-25.

31. CDC. Prevention of perinatal group B streptococcal disease: A public health perspective. MMWR. 1996;p:45.

32. Stoll BJ, Hansen NI, Higgins RD, et al. Very low birth weight preterm infants with early onset neonatal sepsis: The predominance of gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002-2003. Pediatr Infect Dis J. 2005;24(7):635-9.

33. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. Pediatrics. 2005;115(95):1240-6.

34. Schrag SJ, Farley MM, Petit S, et al. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. Pediatrics. 2016;138(6):e20162013.

35. Puopolo K, Eichenwald E. No changes in the incidence of ampicillin-resistant, early-onset sepsis over 18 years. Pediatrics. 2010;125(5):e1031-8.

36. Bizzarro MJ, Shabanova V, Baltimore RS, et al. Neonatal sepsis 2004-2013: The rise and fall of coagulase-negative staphylococci. J Pediatr. 2015;166(5):1193-9

37. Weissman SJ, Hansen NI, Zaterka-Baxter K, et al. Emergence of antibiotic resistance-associated clones among *Escherichia coli* recovered from newborns with early-onset sepsis and meningitis in the United States, 2008-2009. J Pediatric Infect Dis Soc. 2015;5(3):269-76.

38. Mazzola G, Murphy K, Ross RP, et al. Early gut microbiota perturbations following intrapartum antibiotic prophylaxis to prevent group B streptococcal disease. PLoS One. 2016;11(6):e0157527.

39. Nogacka AM, Salazar N, Arboleya S, et al. Early microbiota, antibiotics and health. Cell Mol Life Sci. 2018;75(1):83-91.

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