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Editorial

Group B Streptococcus neonatal infections, the ongoing history

Infección neonatal por estreptococo grupo B, la historia continua

Streptococcus agalactiae, group B streptococcus (GBS) is a physiological component of the intestinal and vaginal microbiota in 10–30% of healthy pregnant women. Colonization may be intermittent, transitory, or persistent. However, though GBS is in general a harmless colonizer it is also a leading cause of neonatal morbidity and mortality worldwide.[1]

During delivery, GBS can be transferred *via* peripartum (vertical transmission) to the newborn (NB). Roughly half of the NB from GBS colonized mothers become GBS-colonized at birth, and about 1% of these will develop early onset disease (EOD). Hence, maternal colonization with GBS of the genitourinary and gastrointestinal tracts at the onset of labor is the main risk factor for neonatal EOD. Additionally, prolonged rupture of membranes, prematurity, chorioamnionitis, intrapartum fever, a previous sibling with EOD, and GBS bacteriuria during pregnancy are additional risk factors that facilitate the development of EOD in an exposed NB.[2]

GBS infections that develop in the first week of life are known as EOD. These are the most common cause of GBS neonatal infections in the absence of intrapartum antibiotic prophylaxis (IAP), and most of the NB become symptomatic within 24 h after birth. EOD commonly manifests as pneumonia and sepsis that frequently develop into bacteremia and septic shock in a few hours. GBS infections that develop between 7 and 90 days of age are designated as late-onset disease (LOD). In contrast to EOD, LOD is not related with intrapartum vertical transmission from the mother to the NB. It is mainly acquired by horizontal transmission from the mother during the perinatal period, from the hospital, or from environmental sources.

The current era of prevention of EOD with intrapartum antibiotic prophylaxis (IAP) dates from the 1980s when it was demonstrated that the administration of intravenous penicillin or ampicillin during labor and delivery interrupts vertical transmission of GBS from the mother to the NB.[3] But unfortunately, in contrast to EOD, there is no preventive strategy to avert LOD today.

The publication of guidelines for prevention of neonatal GBS infections was initiated in 1992 when the consensus "Perinatal Prophylaxis for GBS infection" was published.[4] In 1996 the Centers for Disease Control and Prevention (CDC) issued their first guidelines on the prevention of neonatal GBS infection.[5] These guidelines recommended two different strategies for the administration of IAP to prevent EOD, either a risk-factor approach (IAP is offered only to women with any risk conditions at the time of labor) or a culture-based approach (IAP is offered to women recognized as GBS carriers over a screening culture at 35–37 weeks of pregnancy).

The CDC guidelines were updated in 2002.[6] The main change was a general recommendation for universal culture-based screening, because then it was clear that the risk-based approach was far less effective than universal screening. In 2010, the CDC published a new set of guidelines[7] and the universal antenatal culture–based approach to identify GBS carriers continued to be endorsed. Antenatal culture was considered not necessary if IAP was previously recommended because of the presence of risk factors.

Widespread application of CDC guidelines resulted in a reduction in the incidence of EOD in the United States (US) of more than 85%, from 1.8 NBs per 1000 live births in the 1990s to 0.23 per 1000 live births in 2015.[2,8,9]

In 2018, the management for updating the GBS prophylaxis guidelines was transferred in the US from the CDC to the American College of Obstetricians and Gynecologists (ACOG), the American Society of Microbiology (ASM) and the American Academy of Pediatrics (AAP) who issued updated recommendations.[2,10,11]

It is again stated in new ACOG guidelines that the critical point of preventing EOD continues to be universal screening and appropriate IAP. The main change from the CDC guidelines is that now it is recommended to perform universal GBS screening between weeks 36 and 37 of gestation, instead of at weeks 35–37, as it was advocated in the 2010 CDC guidelines. This change on the timing is based on the fact that the predictive value of prenatal cultures for GBS decreases significantly when collected more than 5 weeks before delivery, and that the use of IAP is recommended anyway when delivery develops before 37 weeks of gestation with unknown results of a GBS screening test. Therefore this timing for screening provides culture results that include births up to 41 weeks of gestational age.

The ACOG guideline also states that asymptomatic GBS bacteriuria in pregnant women with colony counts of less than 10^5 cfu/mL does not require antibiotic therapy, but GBS bacteriuria at levels $\geq 10^5$ cfu/mL always warrants antibiotic treatment and follow-up until delivery. Nevertheless, the finding of GBS in any quantity from urine cultures during all trimesters represents heavy maternal vaginal-rectal colonization and indicates the need for IAP without further GBS screening in these women.

The clinical report issued by the AAP[11] in 2019 for the management of NB at risk of GBS disease supports the procedures recommended by the ACOG. It also describes the evaluation of the

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Table 1
Timeline of guidelines, protocols and main changes cited in this manuscript.

Year	Reference	Country[a]	Strategy/approach	Main changes
1996	5	USA-CDC	- Risk-factors *vs*. culture-based screening - GBS screening between weeks 35–37	- First CDC guidelines.
1998	15	Spain	- Recommendation for universal culture-based screening - GBS screening between weeks 35–37	- First Spanish guidelines endorsed by SEGO and SEN.
2002	6	USA-CDC	- Universal prenatal culture-based screening for vaginal and rectal GBS colonization of all pregnant women at weeks 35–37 of gestation	- Updated prophylaxis regimens for women with penicillin allergy - Detailed instructions on specimen collection and methods of GBS culture - Instructions on antimicrobial susceptibility testing
2003	16	Spain	- Culture based screening - GBS screening between weeks 35–37	- Endorsed by SEIMC, SEQ, SEMFYC, SEGO and SEN
2010	7	USA-CDC	- Universal culture-based screening - Do not endorse direct-specimen detection of GBS by NAAT	- Updated IAP regimens for women with penicillin allergy - Testing for inducible clindamycin resistance - Report GBS in urine when present at concentrations of $\geq 10^4$ colony-forming units/mL
2012	17	Spain	- Universal culture-based screening	- Updated microbiological methods - Instructions for AST
2019	11	USA-AAP	- Universal culture-based screening	- Management of infants at risk for group B streptococcal disease.
2020	2	USA-ACOG	- Universal culture-based screening	- Screening between weeks 36–37 of gestation - Report GBS bacteriuria in any quantity - Weight-based dosage of vancomycin
2021	10	USA-ASM	- Universal culture-based screening	- Use of flocked swabs for collecting specimens - MALDI-TOF (if available) considered the ideal technique for identification of GBS - Typical GBS colonies that are non-hemolytic on blood agar or not-pigmented on Granada agar should be further tested - Options for vancomycin reporting were added to the antimicrobial susceptibility testing

[a] CDC: Centers for Disease Control; AAP: American Academy of Pediatrics; ACOG: American College of Obstetricians and Gynecologists; ASM: American Society of Microbiology.

hazards in infants at risk of developing EOD, and the management of newborns with early onset neonatal sepsis, considering infants born at ≥35 weeks of gestation separately from those born earlier.

Likewise, the ASM issued in 2021 updated ground rules for laboratory practices for detection and identification of GBS.[10] In these guidelines, culture remains the key point to GBS detection, considering that a reliable screening test is more important than a fast and less accurate result. As a novelty, it is recommended to use flocked swabs for collecting vagino-rectal specimens that then should be placed in a transport medium and transported to the laboratory within 24 h or kept refrigerated. Afterwards, in the laboratory, samples should be inoculated in a selective enrichment broth and incubated 18–24 h at 35–37 °C. After this step of enrichment, the selective broth should be plated in a suitable culture media such as chromogenic, blood agar, or Granada medium and examined for GBS-like colonies after 24 and 48 h.

Biochemical tests and latex agglutination are appropriate for GBS identification, MALDI-TOF (if available) is the ideal technique for this task, allowing the differentiation of GBS from *Streptococcus pseudoporcinus* and *Streptococcus halichoeri*, that also agglutinate with GBS antisera. However all these methods of identification need an isolated colony and will increase the time for GBS detection. GBS-like colonies that develop in a chromogenic agar should always be confirmed as GBS using additional tests to avoid frequent false-positive results. An alternative or complement to blood agar is to subculture the enrichment broth to Granada medium where β-hemolytic GBS grows as orange or red colonies. Nevertheless, there are some flaws in these approaches. In blood agar, β-hemolysis could be difficult to recognize, only being observed in some strains when colonies are raised from the agar surface. This requires an experienced technician to identify suspect colonies. In GBS the phenotypic traits of hemolysis and pigment are always linked, so hemolytic colonies are always pigmented in Granada medium. When the enrichment broth is subcultured to Granada medium, β-hemolytic GBS develops as orange or red colonies that are very easy to observe.[12] The identification of GBS by detection of hemolysis and pigment is not 100% sensitive because about 3% of human GBS isolates do not produce pigment and are non-hemolytic. ASM guidelines recommends that typical GBS colonies that are non-hemolytic on blood agar or not-pigmented on Granada agar should be further tested.[10] Hence, an additional significant effort is required to detect these strains, increasing the work required to detect GBS colonization.

Hemolysin is an important virulence factor and a key contributor to all manifestations of GBS infections and strains lacking pigment and hemolysin are less virulent than hemolytic strains. Furthermore, *in vitro* studies and animal models also show that non-hemolytic GBS are less virulent than hemolytic strains.[13,14] Because of that, the role of non-hemolytic non-pigmented GBS strains in neonatal infections continues being unclear.

After the step of enrichment in selective broth, GBS identification by nucleic acid amplification techniques (NAAT) from the selective broth are fast and acceptable, nevertheless the GBS strain has to be retrieved for antimicrobial susceptibility testing (AST) in some cases.

GBS remains predictably susceptible to penicillin, cefazolin, and vancomycin, some rare reports of elevated MICs of these antibiotics appears to be of no clinical significance. Therefore, routine AST is not required prior to administration of these agents, although there are procedures for AST of these antibiotics against GBS both in the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and in the Clinical and Laboratory Standards Institute (CLSI) documents. However, laboratories should perform AST for both erythromycin and clindamycin in cases of penicillin

allergy, but only clindamycin should be reported. Erythromycin is used to detect inducible clindamycin resistance. The recommended dosage of vancomycin, the alternative in case of women with high-risk of penicillin allergy and clindamycin resistance of GBS, is weight-based, 20 mg/kg iv every 8 h, with a maximum of 2 g per single dose.[2] Like the CDC in 2010, the ASM in 2021[10] does not recommend NAAT GBS identification tests using directly clinical vagino-rectal samples because of their lack of sensitivity, although their performance varies depending on the specific test. However, in the future, with increasing sensitivity, lower cost, the ability to detect clindamycin-resistance genes, availability as point-of-care tests round the clock (24/7) and ease of implementation, intrapartum GBS screening by NAAT could be a reliable alternative, at least for some cases.

Following in the wake of the CDC recommendations in 1998, the Spanish Societies of Obstetrics and Gynecology (SEGO) and Neonatology (SEN) published the first Spanish guidelines on the prevention of EOD.[15] In 2003 this document was revised, endorsed and published jointly by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Societies of Chemotherapy (SEQ), Family and Community Medicine (SEMFYC), SEGO and SEN.[16] In 2012 an updated version was issued by the same societies.[17] The Spanish guidelines follow the culture-based approach and most of the recommendations for preventing EOD of the CDC guidelines.

In Table 1 it is summarized an overview of the US and Spanish guidelines and their characteristics.

The follow-up of these recommendations brought an important change in the clinical practice in Spain,[18,19] and a significant reduction (more than 85%) in the rate of GBS EOD.[20] The incidence of EOD in Spain dropped from 1.23 per 1000 live births in 1996 to 0.32 in 2002 and to 0.17 in 2018 (Fernandez Colomer B. Personal communication, November 2021, SEN. Grupo de Hospitales Castrillo).

Nevertheless, some cases of GBS-EOD continue occurring even in places where an IAP policy is in practice. More than 50% of these cases occur in NB from women in whom the laboratory failed to detect GBS in the prenatal screening test. Most of the other cases are the consequence of a failure to follow the recommendations for the prevention of EOD. These situations suggest that there is still potential for improvement in the prevention of GBS-EOD.[8,21,22]

Despite the success of measures recommended in guidelines in preventing EOD, IAP is not effective in preventing LOD, and also GBS cause stillbirths and preterm births. In contrast, an effective GBS vaccine could prevent invasive GBS disease in all groups, including mother, fetus and infants.[23] It has been almost 50 years since an association between transplacental transfer of maternal GBS antibodies and infant protection against invasive GBS infections was found. There is evidence that vulnerability of the NB to GBS infection is caused by a low level of maternal capsular antibodies.[24] Hence, maternal immunization prevents neonatal disease by the transfer of protective antibodies from mother to the fetus and will protect the NB against EOD and LOD. Thus, the development of a vaccine, that could be administered to women in the course of pregnancy and protect against both EOD and LOD, is an appealing option. Maternal vaccination will be the most effective approach for preventing GBS infection in NBs. Developing such a vaccine is deemed a high priority by the World Health Organization.[25] Vaccines based on capsular polysaccharides and protein vaccines have shown promising preliminary results and are now at various advanced phases of development.[26,27] These vaccines are being now investigated in clinical trials,[27] but at present there is no vaccine to prevent GBS infections applicable for general clinical practice.

Now, 10 years after the last Spanish guidelines for prevention of neonatal GBS infections were issued, its recommendations are still utterly valid. However, some new developments in the microbiology laboratory and clinical data, highlighted in the new ACOG and ASM guidelines, point out that perhaps the time has arrived for a new update.

Conflict of interest

This article does not present any conflict of interest, nor has it received funding for its realization.

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