GUIDELINES

Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference

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Abstract

Group B streptococcus (GBS) remains worldwide a leading cause of severe neonatal disease. Since the end of the 1990s, various strategies for prevention of the early onset neonatal disease have been implemented and have evolved. When a universal antenatal GBS screening-based strategy is used to identify women who are given an intrapartum antimicrobial prophylaxis, a substantial reduction of incidence up to 80% has been reported in the USA as in other countries including European countries. However recommendations are still a matter of debate due to challenges and controversies on how best to identify candidates for prophylaxis and to drawbacks of intrapartum administration of antibiotics. In Europe, some countries recommend either antenatal GBS screening or risk-based strategies, or any combination, and others do not have national or any other kind of guidelines for prevention of GBS perinatal disease. Furthermore, accurate population-based data of incidence of GBS neonatal disease are not available in some countries and hamper good effectiveness evaluation of prevention strategies. To facilitate a consensus towards European guidelines for the management of pregnant women in labor and during pregnancy for the prevention of GBS perinatal disease, a conference was organized in 2013 with a group of experts in neonatology, gynecology-obstetrics and clinical microbiology coming from European representative countries. The group reviewed available data, identified areas where results were suboptimal, where revised procedures and new technologies could improve current practices for prevention of perinatal GBS disease. The key decision issued after the conference is to recommend intrapartum antimicrobial prophylaxis based on a universal intrapartum GBS screening strategy using a rapid real time testing.

Introduction

Streptococcus agalactiae, also referred to as group B streptococcus (GBS) remains the most common cause of neonatal sepsis and meningitis in many countries affecting 0.5 to 3 newborns in every 1000 live births [1–4]. Associated to high morbidity and mortality, GBS neonatal infections are considered as a major public health problem. In addition, GBS diseases are not restricted to newborns: they are also a common cause of disease in pregnant or postpartum women, and have been recognized as an ever-growing cause of severe invasive infections in non-pregnant adults, particularly older adults and immune-compromised patients [1,5–9]. Amongst infants with GBS invasive disease two distinct clinical syndromes are identified according to age at onset: early onset disease (EOD) presenting with mainly sepsis during the first week of life (0–6 days), and late onset disease (LOD) affecting infants aged >1 week to three months old (7–90 days), with bacteremia and/or meningitis [1,6,10,11].
By the 1990s, the estimated incidence of GBS early onset disease reported in the US was 2 per 1000 live births and in European countries varied up to 3 per 1000 live births [2,3,12,13]. After the widespread use of GBS antenatal screening and intrapartum antibiotic prophylaxis (IAP) of all GBS carriers, a more than 80% reduction in early onset have been observed [3,14]. Contrasting, the incidence of late onset has remained quite stable ranging from 0.25 to 0.5 per 1000 live births [1,4,7,8,10,15,16].

The most predictive factor for GBS EOD in newborns is the presence of GBS in the maternal genital tract during childbirth. Commonly GBS in the maternal genital tract leads to colonization of 40 to 60% of neonates and in a small proportion of cases, 1 to 2%, colonization leads to the early onset of invasive disease [1,6,17,18].

In addition to maternal GBS colonization, other factors are associated to an increase risk for EOD in the newborn, mainly preterm labor and delivery prior to gestational age <37 weeks, duration of rupture of membranes 18 or more hours before delivery [1,16,19], intrapartum maternal fever, GBS found in the urine at any time during the current pregnancy [6], and previous delivery of an infant with invasive GBS disease [1,20–22]. However, a substantial proportion, up to 50%, of GBS EOD develops in neonates born to mothers colonized with GBS but who do not demonstrate any of these risk factors [23–25].

In the 1980s, clinical trials demonstrated that GBS EOD might be prevented by systemic antibiotic prophylaxis given at onset of labor to women colonized by GBS [1,18,26–28]. Since the 1990s, major initiatives have been proposed to prevent neonatal GBS EOD. The main goal of preventive strategies is to reduce or eliminate transmission of GBS to the infant by intrapartum systemic administration of antibiotics to GBS-colonized women or to women presenting specific risks factors.

Current prevention strategies used in European countries and controversies

In some European countries using the risk-based strategy, intrapartum antibiotic prophylaxis (IAP), is offered to all women with recognized risk factors (previous infant affected by EOD, GBS bacteriuria during the current pregnancy, preterm labor <37 weeks, pre-labor rupture of membranes ≥18 hours and/or fever in labor ≥38°C). Some individual European nations have adopted a modified approach of this strategy by excluding preterm labor or ruptured membranes from these specific risk factors [29]. The use of risk-based policy in these nations reflect the belief that their low national incidence of GBS EOD will likely not decrease further with the introduction of universal culture-based screening, and solely increase maternal-fetal exposure to the adverse effects of antibiotics, mainly antimicrobial resistance and potential anaphylactic reactions [30,31]. For these countries, the implementation of universal GBS screening may lead as well to further medicalization of labor and require more counseling and a higher level of care for many more women, increasing costs and increasing the risk of obstetrical interventions [29,32].

In European countries, where universal antenatal GBS screening strategy is recommended, cultures of vaginal and rectal sites are obtained during the last trimester of pregnancy, generally between 35 and 37 weeks of gestation and IAP is administered to GBS colonized women. Support for this strategy was largely based on a large retrospective study by Schrag et al. highlighting that antenatal culture-based strategy, when compared to risk factors based policy, was more than 50% effective in preventing GBS EOD [33]. However, many criticisms have arisen over this recommendation. There is a lack of a well-designed randomized control trial supporting this statement, and there are concerns with bias and confounds within available evidence, including the large Schrag et al. study itself [33], limiting their applicability [34,35]. In addition, despite the compliance with the antenatal screening strategy, 52 to 82% of the remaining cases were born to women who were screened negative in the third trimester and thus did not receive IAP [36–38].

However, as in the USA since 2002, this strategy has been recommended by a number of European countries [39–41] and has resulted in a decline in the incidence of neonatal GBS EOD [1,3,14,42,43].

IAP is not widely adopted in all European nations due to the challenges and controversies among obstetricians and pediatricians focused on how best to identify candidates for IAP, and to low reported incidences of GBS EOD in some countries. These low incidences may be realistic or may be related to sub-reporting or to lack of available proofs confirming a case due to low-sensitivity of blood culture for newborns, i.e. Amongst nations with low reported incidence, concerns related to costs, logistics, medicalization of pregnancy and drawbacks associated to exposure to IAP, either antenatal screening-based for GBS or risk-based strategies do not seem positively balanced by the perceptions in effectiveness in implementing a screening-based policy. Further, due to poor reported predictive values for GBS colonization in labor, that can result from antenatal screening cultures performed between 35–37 weeks gestation according to suboptimal or improperly implemented procedures, some countries do not want to recommend a screening-based strategy for IAP. Recent advances in diagnostic molecular technologies may overcome limitations associated to culture screening method performed in the antenatal period, and may offer point-of-care tests for intrapartum screening which are characterized by high-sensitivity, specificity and predictive values.

In 2013, despite the considerable effort and economic resources spent on IAP for EOGBS disease, cases continue to occur.

Other strategies to reduce maternal GBS colonization and vertical transmission have been studied. Vaginal chlorhexidine may provide an additional tool in reducing GBS vaginal colonization. Stray-Pedersen et al. demonstrated a significant decrease in both maternal and early neonatal infectious morbidity using vaginal douching with 120 ml of a solution of 0.2% chlorhexidine diacetate during childbirth [44]. However, in other studies in developed countries it has not been shown to significantly reduce life threatening infections in neonates and their mothers [45,46]. These different results may be influenced by methods of chlorhexidine application that were used. In developing nations studies, vaginal chlorhexidine resulted in significant reduction in neonatal mortality and
maternal and neonatal sepsis suggesting that vaginal chlorhexidine treatment may be useful [44,47,48]. Further studies examining its role in inhibiting GBS transmission are warranted.

**Consensus conference**

A consensus conference was organized to address the many controversial issues related to GBS screening and peripartum prophylaxis in European countries. The Conference was held in Florence in June 2013 and engaged 16 experts from different countries representing all the major scientific societies interested on the topic: the European Association of Perinatal Medicine (EAPM), the European Society for Pediatric Research and the European Society of Neonatology (ESPR-ESN) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). The working group of experts had reviewed available data, identified areas of prevention strategies where results were suboptimal, where revised procedures and new technologies could improve current practices for prevention of perinatal GBS disease and facilitate consensus towards European guidelines and their implementation.

**About the bacteria and GBS epidemiology**

**Description of the bacteria**

*Streptococcus agalactiae* is a β-hemolytic streptococcus belonging to the group B of Lancefield. To date, GBS can be further distinguished on the basis of their described type-specific capsular polysaccharides into 10 antigenically unique types (Ia, Ib, II–IX) [6,11]. This capsule represents a major virulence factor, which helps bacterial evasion by interfering with phagocytic clearance except in the presence of type specific opsonophagocytic antibodies [6,11]. All GBS serotypes are capable of causing neonatal infection and observed distributions amongst EOD and LOD cases are different. Whilst some geographic differences are also reported, type III predominates amongst all neonatal infections and is far above the most frequent amongst infant with GBS meningitis. Between 2002–2011, no major change were reported in a systematic review published by Edmond et al [13]. Further molecular characterization of GBS isolates has enhanced epidemiological studies even further. Multilocus sequence typing has clearly revealed the strong association of a homogenous clone with neonatal meningitis: the clonal complex CC-17 classified as Sequence-Type 17 (ST-17), defined as the ‘‘highly virulent’’ clone amongst GBS of serotype III [49–52]. A rapid detection of this ‘‘highly virulent’’ clone ST-17 in vaginal specimens in pregnant women would allow the identification of a population of neonates at high risk for GBS disease and may suggest a rigorous follow-up of these infants. Lamy et al. had developed a real time PCR assay enabling a rapid, simple, reliable and accurate detection of this ST-17 clone [53]. Today, development is ongoing for a rapid cheap test that would allow the detection of ST-17 marker among GBS isolates at time of culture. Routinely in many laboratories MALDI-TOF mass spectrometry is an effective tool used for bacterial identification; a study has suggested that use of appropriate analysis software for GBS submitted to analysis by may be able to identify simultaneously whether or not strains belong to this ST-17 clone [54]. Clinical studies are needed to confirm the robustness of the detection of the ST-17 clones by this new technical approach and to evaluate the clinical impact on current prevention strategy, on the management and follow-up of neonates. More recently other important virulence structures as pilus proteins have been discovered and are used also to characterize GBS isolates. All these typing results are highly valuable for epidemiological purposes but currently they have not been used for the clinical management of newborns. Furthermore, used methods are quite expensive and not implemented in routine laboratories. National reference laboratories usually perform these characterizations.

**GBS carriage**

GBS is a human commensal of the gastrointestinal tract. This natural reservoir is likely the source for vaginal colonization [1,6]. GBS carriage rate among pregnant women in the vaginal and rectal microbiota ranges approximately from 10 to 35% [16,40,55,56]. GBS colonization can be transient, intermittent, or persistent [1,16] and is commonly asymptomatic, therefore the identification of carriers must be performed by bacteriological screening. Large reported variations in colonization rates may be related to age, ethnicity, body sites sampled and microbiological procedures.

**GBS clinically relevant antimicrobial susceptibility profile**

Penicillins including penicillin G are the first line drugs of choice for intrapartum antibiotic prophylaxis and for treatment of *S. agalactiae* infections either in infants or adults since all GBS isolates are considered to be uniformly susceptible to all β-lactams. Globally, GBS clinical isolates remain fully susceptible to penicillin as well as to most β-lactams, except from the emergence of very rare isolates with a decreased susceptibility to penicillin as recently reported in Japan and USA [57,58]. Currently of more concern is the resistance to macrolides and lincosamides, which has increased worldwide amongst GBS over the last two decades: from <5% to a common resistance of 20% to 35% or even more as recently published [4,59,60]. In Belgium, as determined by the National Reference Centre for GBS, macrolide resistance increased from 10.4% in the early 2000s to 33% among invasive strains isolated from 2008 to 2011 [59]. These figures are consistent with similar reports from Europe [61–65], North America [60,66–70], and Asia [71,72], except some surveillance studies in Sweden reported <10% [73], thus showing some geographical differences. Different mechanisms account for the acquired resistance to macrolides in streptococci [74]. The most prevalent of these is target site modification, which confers resistance to macrolides and inducible or constitutive resistance to lincosamides and streptogramin B, so-called MLSB phenotype. Another mechanism involving active drug efflux, only affects 14- and 15- membered ring macrolides but not 16-membered macrolides, neither lincosamides nor streptogramin B.
The European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommends disk diffusion or other validated tests for the detection of inducible clindamycin resistance [75]. The EUCAST Disk Diffusion Method for Antimicrobial Susceptibility Testing is published by EUCAST and is freely available from the EUCAST website (http://www.eucast.org). For interpretation, clinical breakpoint tables are updated on the 1st of January each year: the table for streptococcus groups A, B, C and G must be used.

For clindamycin susceptible GBS isolates, which are resistant to erythromycin, to ensure accurate results, laboratories should include a test for detection of inducible clindamycin resistance as a D-zone test. D-zone test shows antagonism of clindamycin activity by a macrolide agent.

To perform a D-zone test, according to the procedure for disk diffusion method, place the erythromycin and clindamycin disks 12–20 mm apart (edge to edge). After 16–20 hours of incubation at 35 ± 1°C in 4–6% CO2 in air look for antagonism (the D phenomenon).

- D-test positive: inducible clindamycin resistance is identified by an apparent antagonism of clindamycin by erythromycin. If there is flattening of the clindamycin inhibition zone facing the erythromycin disk, then clindamycin is presumed to be resistant.
  - If inducible resistance is detected, then report as resistant and add this comment to the report: “Patients with vaginal colonization by GBS isolates demonstrating inducible clindamycin resistance should not received clindamycin for GBS intrapartum prophylaxis”.
- D-test negative: if a GBS isolate is resistant to erythromycin, susceptible to clindamycin and there is no inducible resistance, then clindamycin can be used for GBS intrapartum prophylaxis for penicillin allergic women.
  - If inducible resistance is not detected, then report clindamycin as susceptible.

(M phenotype). This increased resistance to macrolides has been reported amongst all Streptococcus species [74] and is not specific to GBS strains. Recently the L phenotype involving isolated low-level clindamycin resistance has been reported amongst GBS isolated on all continents. This increase of macrolide and lincomamide resistance rates stresses the importance of performing susceptibility testing for GBS strains isolated from antenatal screening specimens collected from penicillin-allergic women to assess their susceptibility profile to clindamycin, including specific testing for inducible resistance to clindamycin as described in Table 1.

**Specimen collection and processing for GBS screening**

In screening-based strategies for prevention of perinatal GBS disease, the main challenge is to identify accurately the pregnant women colonized with GBS in the genital tract at time of delivery and who should receive intrapartum antibiotic prophylaxis. The crucial criteria impacting accuracy are timing of screening, origin of collected specimen(s), transport conditions and microbiological procedures.

**Timing of screening**

Limited by time for detection of bacterial growth, culture for GBS carriage detection is obtained during pregnancy. Since GBS colonization is dynamic and highly variable, the predictive values of antenatal screening cultures performed too early have been shown to be very low. Therefore, the closer to delivery that bacteriological screening is performed, the greater its utility, as sensitivity and specificity are both increased [1,76]. Based on Yancey’s study, antenatal GBS screening between 35 and 37 weeks of gestation has been used as a surrogate marker for GBS colonization at delivery [6,40,41,77,78] and predictive values has been improved. However the expected predictive values were too optimistic. In studies evaluating antenatal culture to predict intrapartum status for genital colonization with GBS, reported sensitivities range from 51% to 87%, specificities from 93.7% to 97.1%, positive and negative predictive values from 60.6% to 87% and from 88% to 96% [77,79–87].

A substantial number of positive mothers for GBS at delivery, up to 30–50%, are not identified as carriers by antenatal cultures and up to 25–40% of women identified as GBS carriers are no longer positive at the time of delivery [10,79,82]. Whether negative antenatal cultures were false-negative results or the mothers acquired GBS in the interval between the screening culture and the time of delivery is unknown.

Therefore, a rapid non-culture based screening performed intrapartum that would identify accurately GBS colonized women at time of risk is highly desirable.

**Specimen collection**

Swabbing both the lower vagina and the rectum increases the yield of GBS-positive antenatal culture and the predictive values for intrapartum colonization status [1,4,88,89]. Speculum should not be used for vaginal collection. In some countries or places, collection of anal swabs is not acceptable [39,90], declining by the way sensitivity and negative predictive values. With proper explanation provided to the patient, self-collected specimens can be a reasonable option as already performed in some European countries. Cervical, perianal or perineal specimens are not acceptable.

The type of swab used for collection is also sensitive for any kind of cultures. Flocked swabs are currently the most efficient to collect larger volume of secretion and to release more easily bacteria in culture [91]. Their use for collection and transport of vaginal-rectal swabs should increase sensitivity of culture especially for lightly colonized women with GBS.

**Specimen transport conditions**

CDC Guidelines as many others recommends use of appropriate non-nutritive preserving transport media (e.g. Amies or Stuart’s) and processing of specimen as soon as possible within 1 to 4 days, even if progressive loss of viability is well known after 24 hours. If achievable, specimens should be stored at 4°C until processing. Several studies showed the negative impact of the length of time that has elapsed between collection and inoculation to the recovery of GBS. For sure, loss of GBS viability during transport contributes partly to false negative cultures. Therefore a key improvement for screening GBS cultures would be the preservation of GBS viability during storage and transportation of specimens to the lab, which could last for several days and be exposed to various temperatures. Use as transport media of a selective enrichment broth as Todd-Hewitt broth supplemented with colistin and nalidixic acid (Lim broth) already recommended for culture, could represent a true improvement to sustain
GBS viability. In a recent study, viability was showed not only sustained at least >4 days for a wide range of temperatures up to 35°C, but the initial inoculum of GBS was also amplified resulting in increase of culture sensitivity even for low initial inoculum [92]. Refrigeration during storage and transportation in Lim broth is not advisable due to a progressive slow reduction of the initial inoculum as observed in any transport media. Use of Lim broth as part of a transport device kept at room temperature after collection until processing in the lab, should increase substantially sensitivity and negative predictive values of antenatal screening, and is cost effective.

Further clinical evaluations will be necessary to confirm these benefits from flocked swab and Lim broth as collection and transport device. These studies should also evaluate the risk of overgrowth by *Proteus sp* which can be present in rare specimens. In the same study, use of Granada broth for transportation did not show the same advantages: after amplification of the initial inoculum, an abrupt loss of viability was observed after 48–72 hours for some strains and was not recommended as transportation media.

**Antenatal specimen processing**

*Culture-based procedure*

Even if the risk of vertical transmission to newborn is increased for heavy colonization at time of childbirth, quantitative results of antenatal screening are not correlated with their predictive values on intrapartum vaginal colonization status, and can be misleading for the management during pregnancy and at delivery. To maximize the likelihood of recovering GBS upon plating antenatal screening cultures, use of a selective enrichment broth medium that inhibits the growth of competing organisms, Gram negative enteric bacilli and normal flora is recommended. In Europe the most widely used selective medium is Todd-Hewitt broth supplemented with colistin (10 μg/ml) and nalidixic acid (15 μg/ml), also named Lim broth, incubated overnight at 35°C and further sub-cultured to blood agar plates; it has been showed superior to direct agar plating of the specimen. When direct agar plating is used instead of a selective enrichment step, 20 to 50% of women who are GBS carriers have false-negative culture results [4,93,94]. However, this step in the culture protocol has not been implemented in all countries recommending universal screening. As this selective broth is not totally selective, in Spain and Belgium, since more than 10 years, and more recently as recommended by CDC and other nations, plating to differential agar as the Granada agar or to GBS specific chromogenic media has further improved yield of screening cultures for GBS detection.

To overcome lack of sensitivity of antenatal GBS screening culture and to reduce the turn-around-time of GBS screening, non-culture methods as immune-assay, peptide nucleic acid (PNA) fluorescent in situ hybridization (FISH) assay or nucleic acid amplification tests performed on Lim broth after several hours of incubation has been proposed. They compare well to subculture on selective differential media [95]. According to CDC’s recommendations [2010], as far as the use of available nuclear acid amplification test (NAAT) for GBS after enrichment step increases sensitivity up to 90–100%, they could be used for antenatal screening at 35–37 weeks’ gestation [4]. These tests remains expensive and their use have not been showed cost-effective.

In summary, to increase sensitivity of the antenatal screening and to reduce false-negative results, several improvements have been proposed [4,40–96] but clinical evaluation has not yet been done for their use at the same time. The theoretical best combination is (a) to use a flocked swab, (b) for collection of a vaginal-rectal specimen, (c) at 35–37 weeks of gestation, (d) stored and transported in a Lim broth tube, (e) at room temperature as soon as possible within 4 days, and (f) to subculture Lim broth to differential selective agars as Granada like and/or specific GBS chromogenic media.

Despite all these proposed improvements, in 2013, there are still women colonized with GBS at delivery and who were not identified GBS positive by antenatal screening cultures. Either a significant number of pregnant women are not tested for GBS vaginal-rectal colonization or the false negative screening result can be due to either new acquisition of GBS after screening or to false negative culture. A large multistate evaluation of universal antenatal GBS screening in USA, showed that a total of 61.4% of term infants with GBS EOD were born to women who had tested GBS negative between 35–37 weeks while 13.4% occurred in missed screening among mothers [37]. Failure to culture GBS, unrelated to culture process can be associated with transportation conditions or to oral antibiotic therapy taken before screening or to some feminine hygiene. Conversely, there are “false positive screening” obtained from women colonized with GBS who are no longer colonized by the time of labor and will unnecessarily receive IAP. Whilst increasing sensitivity of antenatal screening, false negative results declines but with the risk of an increase of “false positive screening” leading to unnecessary IAP.

**Non-culture method for intrapartum specimen processing**

Thus, a desirable alternative to antenatal GBS screening culture is the identification of colonization with GBS at presentation for delivery. In practice, a point-of-care test for GBS detection performed in the delivery department, bypassing the length of time and logistics to transfer the specimen to the laboratory and to have the results available, would allow the administration of an appropriate IAP in most candidates. The greatest strengths of such kind of test lie in their ability to identify women and infants at risk at the time of labor, thereby decreasing the number of false-positives and false-negatives seen with either the screening-based or risk-based strategies and thus allowing for more accurate and effective IAP. Such test used intrapartum, to be clinically useful, should gather several crucial characteristics as (a) a short turnaround time, (b) accuracy with high sensitivity and specificity, not inferior to 90–95% and 95–98% respectively, (c) easiness to perform and to interpret by labor and delivery staff with a minimum of skill and training, and (d) availability at all times 24 hours a day, seven days a week. Turnaround time should not exceed 30–45 minutes to reach an appropriate antibiotic prophylaxis amongst the highest number of GBS positive pregnant women. Full traceability of results should be warranted. An automated system requiring the minimum of maintenance and set-up is desirable. Indeed a reliable,
robust and rapid test should be cost-effective, leading to the prevention of more cases of neonatal GBS EOD while reducing the number of women receiving unnecessary IAP [97,98].

Since two decades, non-culture based diagnostic tools have been developed with minimal success and uptake until very recently. They have been evaluated for the rapid detection of GBS on vaginal-rectal swabs collected from pregnant women at 35-37 weeks of gestation or on vaginal swab collected in labor.

The first generation of rapid diagnostic tests was based on identification of the GBS group specific antigen from swab specimens and included latex agglutination or enzyme linked immune-sorbent or optical-immunotechnology or DNA-hybridization. Evaluated for intrapartum GBS screening, although they had good specificity (>95%), they showed disappointing performance with low sensitivity (33–65%), which only increased with heavy colonization; hence a negative test could not rule out GBS colonization [79,99,100].

In 2000, Bergeron et al. demonstrated that a polymerase chain reaction (PCR) test, a type of nucleic acid amplification test (NAAT), could detect GBS from vaginal specimens rapidly and reliably among pregnant women in labor, but a clinical validation was not available at that time [101]. In the last decade, with the advances in the PCR technologies providing new detection platforms for bacterial identification [102], a new generation of tests has now become available and considerable efforts have targeted the detection of GBS among women in labor. Rapid real-time PCR assays for GBS detection have been further developed and their performances have been evaluated these last years as summed up in Table 2. When compared to enriched GBS cultures, sensitivity and specificity for PCR tests range from 62.5%–100% and 84.6–100% while PPV and NPV range from 65–100% and 92.3–100% [80,82,84–86,103–111]. Today, real-time PCR-based tests (NAAT) can equal or surpass the sensitivity of antenatal culture at 35–37 weeks’ gestation and compare favorably with reference to bacterial culture performed at presentation for delivery taken as gold standard for the detection of GBS colonization [80,82,101,102,112].

Studies have showed utility to assess intrapartum GBS colonization and thus avoiding need for antenatal screening, but they remain limited [80]. At least, rapid real-time PCR assays offer the advantage of GBS detection among women delivering preterm, women without antenatal care or in whom no antenatal culture was performed, or women for whom no result was available at delivery as mentioned in the revised 2010 CDC recommendations.

Among tests approved by the Food and Drug Administration (USA), the Xpert™ GBS assay (Cepheid, Sunnyvale, CA, USA), can yield results in 30 to 50 minutes and is characterized by an extremely low workload. Others like the BD GeneOhm StrepB Assay, even when they present good analytical performances [108], cannot be used as a bedside testing kit but must be run by skilled operators in a laboratory setting and requires several operating steps. Unlike the others, the Xpert™ GBS assay is performed on a platform (GeneXpert Dx System) where sample preparation, amplification and detection steps are fully automated and completely integrated. The test is simple enough for even inexperienced technicians or medical staff to perform. However, use of this relatively new and more expensive technology is not currently widespread among European hospitals. Initial studies on GBS EOD prevention, suggested that strategies using intrapartum GBS PCR screening would be superior to antenatal vaginal and rectal screening or risk factors screening strategies. In 2002, Haberland and Benitz from their cost analysis model have also demonstrated that rapid and simple NAAT benefits exceed their costs, but these tests become less attractive as their costs increase [98]. Further studies using real-time PCR performed in intrapartum setting were needed to identify targeted population and settings where the test will be most useful. In these last years, studies not supporting the intrapartum PCR screening as a cost-effective strategy in comparison with culture screening at around 35–37 weeks of gestation, used data from older less accurate PCR equipment [32,113].

In France, following a one-year study assessing the high diagnostic accuracy of the Xpert™ GBS assay in 968 term deliveries [82], a big maternity hospital has implemented a strategy for prevention of GBS perinatal disease where IAP is based on screening results provided uniquely by this NAAT, the Xpert™ GBS assay performed in term deliveries by midwives at the point of care in the delivery setting. A key success factor was the empowerment of the midwives in the management of PCR processing when the women need it, without loosing time in bringing the sample to the laboratory or in waiting for the communication of the screening result. In 2012, El Helali et al. reported this experience in 2814 deliveries and showed the superiority of this new strategy for prevention of perinatal GBS early onset disease at a neutral cost when compared to the vaginal antenatal cultures performed at 35–37 weeks gestation in 2761 deliveries [97]. According to this study, the number and severity of GBS EOD cases and the resulting hospital costs were significantly lower. In their study, the drawback of delay in the administration of IAP when using the intrapartum screening was limited. When comparing the two approaches, in women receiving IAP, 50% in the intrapartum screening and 55% in the antenatal screening were treated with at least two penicillin doses. Thus, intrapartum GBS PCR at the point of care provides a direct and accurate evaluation of the current GBS colonization status at the time of labor, avoiding unnecessary exposure to antibiotics by treating women who really need it. Further studies are needed to validate and confirm cost-effectiveness in different European countries that present different rates of GBS carriage and GBS EOD incidence, and importantly have diverse national or private health care systems. All these parameters could impact differently the cost analysis.

Importantly, women in preterm labor and with premature ruptured membranes can also be GBS screened using rapid PCR allowing a selective administration of IAP only in GBS colonized women, therefore further limiting antibiotic exposure. In a prospective study on 139 women with premature rupture of membranes, it has been documented that results of antenatal GBS screening cultures do not always accurately predict intrapartum GBS status [114]. Thus, the intrapartum rapid GBS-PCR test was the only method available to identify GBS colonized women at risk, who delivered preterm and potentially avoid the delivery of a GBS colonized neonate by the administration of IAP. The accurate administration of
Table 2. Performance of Nucleic Acid Amplification tests (NAAT) compared with enriched and non-enriched group B streptococcus culture.

| References | No of patients | NAAT TEST | Timing | Sampled site (enrichment) | Number positive by NAAT/ Number positive by culture | NAAT sensitivity | Number negative by NAAT/ Number negative by culture | NAAT specificity | NAAT PPV | NAAT NPV |
|------------|----------------|-----------|--------|---------------------------|---------------------------------------------------|-----------------|---------------------------------------------------|-----------------|----------|----------|
| [111]      | 445            | Xpert™ GBS | IP     | V (Todd Hewitt)           | 113/115                                           | 98.3%           | 307/310                                           | 99%             | 97.4%    | 99.4%    |
| [110]      | 175            | Xpert™ GBS | AP     | V/R (Todd Hewitt)        | 13/15                                             | 86.6%           | 153/160                                           | 95.6%           | 65%      | 98.7%    |
| [84]       | 231            | Xpert™ GBS | AP     | V/R (StrepBcarrot)       | 45/45                                             | 100%            | 185/185                                           | 100%            | 100%     | 100%     |
| [85]       | 695            | Xpert™ GBS | IP     | V/R (Todd Hewitt)        | 108/127                                           | 85.00%          | 492/510                                           | 96.6%           | 85.7%    | 96.3%    |
| [86]       | 559            | Xpert™ GBS | IP     | V/R (Todd Hewitt)        | 119/131                                           | 90.8%           | 406/416                                           | 97.6%           | 92.2%    | 97.12     |
| [109]      | 196            | IDI strepB™ | IP     | V/R (Todd Hewitt)        | 38/42                                             | 90.5%           | 148/152                                           | 96.1%           | 86.7%    | 97.4%    |
| [82]       | 968            | Xpert™ GBS | IP     | V (Todd Hewitt)          | 135/137                                           | 98.6%           | 723/726                                           | 99.6%           | 97.8%    | 99.7%    |
| [106]      | 784            | Xpert™ GBS | IP     | V/R (Lim broth)          | 173/190                                           | 91.1%           | 570/594                                           | 96%             | 87.8%    | 97.1%    |
| [79]       | 791            | IDI strepB™ | IP     | V/R (Lim broth)          | 149/188                                           | 79.3%           | 575/603                                           | 95.4%           | 84.2%    | 93.7%    |
| [107]      | 162            | IDI strepB™ | IP     | V/R (enrichment)         | 38/42                                             | 90.5%           | 148/154                                           | 96.1%           | 86.7%    | 97.4%    |
| [108]      | 200            | BD GeneOhm strepB™ | AP | V (Todd Hewitt) | 64/83 | 77.1% | 99/117 | 84.6% | 79.3% | Non-specified |
| [105]      | 55             | Xpert™ GBS | IP     | V/R (enrichment)         | 23/24                                             | 95.8%           | 20/31                                              | 64.5%           | 67.6%    | 95.2%    |
| [104]      | 233            | IDI strepB™ | AP     | V/R (Lim broth)          | 59/68                                             | 86.8%           | 157/165                                           | 95.2%           | 86.8%    | 95.2%    |
| [103]      | 315            | IDI strepB™ | AP     | V (Lim broth)            | 35/56                                             | 62.5%           | 252/259                                           | 97.3%           | 83.3%    | 92.3%    |
| [80]       | 729            | IDI strepB™ | IP     | V/R (Todd Hewitt/Lim broth) | 140/149 | 94% | 626/653 | 95.9% | 83.8% | 98.6% |

Performance of NAAT versus non-enriched GBS culture

| References | No of patients | NAAT TEST | Timing | Sampled site (enrichment) | Number positive by NAAT/ Number positive by culture | NAAT sensitivity | Number negative by NAAT/ Number negative by culture | NAAT specificity | NAAT PPV | NAAT NPV |
|------------|----------------|-----------|--------|---------------------------|---------------------------------------------------|-----------------|---------------------------------------------------|-----------------|----------|----------|
| [114]      | 139            | Xpert™ GBS | IP     | AF                        | 10/11                                             | 90.11%          | 126/128                                           | 98.4%           | 83.3%    | 99.2%    |
| [137]      | 225            | Xpert™ GBS | IP     | V                         | 17/25                                             | 66.7%           | 187/197                                           | 94.9%           | 64.3%    | 95.4%    |
| [25]       | 206            | Xpert™ GBS | IP     | V                         | 24/29                                             | 82.8%           | 43/46                                             | 93.4%           | 88.8%    | 89.5%    |

Abbreviations: AP: antenatal, IP: intrapartum, V: vaginal only, V/R: vaginal-rectal, AF: amniotic fluid, PPV: positive predictive value, NPV: negative predictive value.
IAP is crucial in limiting exposure to antibiotics that can promote resistance, anaphylaxis and importantly changes in the neonatal microbiome that may affect immunological priming and rates of allergy, asthma and obesity [115,116].

Next to the advantages provided by the new generation of PCR assays, there is some concern about the absence of antibiotic susceptibility result for their use for penicillin allergic women. An expected improvement would be the combined detection of GBS and of mutations likely to confer resistance to clindamycin, in order to guide the appropriate IAP for penicillin-allergic women at high risk of anaphylaxis. In the meantime, for penicillin allergic women with a high risk of anaphylaxis, antenatal screening would be still recommended in order to assess clindamycin susceptibility on all GBS isolates.

Towards a European consensus

Intrapartum antibiotic prophylaxis

Following an exhaustive review of evidence-based convincing arguments and the cons for the administration of intrapartum antibiotic prophylaxis (IAP) for prevention of perinatal GBS disease, the first step towards a consensus has been to decide to recommend IAP as the core of a strategy for prevention of GBS perinatal disease.

The second main step has been the design of a strategy to recommend for identifying candidates for IAP: risk-based, or antenatal GBS screening-based, or intrapartum GBS screening-based, or any combination of these.

Since up to 50–60% of GBS EOD in neonates occur in neonates born to mother without any other risk factor than presence of GBS in the maternal genital tract during childbirth, a screening-based policy was desirable. However, there were concerns related to an antenatal screening-based strategy, as the required systematic follow-up of pregnant women during pregnancy and antenatal screening detection of GBS performed at 35–37 weeks gestation, as having the results available at time of delivery to guide management during labor, or as the appropriate level of coordination between the different health care providers and access to care that are not often possible. In practice, poor to sub-optimal positive and negative predictive values of antenatal cultures can result in missed opportunities for IAP in women falsely identified not colonized with GBS and induced unnecessary IAP in others who are no more at risk at time of delivery due to change of their GBS status. On the other hand, the use of a clinical risk-based strategy alone will inevitably result in missed opportunities for IAP and the prevention of 50–60% of neonatal GBS EOD not associated to other risk factors except from the colonization with GBS in their mother’s genital tract at delivery. Further, with the risk factors strategy, numerous unnecessary IAP are also promoted, as the incidences of the identified maternal risk factors are not significantly different among pregnant women colonized or not with GBS [117].

To improve both negative and predictive values of antenatal screening for GBS detection or to reduce rates of missed opportunities for IAP and of unnecessary IAP, intrapartum testing is highly desirable. Though a risk-factor based strategy coupled to intrapartum PCR performed selectively on swab collected from women presenting a risk factor, and IAP given only to GBS positive women, would reduce the exposure of antibiotics among women in labor, the deficiency in catching approximately 40–60% of EOD infants born of mothers without risk-factors, presents limits to the utilization of this approach [23,24,118].

At this point of knowledge, with the availability of highly sensitive and specific rapid tests, an agreement has been reached to switch from a policy of antenatal testing to intrapartum testing. Therefore the chosen strategy to recommend for all women is to perform intrapartum a rapid screening to assess GBS colonization on a vaginal swab and to offer IAP to all GBS positive women. This approach can solve the problem of preterm delivery <35 weeks gestation, the transient presence of GBS resulting in poor predictive values of antenatal screening, and can simplify the logistics. Rapid accurate testing performed intrapartum can allow improvement of targeting IAP and withholding unnecessary antibiotic administration in a substantial number of women.

The main drawbacks related to this strategy are a delay, which should remain inferior to one hour, in administration of antibiotics while waiting for the result, no antimicrobial susceptibility results for penicillin-allergic women, and their high costs. If universal intrapartum screening with NAAT becomes a European recommendation, with a large-scale production, the cost of NAAT should decline significantly. Waiting for expected improvement related to the detection of clindamycin resistance, penicillin allergic pregnant women should be informed on the limits of PCR analysis on GBS antibiotic susceptibility and antenatal cultures collected at 35–37 weeks of gestation should be obtained in order to test clindamycin susceptibility of colonizing GBS.

In conclusion, in the absence of an immediate universal intrapartum PCR screening program, which may take a certain period of time to implement in given European countries, there is not sufficient evidence to recommend either prevention strategy before the other. In case universal antenatal screening is used, we recommend the utilization of an enhanced culture program, including the improvements described above for sampling/transporting swabs and for culture procedure. In case a risk-based prevention strategy is used, providers should be aware of the high number of EOD infants, approximately 40–60%, presenting without risk factors. Although mortality in these EOD infants without risk-factors is reportedly low, the effect of morbidity should not be underestimated.

Vaccination

Beside these expected improvements resulting in reduction of incidence and attributable mortality to GBS EOD, nearly a third of pregnant women will be treated with antibiotics with their related drawbacks. Even if GBS remains fully susceptible to penicillin, how long will it last? Further, IAP has no effect on the incidence of GBS LOD. Awaiting since decades, a preventative method that can impact both GBS early and late onset disease is desirable. Development of vaccine to immunize the mother to develop high protective circulating levels of specific GBS antibodies is ongoing. Capsular polysaccharides were the first candidates for the development of vaccine but recently pilus proteins have become highly desirable vaccine candidates [119,120].
In the future, vaccination could represent the most attractive strategy for prevention of GBS diseases including EOD and LOD but also GBS associated miscarriage, stillbirth and maternal infections [121].

**Recommendations**

The recommendations for the prevention of GBS EOD presented thereafter should be adopted by obstetricians, microbiologists, neonatologists, labor and delivery staffs.

**Identification of candidates for intrapartum antibiotic prophylaxis**

The identification of candidates to benefit of intrapartum antibiotic prophylaxis should be conducted according to indications and non-indications listed in Table 3. Criteria were adapted from the revised guidelines edited by CDC in 2010.

The key points of the recommended strategy is a universal intrapartum GBS screening with a rapid real time PCR testing, or other NAAT showing high analytical performances: sensitivity and specificity should not be inferior to 90% and 95%, respectively. If rapid real time PCR testing is not available, strict adherence to an optimized antenatal 35–37 weeks GBS culture screening is recommended (Figure 1).

- Women who had previously an infant with GBS invasive disease or if a GBS has been cultured from the urine during any trimester of the current pregnancy should receive IAP and should not be further tested for GBS colonization.
- For penicillin-allergic women with a history of anaphylaxis, angioedema, respiratory distress or urticarial following administration of penicillin or cephalosporin, antenatal 35–37 weeks GBS culture screening is recommended and antimicrobial susceptibility testing should be ordered.
- Pregnant women who present at the time of labor with suspicion of chorioamnionitis should receive antibiotic therapy that includes usually antibiotics adequate for GBS prophylaxis and if other regimens are used, GBS IAP should be added.
- All other pregnant women should be screened for vaginal GBS colonization with a rapid real time PCR testing (unless it is not available), at the admission for delivery, when they present signs and symptoms of labor, either in term labor or preterm labor.
- IAP should be then given at the onset of labor or rupture of membranes to all pregnant women screened positive for GBS colonization, except in case of cesarean delivery performed before onset of labor on a woman with intact amniotic membranes.
- In circumstances in which the GBS status is not available or indeterminate (PCR result either invalid or presenting an error in the process of the test) at the onset of labor, IAP should be given according to the presence of at least one risk factor as preterm delivery (<37 weeks gestation) or a duration of membrane rupture ≥18 hours or intrapartum temperature ≥38°C.
- IAP is also indicated for women tested negative intrapartum by NAAT test, who have a duration of...

Table 3. Indications and non-indications for intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal (GBS) disease for term deliveries and preterm labor <37 weeks gestation. Adapted from revised guidelines from CDC 2010 [4].

| Intrapartum GBS prophylaxis indicated | Intrapartum GBS prophylaxis non indicated |
|---------------------------------------|------------------------------------------|
| • Previous infant with GBS invasive disease | • GBS colonization during a previous pregnancy (unless an indication for GBS prophylaxis is present during the current pregnancy) |
| • GBS bacteriuria during any trimester of the current pregnancy | • GBS bacteriuria during a previous pregnancy (unless an indication for GBS prophylaxis is present during the current pregnancy) |
| • Positive late antenatal GBS vaginal-rectal screening culture performed during the current pregnancy in the following cases: | • Negative intrapartum GBS vaginal screening with rapid real time PCR unless the duration of amniotic membrane rupture is ≥18 hours following PCR testing or if intrapartum temperature is ≥38°C. |
| – If intrapartum PCR screening strategy is adopted and the patient is allergic to penicillin | • Ceasarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age. |
| – If late antenatal vaginal-rectal GBS culture screening strategy is used for GBS EOD prevention. | |
| • Positive intrapartum GBS vaginal screening with rapid real time PCR | |
| • Negative intrapartum GBS vaginal screening with rapid real time PCR and any of the following: | |
| – Amniotic membrane rupture ≥18 hours following the PCR testing | |
| – Intrapartum temperature ≥38°C | |
| • Unknown GBS status at the onset of labor (results indeterminate for intrapartum PCR or missed PCR testing, missed antenatal culture screening or antenatal culture screening results not available) and any of the following: | |
| – Amniotic membrane rupture ≥18 hours | |
| – Intrapartum temperature ≥38°C | |
| – Preterm labor <37 weeks | |

1 Intrapartum antibiotic prophylaxis is not indicated in this circumstance if a cesarean delivery is performed before onset of labor on women with intact amniotic membranes.
2 The optimal timing for antenatal vaginal-rectal GBS culture screening is at 35–37 weeks gestation.
3 Intrapartum rapid real time PCR testing for GBS or other NAAT showing high analytical performances, might not be available in all maternities, then these settings should adopt the antenatal 35–37 weeks GBS culture screening strategy with strict adherence to either timing of screening or recommended protocols of specimen collection and processing for GBS screening.
4 When the intrapartum rapid real time PCR screening strategy is used and the patient is allergic to penicillin, a vaginal-rectal GBS culture should be done at 35–37 weeks in order to test clindamycin susceptibility (Table 1).
5 If chorioamnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS antibiotic prophylaxis.
membrane rupture following NAAT testing ≥18 hours or develop intrapartum temperature ≥38°C

**Threatened preterm delivery or premature rupture of membranes**

In the case of women admitted with signs of threatened preterm delivery or premature rupture of membranes (pPROM), assessing whether preterm labor or rupture of membranes will result in preterm delivery can be difficult; therefore GBS PCR testing should be performed on a vaginal-rectal sample to evaluate GBS colonization which is then considered valid for 5 weeks.

Patient should be regularly assessed for progression to true labor and IAP should be given to patients with a positive GBS screening when entering in true labor. If a woman has not yet delivered 5 weeks after a negative vaginal-rectal GBS NAAT testing, she should be re-screened to re-evaluate GBS colonization.

Administration of IAP in patients in threatened preterm delivery should be weighed against exposing patients in false labor to antibiotics with potential detrimental effects as demonstrated by the ORACLE II study [122].

Figure 2 provides an algorithm with recommendations for the management of women admitted with signs of threatened preterm delivery or with preterm premature rupture of membranes (pPROM) in settings where rapid real time PCR GBS test is available. The algorithm has been adapted from the revised guidelines edited by CDC in 2010.

**Screening**

**Intrapartum non-culture rapid test**

*Conditions to fulfill implementation of intrapartum screening:*

- Rapid real-time PCR or other chosen NAAT testing for GBS should gather the following characteristics:
  - Sensitivity and specificity not inferior to 90% and 95% respectively.
  - Fully automated processing with integrated internal controls, full traceability of the results and minimum of maintenance.
  - Easiness to perform and interpret results by delivery staff with a minimum of training.
  - Short turnaround time not exceeding one hour.
  - Availability 24 hours a day and seven days a week.

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Figure 1. Algorithm for screening for GBS colonization and use of IAP for women with term labor or preterm labor <37 weeks.

IAP is started either at the onset of true labor or rupture of membranes, except in the instance of cesarean delivery performed before onset of labor on a woman with intact amniotic membranes. In penicillin allergic women at high risk for anaphylaxis, clindamycin is given for susceptible isolate and vancomycin for resistant isolate to clindamycin. Penicillin allergic women entering in spontaneous labor before either vaginal-rectal 35–37 weeks screening or susceptibility testing were done should receive vancomycin.

*Routine screening for asymptomatic bacteriuria is recommended in pregnant women. Laboratories should screen urine culture specimen for the presence of GBS in concentration ≥ 10⁴ cfu/ml either in pure culture or mixed with a second microorganism. Women with symptomatic or asymptomatic GBS urinary tract infection detected during pregnancy should be treated according to current standards of care for urinary tract infection during pregnancy and they should also receive IAP at the onset of labor.

**Antimicrobial susceptibility testing should be performed on antenatal GBS isolates and include detection of clindamycin resistance either constitutive or inducible.

*Before 35 weeks gestation, the pregnant women’s potential allergic status should have been established by an anesthetist or other specialist.

In case of suspicion of chorioamnionitis, antibiotics given for therapy usually include antibiotics effective on GBS. If other regimens are used IAP for GBS prevention should be added.

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As the effectiveness of GBS screening strategy depends on timely administration of IAP, the rapid NAAT test should be performed quickly after the specimen collection to avoid delay in results and the start of IAP. Thus, the rapid NAAT test should be implemented at the point of care, in delivery settings except if the premises of laboratory are adjacent.

Physicians, midwives or other caregivers should be trained and qualified to perform the rapid NAAT GBS test, under the responsibility of the laboratory.

The laboratory should be in charge of either system maintenances or external quality controls processing and their validation.

The automated system may be connected to hospital information system to securely get identity and demographics of the patient, as well as the hospital medical record number. It should also be connected to laboratory information system for a secure transmission and validation of the results.

A virtual private network may be created to communicate between the system and laboratory in case of any problem during process or interpretation of the results.

**Specimen collection**

Physicians, midwives or other qualified caregivers should collect vaginal specimen for rapid GBS testing at the beginning of signs and symptoms of labor. For patients entering labor (either term or preterm), only secretions from the lower one-third of the vagina should be swabbed without using a speculum (Figure 1). Sampling the rectum site is not warranted for intrapartum GBS screening.
**Table 4. Recommended regimens for intrapartum antibiotic prophylaxis for prevention of early onset GBS disease (Adapted from revised guidelines from CDC 2010 [4]).**

| For patient non-allergic to penicillin | Penicillin G | 5 million units IV initial dose, then 2.5–3.0 million units every 4 hours until delivery |
|---------------------------------------|--------------|-------------------------------------------------------------------------------------|
| Acceptable alternative:               | Ampicillin/Amoxicillin 2 g IV initial dose, then 1 g IV every 4 hours until delivery |

| For patient allergic to penicillin   |                                          |
|--------------------------------------|------------------------------------------|
| – And no history of anaphylaxis or angiodema or respiratory distress or urticaria after receiving penicillin or a cephalosporin. | Cefazolin 2 g IV initial dose, then 1 g IV every 8 hours until delivery. |
| – With a history of anaphylaxis or angiodema or respiratory distress or urticaria after receiving penicillin or a cephalosporin. | Clindamycin 900 mg IV every 8 hours until delivery |
| And GBS isolate susceptible to clindamycin* | Or GBS isolate resistant to clindamycin or if unknown susceptibility result |
| Vancomycin | 1 g IV every 12 hours until delivery |

*If the isolate is resistant to erythromycin and apparently susceptible to clindamycin: testing for inducible clindamycin resistance must be performed, and if negative, clindamycin can be used (Table 1).

- Swabbing both the lower vagina and the rectum is warranted only for women with threatened preterm delivery or preterm premature rupture of membranes (pPROM) who are not already entering labor (Figure 2).
- Use the collection device validated and recommended by the manufacturer of the rapid NAAT test. Flocked-swabs are not recommended for the Xpert™ GBS assay.
- A double swab is recommended to be able to perform GBS cultures on the second swab, in case of indeterminate results; it is useful to know the mother’s GBS status in case of EOD in the newborn.
- Before collecting vaginal specimen, excessive external amounts of secrections should be wiped. An excess of mucus on the tip or the stem of the swab could result in indeterminate results if using Xpert™ GBS assay. The excess of mucus should then be removed using sterile gauze before inserting the swab into the cartridge.

**Performing the NAAT testing for GBS and reporting the results:**
- Follow procedures of the manufacturer to perform the NAAT testing.
- Enclose the printed report of the result in the medical record of the patient. If the NAAT assay result indicates an invalid NAAT testing or an error in the process of the test, then GBS status should be considered as “indeterminate”.

Indications and non-indications of IAP at the onset of labor or rupture of membranes are reported in Table 3 and recommended regimens in Table 4.

**Antenatal culture method and antimicrobial susceptibility testing**

**Collection:**
- At 35–37 weeks of gestation, collection of specimen(s) for culture may be done by physician or other qualified caregivers (or either self-collected by the patient, with appropriate instruction). This involves swabbing the distal vagina (vaginal introitus), followed by the rectum (i.e. through the anal sphincter). A unique swab for both sites of collection is rational and recommended. Because lower vaginal, as opposed to cervical, cultures are recommended, specimen should not be collected by speculum examination.
- Use of flocked-swab as eSwab (Copan, Italy) or (Becton Dickinson) is recommended.

**Specimen transport**
- One or both swabs should be placed in a Todd Hewitt broth containing colistin (10 mg/L) and nalidixic acid (15 mg/L) also named Lim broth. In these conditions, viability of GBS is warranted for at least 4 days at room temperature.
- If Lim broth is not available, swab(s) should be placed in a non-nutritive transport medium (e.g. Amies or Stuart’s without charcoal). In these conditions, viability of GBS is warranted for at least 24 h at room temperature or in a refrigerator (2–8 °C).
- Specimens and accompanying requisition should be labeled with patient name, hospital medical record number, other patient demographics, date and time of collection.
- The order should clearly identify that specimens are for group B streptococcal culture.
- If a woman is determined to be at high risk for anaphylaxis, susceptibility testing for clindamycin and erythromycin should be ordered.
- Swabs should reach the lab as soon as possible after collection.

**Inoculation**
- Upon reception, swabs transported in Lim broth should be incubated overnight at 35 °C.
- For swabs received in non-nutritive transport medium, they should be placed into selective enrichment broth medium (such as Lim broth) further incubated overnight at 35 °C to enhance the recovery of GBS.
- Optional, in addition (not instead) to the broth inoculation: some laboratories may choose to inoculate the swab to a plate of CNA sheep blood agar or to a selective streptococcal medium as Granada agar or a specific chromogenic agar, immediately upon receipt. Plate(s) should be streaked for isolation.

**Incubation**
- Selective direct plate(s) should be incubated at 35–37 °C in the appropriate atmosphere: blood agar in 5% CO₂, Granada agar anaerobically and chromogenic agars in ambient air.
Broth should be incubated at 35–37 °C in ambient air, or in CO₂.
- After 18–24 h of incubation, the broth is subcultured to a Granada agar plate or to a GBS selective chromogenic agar as StrepBSelect™ (BioRad) or ChromID™ Strepto B (bioMerieux) or Brillance GBS (ThermoScientific), if GBS have not been isolated on optional direct plate(s).
- Incubate the subculture plate(s) at 35–37 °C in the appropriate atmosphere for 48 h.

Culture examination
- After overnight incubation and 48 h, observe plates for suggestive GBS colonies and identify them.
  - Upon Granada medium, the development of orange or red colonies is specific (100%) of GBS. (cf. Figure 3A).
  - On StrepBSelect™ medium, suggestive colonies of GBS are pale to dark blue turquoise, on ChromID™ Strepto B medium, suggestive colonies of GBS are pale pink to red and, on Brillance GBS medium suggestive colonies of GBS are bright dark pink to red (cf. Figure 3B, C and D). On these chromogenic media, colonies suggestive of GBS should be specifically identified with a grouping latex or co-agglutination test or other tests for GBS antigen detection or by MALDI-TOF mass spectrometry.
  - On blood agar, suggestive colonies of GBS are gray, translucent, with a small zone of beta-hemolysis (or no hemolysis).

Reporting results
- If the culture is negative, report “No group B streptococcus isolated”.
- If the culture is positive, whatever is the density:
  - Report “Presence of group B streptococci”;
  - Do not report any enumeration.

Antimicrobial susceptibility testing
- Susceptibility to clindamycin and erythromycin should be performed, according to EUCAST procedure, on antenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis. If isolates are susceptible to clindamycin and resistant to erythromycin, testing for inducible clindamycin resistance should be performed by the D-zone test (Table 1).

Intrapartum antibiotic prophylaxis
Agents and dosing for intrapartum antibiotic prophylaxis should be administered according to the recommendations shown in Table 4.

Penicillin G remains the first line drug of choice for intrapartum antibiotic prophylaxis, because of its narrow spectrum. The recommended dosing regimen of penicillin G is an initial dose of 5 million units (3 g) intravenously, followed by 2.5–3 million units intravenously every 4 hours until delivery. This dosage should be strictly adhered in order to achieve rapidly adequate drug levels in the fetal circulation and amniotic fluid while avoiding neurotoxicity [123–127]. Attention should be paid to the propensity to administer reduced dosages given the set dosages in commercially available vials. Ampicillin or amoxicillin are acceptable alternatives and should be administered in an initial dose of 2 g intravenously, followed by 1 g intravenously every 4 hours until delivery.

Given potential penicillin-allergy in some women, the allergic status of pregnant women should have been carefully established by an anesthetist or other specialist before 35 weeks. The physician should evaluate if the patient is at high risk of anaphylaxis because a prior history of anaphylaxis, angioedema, respiratory distress or urticarial following the administration of a penicillin or a cephalosporin. These patients should not receive penicillin G, ampicillin, amoxicillin or a cephalosporin. Under the discretion of the physician, in penicillin allergic women who do not have a history of those reactions, and thus are at low risk for anaphylaxis, cefazolin is the preferred agent. Cefazolin has a relatively narrow spectrum, similar pharmacodynamics to penicillins and also achieve high intra amniotic concentrations [128–130]. Then cefazolin should be administered at an initial dose of 2 g intravenously, followed by 1 g intravenously every 8 hours until delivery.

In penicillin-allergic women who could not receive cefazolin, a vaginal-rectal swab should be collected between 35–37 weeks gestation, to isolate GBS strain and assess its susceptibility profile to clindamycin, including specific testing for inducible resistance to clindamycin (cf procedures for clindamycin and erythromycin testing – Table 1) either if the antenatal GBS culture screening or if the intrapartum GBS PCR screening strategies are adopted. In penicillin-allergic
women antenatal GBS susceptibility testing is also recommended in the PCR screening strategy until the development of new GBS PCR assays that could combine the rapid detection of GBS and mutations likely to confer resistance to clindamycin.

Then, penicillin-allergic women at high risk of anaphylaxis should receive clindamycin if their GBS isolate is susceptible to clindamycin and erythromycin. If the strain is susceptible to clindamycin but resistant to erythromycin, clindamycin could be used if testing for inducible clindamycin resistance is negative. The recommended dosing regimen for clindamycin is Clindamycin 900 mg intravenously every 8 hours until delivery. Erythromycin is not recommended given the high rates of resistance present in GBS [16] and to subtherapeutic concentrations in amniotic fluid and fetal serum.

Otherwise, if GBS strain is intrinsically resistant to clindamycin, if the isolate demonstrates inducible resistance to clindamycin, or if its susceptibility is unknown, vancomycin 1g intravenously every 12 hours until delivery is recommended though its usage is suggested only as a last resort.

Duration of IAP of ≥4 hours of beta-lactam antibiotics has been shown to be highly effective in preventing vertical transmission of GBS and GBS EOD [18,124,126,131,132]. Even though not ideal, duration of IAP ≥2 hours can provide acceptable coverage [131,133–135]. In cases of less than acceptable coverage (<2 hours) the neonatologist should be informed.

The administration of IAP is unnecessary for elective cesarean section (CS) performed before labor onset with intact membranes. IAP should be administered for all non-electives CS in case of a positive or unknown GBS status [136].

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Declaration of interest

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References

1. Centers for Disease Control and Prevention. Prevention of perinatal Group B streptococcal disease. MMWR 2002;51:22–22.
2. Melin P, Verschraegen G, Mathieu L, et al. Towards a Belgian consensus for prevention of perinatal group B streptococcal disease. Indian J Med Res 2004;119:197–200.
3. Lopez Sastre JB, Fernandez Colomer B, Coto Cotallo GD, et al. Trends in the epidemiology of neonatal sepsis of vertical transmission in the era of group B streptococcal disease. Acta Paediatr 2005;94:451–7.
4. Centers for Disease Control and Prevention. Prevention of perinatal Group B streptococcal disease. Revised guidelines from CDC, 2010. MMWR 2010;59:No.RR-10:1–32.
5. Baker CJ, Kasper DL. Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. N Engl J Med 1976;294:753–6.
6. Baker C. Group B streptococcal infections. In: Stevens DL, Kaplan EL, eds. Streptococcal infections. New York (NY): Oxford University Press; 2000:222–37.
7. Centers for Disease Control and Prevention. Perinatal group B streptococcal disease after universal screening recommendations United States 2003–2005. MMWR Morb Mortal Wkly Rep 2007;56:701–5.
8. Heath PT, Schuchat A. Perinatal group B streptococcal disease. Best Pract Res Clin Obstet Gynaecol 2007;21:411–24.
9. Skoff TH, Farley MM, Petit S, et al. Increasing burden of invasive group B streptococcal disease in non pregnant adults, 1990–2007. CID 2009;49:85–92.
10. 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.
11. Nizet V, Ferrieri P, Rubens CE. Molecular pathogenesis of group B streptococcal disease in newborns. In: Stevens DL, Kaplan EL, eds. Streptococcal infections. New York: Oxford University Press, 2000:180–221.
12. Trijbels-Smeulders MAJM, Kolee LAA, Adriaanse AH, et al. Neonatal group B streptococcal infection: incidence and strategies for prevention in Europe. Pediatr Infect Dis J 2004;23:172–3.
13. Edmond KE, Kortsaliosdaki 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.
14. Melin P. Neonatal group B streptococcal disease: from pathogenesis to preventive strategies. Clin Microbiol Infect 2011;17:1294–303.
15. Jordan HT, Farley MM, Craig A, et al. Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease: a multistate, population-based analysis. Pediatr Infect Dis J 2008;27:1057–64.
16. Verani JR, Schrag SJ. Group B streptococcal disease in infants: progress in prevention and continued challenges. Clin Perinatol 2010;37:375–92.
17. Anthony BF, Okada DM, Hobel CJ. Epidemiology of the group B streptococcus: maternal and nosocomial sources for infant acquisitions. J Pediatr 1979;95:431–6.
18. Boyer KM, Gotoff SP. Prevention of early-onset neonatal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986;314:1665–9.
19. Dillon HC, Khare S, Gray BM. Group B streptococcal carriage and disease: a 6-year prospective study. J Pediatr 1987;110:31–6.
20. Christensen KK, Dahlander K, Linden V, et al. Obstetric care in future pregnancies after fetal loss in group B streptococcal septicaemia. A prevention program based on bacteriological and immunological follow-up. Eur J Obstet Gynecol Reprod Biol 1981;12:143–50.
21. Carstensen H, Christensen KK, Gunnert L, et al. Early-onset neonatal group B streptococcal septicaemia in siblings. J Infect 1988;17:201–4.
22. Fæxielius G, Bremke K, Kvist-Christensen K, et al. Neonatal septicaemia due to group B streptococci – perinatal risk factors and outcome of subsequent pregnancies. J Perinat Med 1988;16:423–30.
23. Flidel-Rimon O, Galstyan S, Juster-Reicher A, et al. Limitations of the risk factor based approach in early neonatal sepsis evaluations. Acta Paediatr 2012;101:540–4.
24. Heath PT, Balfour G, Weisner AM, et al.; PHLS Group B Streptococcus Working Group. Group B streptococcal disease in the UK and Irish infants younger than 90 days. Lancet 2004;363:292–4.
25. Håkansson S, Kallén K, Bullarbo M, et al. Real-time PCR-assay in the delivery suite for determination of group B streptococcal colonization in a setting with risk-based antibiotic prophylaxis. J Matern Fetal Neonatal Med. 2014;27:328–32.
26. Easton CS, Hastings MJ, Deely J, et al. The effect of intrapartum chemoprophylaxis on the vertical transmission of group B streptococci. Br J Obstet Gynaecol 1983;90:633–5.
27. Nizet V, Ferrieri P, Rubens CE. Molecular pathogenesis of group B streptococci. Br J Obstet Gynaecol 1983;90:633–5.
28. Tuppurainen N, Hallman M. Prevention of neonatal group B streptococcal disease. MMWR 2002;51:22–22.
29. Royal College of Obstetricians and Gynaecologists. The prevention of early-onset neonatal group B streptococcal disease. Green-top Guideline No. 36. London: RCOG; 2012 [http://www.rcog.org.uk/
women’s health/clinical guidance/prevention-early-onset-neonatal-group-b-streptococcal-disease-green]-
Håkansson S, Axemo P, Bremke K, et al; Swedish Working Group For The Prevention of Perinatal Group B Streptococcal Infections. Group B streptococcal carriage in Sweden: a national study on risk factors for mother and infant colonisation. Acta Obstet Gynecol Scand 2008;87:50–8.
Steer PJ, Plumb J. Myth: Group B streptococcal infection in pregnancy: comprehended and conquered. Semin Fetal Neonatal Med 2011;16:254–8.
Akker-van Maarse ME, Rijnders ME, Dommelen P, et al. Cost-effectiveness of different treatment strategies with intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal disease. BJOG 2005;112:820–6.
Schrag SJ, Zell ER, Lynfield R, et al.; Active Bacterial Core Surveillance Team. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. N Engl J Med 2002;347:233–9.
Gilbert R. Prenatal screening for group B streptococcal infection: gaps in the evidence. Int J Epidemiol 2004;33:2–8.
Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst Rev 2013;1:CD007467.
Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. Pediatrics 2005;115:1240–6.
Van Dyke MK, Phares CR, Lynfield R, et al. Evaluation of universal antenatal screening for group B streptococcus. N Engl J Med 2009;360:2626–36.
Pulver LS, Hopfenbeck MM, Young PC, et al. Continued early-onset group B streptococcal infections in the era of intrapartum prophylaxis. J Perinatol 2009;29:20–5.
Agence Nationale d’Accréditation et d’évaluation en Santé. Antenatal prevention of the risk of early neonatal bacterial infection: Clinical practice guidelines. September 2001;1–10. Available from: http://www.has-sante.fr/portail/upload/docs/application/pdf/antenatal_prevention.pdf [last accessed 14 Jan 2014].
Superior Health Council. Guidelines from the Belgian Health Council, 2003 (SHC 7721): Prevention of perinatal group B streptococcal infections. Brussels, Belgium: Service Public Federal Sante publique, Securite de la Chaine alimentaire et Environnement, 2003 (In English, in French, in Dutch).
Alcoum Cérites JC, Andreu Domingo A, Arribas Mir L, et al. Prevention of Neonatal Group B Streptococcal Infection. Spanish Recommendations. Update 2012. SEMIC/SEGO/SEN/SEQ/ SEMFYC Consensus Document. Enferm Infecct Microbiol Clin 2013;31:159–72.
Stan CM, Bouvain M, Bovier PA, et al. Choosing a strategy to prevent neonatal early-onset group B streptococcal sepsis: economic evaluation. BJOG 2001;108:840–7.
Neonatal Group B streptococcal infections in France: incidence from 1997 to 2006 and current prevention practices in maternity wards. Bulletin Epidemiologique Hebdomadaire 2008;14–15:110–13.
Strey-Pedersen B, Bergan T, Hafstad A. Vaginal early-onset group B streptococcal infections in adults, France (2007–2010). Clin Microbiol Infect 2011;17:1587–9.
Decay E, O’Grady EJ, Back JD. High rates of perinatal group B streptococcal clindamycin and erythromycin resistance in an upstate New York hospital. Antimicrob Agents Chemother 2009;52:2915–18.
Kimura K, Suzuki S, Wachino J, et al. First molecular characterization of group B streptococci with reduced penicillin susceptibility. Antimicrob Agents Chemother 2008;52:2890–7.
Melin P. Table 3O Resistance of Streptococcus agalactiae in Belgium. In: SBMC-BVIKM ed. The Sanford guide to antimicrobial therapy, 23rd edition of the Belgian/Luxembourg Version 2012–2013. Brussels, Belgium: Societe Belge d’Infectiologie et de Microbiologie Clinique – Belgische Vereniging voor Infectiologie en Klinische Microbiologie; 2012:178–9.
Back EE, O’Grady EJ. High rates of group B streptococcal infections in adults, France (2007–2010). Clin Microbiol Infect 2011;17:1587–9.
Imperi M, Gherardi G, Berardi A, et al. Invasive neonatal GBS infections from an area-based surveillance study in Italy. Clin Microbiol Infect 2011:17:1834–9.
de Azavedo JC, McGavin M, Duncan C, et al. Prevalence and mechanisms of erythromycin resistance in Streptococcus agalactiae from healthy pregnant women. Microb Drug Resist 2009;15:121–4.
Bergseng H, Aftset JE, Radtke A, et al. Molecular and phenotypic characterization of invasive group B streptococcal strains from infants in Norway 2006–2007. Clin Microbiol Infect 2009;12:1182–5 (Research note 1–4).
Tazi A, Morand PC, Réglier-Poupet H, et al. Invasive group B streptococcal infections in adults, France (2007–2010). Clin Microbiol Infect 2011;17:1587–9.
Desjardins M, Delgaty KL, Ramotar K, et al. Prevalence and mechanisms of erythromycin resistance in group A and group B streptococci: implications for reporting susceptibility results. J Clin Microbiol 2004;42:5620–3.
Gygas SE, Schuyler JA, Kimmel LE, et al. Erythromycin and clindamycin resistance in group B streptococcal clinical isolates. Antimicrob Agents Chemother 2001;45:3504–8.
Castor ML, Whitney CG, Como-Sabetti K, et al. Antibiotic resistance patterns in invasive group B streptococcal isolates. Infect Dis Obstet Gynecol 2008;2008:1–5.
71. Janapatla RP, Ho YR, Yan JJ, et al. The prevalence of erythromycin resistance in group B streptococcal isolates at a University Hospital in Taiwan. Microb Drug Resis 2008;14:293–7.

72. Seo YS, Srinivasan U, Oh KY, et al. Changing molecular epidemiology of group B streptococcus in Korea. J Korean Med Sci 2010;25:817–23.

73. Granlund M, Axemo P, Bremke K, et al; Swedish Working Group for the Prevention of Perinatal Group B Streptococcal Infections. Antimicrobial resistance in colonizing group B Streptococci before the implementation of a Swedish intrapartum antibiotic prophylaxis program. Eur J Clin Microbiol Infect Dis 2010;29:195–201.

74. Leclercq R. Mechanisms of resistance to macrolides and linco- mides: nature of the resistance elements and their clinical implications. Clin Infect Dis 2002;34:482–92.

75. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, 2014. http://www.eucast.org.

76. Gilbert GL, Isaacs D, Burgess MA, et al. Prevention of neonatal group B streptococcal sepsis: is routine antenatal screening appropriate. Aust N Z J Obstet Gynaecol 1995;35:120–126.

77. Yancey MK, Schuchat A, Brown LK, et al. The accuracy of late antenatal screening for rectal genital group B streptococcal colonization at delivery. Obstet Gynecol 1996;88:811–15.

78. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Screening and treatment for Group B streptococcus in pregnancy. College Statement C-Obs 19. 2009 [cited 2010 Feb 17]. Available from: www.ranzcog.edu.au/publications/statements/C-obs19.pdf

79. Melin P, Schmitz M, Tsobo C, et al. Rapid intrapartum test (Strep B OA) and prenatal cultures for identification of group B streptococcal carriers at delivery: a prospective study. In American Society of Microbiology (Ed.) Program and Abstracts of the 40th Intersciences Conference on Antimicrobial Agents and Chemotherapy 2000 (p145 No 357 session 30). Washington, USA: American Society for Microbiology (ASM). http://hdl.handle.net/2268/36477

80. Davies HD, Miller MA, Faro S, et al. Multicenter study of a rapid molecular-based assay for the diagnosis of group B Streptococcus colonization in pregnant women. Clin Infect Dis 2004;39:1129–35.

81. Valkenburg-van den Berg MS, Houtman-Roelofsen RL, Oostvogel PM, et al. Timing of group B streptococcus screening in pregnancy: a systematic review. Gynecol Obstet Invest 2010;69:174–83.

82. de Tejada BM, Pfister RE, Renzi G, et al. Intrapartum Group B streptococcus detection by rapid polymerase chain reaction assay for universal intrapartum group B streptococcus screening. Clin Infect Dis 2009 Aug 1;49:417–23.

83. Towers CV, Rumney PJ, Asrat T, et al. The accuracy of late third-trimester antenatal screening for group B streptococcus in predicting colonization at delivery. Am J Perinatol 2010;27:785–90.

84. Church DL, Baxter H, Lloyd T, et al. Evaluation of the Xpert® group B streptococcus real-time polymerase chain reaction assay compared to StrepB Carrot Broth™ for the rapid intrapartum detection of group B streptococcal colonization. Diagn Microbiol Infect Dis 2011;69:460–2.

85. de Tejada BM, Pfister RE, Renzi G, et al. Intrapartum Group B streptococcus detection by rapid polymerase chain reaction assay for the prevention of neonatal sepsis. Clin Microbiol Infect 2011; 17:1786–91.

86. Young BC, Dodge LE, Gupta M, et al. Evaluation of a rapid, real-time intrapartum group B streptococcus assay. Am J Obstet Gynecol 2011;205:372.e1–6.

87. Lin FY, Weisman LE, Azimi P, et al. Assessment of intrapartum antibiotic prophylaxis for the prevention of early-onset group B Streptococcal disease. Pediatr Infect Dis J 2011;30:759–63.

88. Badri MS, Zawaneh S, Cruz AC, et al. Rectal colonization with group B Streptococcus: relation to vaginal colonization of pregnant women. J Infect Dis 1977;135:308–12.

89. Dillón HC, Gray E, Pass MA, Gray BM. Anorectal and vaginal carriage of group B streptococci during pregnancy. J Infect Dis 1982;145:794–9.

90. Connelian M, Wallace EM. Prevention of perinatal group B streptococcal disease: screening practice in public hospitals in Victoria. MJA 2000;172:317–20.

91. Nys S, Vigen S, Magerman K, Cartuyvels R. Comparison of Copan eSwab with the Copan Venturi Transys for the quantitative survival of Escherichia coli, Streptococcus agalactiae and Candida albicans. Eur J Clin Microbiol Infect Dis 2010;29:453–6.

92. Melin P, Dodemont M, Sarlet G, et al. Improvement of transport condition of swabs for group B streptococcal screening. In American Society of Microbiology, Program and Abstracts of the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy 2013 (poster D1662). Washington, USA: American Society for Microbiology (ASM).

93. Philipson EH, Palermo DA, Robinson A. Enhanced antenatal detection of group B streptococcus colonization. Obstet Gynecol 1995;85:437–9.

94. Platt MW, McLaughlin JC, Gilson GJ, et al. Increased recovery of group B Streptococcus by the inclusion of rectal culturing and enrichment. Diagn Microbiol Infect Dis 1995;21:65–8.

95. Montague N, Cleary T, Martinez O, Procop G. Detection of group B streptococci in Lim broth by use of group B Streptococcus peptide nucleic acid fluorescent in situ hybridization and selective and nonselective agars. J Clin Microbiol 2008;46:3470–2.

96. Sociedad Española de Obstetricia y Ginecología. Sociedad Española de Neonatología. Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. Sociedad Española de Quimioterapia. Sociedad Española de Medicina Familiar y Comunitaria. 2003. Prevención de la infección perinatal por estreptococo del grupo B. Recomendaciones españolas revisadas. Enferm Infec Microbiol Clin 2003;21:417–23.

97. El Helali N, Giovagnardi Y, Guyot K, et al. Cost and effectiveness of intrapartum group B streptococcus polymerase chain reaction screening for term deliveries. Obstet Gynecol 2012;119:822–9.

98. Haberland CA, Benitez WE, Sanders GD, et al. Perinatal screening for group B streptococci: cost-benefit analysis of rapid polymerase chain reaction. Pediatrics 2002;110:471–80.

99. Baker CJ. Inadequacy of rapid immunoassays for intrapartum detection of group B streptococcal carriers. Obstet Gynecol 1996;88:51–5.

100. Picard FJ, Bergeron MG. Laboratory detection of group B Streptococcus for prevention of perinatal disease. Eur J Clin Microbiol Infect Dis 2004;23:665–71.

101. Bergeron MG, Ke D, Ménard C, Picard FJ, et al. Rapid detection of group B streptococci in pregnant women at delivery. N Engl J Med 2000;343:175–9.

102. Bergeron MG, Danbing K. New DNA-based PCR approaches for rapid real-time detection and prevention of group B streptococcal infections in newborns and pregnant women. Reprod Med Rev 2004;11:25–41.

103. Aziz N, Baron EJ, D’Souza H, et al. Comparison of rapid intrapartum screening methods for group B streptococcal vaginal colonization. J Matern Fetal Neonatal Med 2005;18:225–9.

104. Atkins KL, Atkinson RM, Shanks A, et al. Evaluation of polymerase chain reaction for group B streptococci detection using an improved culture method. Obstet Gynecol 2006;108:488–91.

105. Gavino M, Wang E. A comparison of a new rapid real-time polymerase chain reaction system to traditional culture in determining group B Streptococcus colonization. Am J Obstet Gynecol 2007;197:388 e1–4.

106. Edwards KK, Novak-Weekley SM, Kory PP, et al. Rapid group B streptococci screening using a real-time polymerase chain reaction assay. Obstet Gynecol 2008;111:1335–41.

107. Money D, Dobson S, Cole L, et al. An evaluation of a rapid real-time polymerase chain reaction assay for detection of group B streptococcus as part of a neonatal group B streptococcus prevention strategy. J Obstet Gynaecol Can 2008;30:770–5.

108. Lin FY, Weisman LE, Azimi P, et al. Evaluation of a rapid, real-time intrapartum group B streptococcus assay. Am J Obstet Gynecol 2011;205:372.e1–6.

109. Smith D, Perry JD, Laine L, et al. Comparison of BD GeneOhm real-time polymerase chain reaction with chromogenic and conventional culture methods for detection of group B Streptococcus in clinical samples. Diagn Microbiol Infect Dis 2008;61:369–72.

110. Alfa MJ, Sepheri S, De Gagne P, et al. Real-time PCR assay provides reliable assessment of intrapartum carriage of group B Streptococcus. J Clin Microbiol 2010;48:3095–9.
110. Park JS, Cho DH, Yang JH, et al. Usefulness of a rapid real-time PCR assay in prenatal screening for group B streptococcus colonization. Ann Lab Med 2013;33:39–44.
111. Abdelazim IA. Intrapartum polymerase chain reaction for detection of group B streptococcus colonization. Aust N Z J Obstet Gynaecol 2013;53:236–42.
112. Daniels J, Gray J, Pattison H, et al. Intrapartum tests for group B streptococcus: accuracy and acceptability of screening. BJOG 2011;118:257–65.
113. Kaambwa B, Bryan S, Gray J, et al. Intrapartum tests for group B streptococcus: accuracy and acceptability of screening. BJOG 2011;118:257–65.
114. Bourgeois-Nicolaos N, Cordier AG, Guillet-Caruba C, et al. Evaluation of the Cepheid Xpert GBS assay for rapid detection of group B Streptococci in amniotic fluids from pregnant women with premature rupture of membranes. J Clin Microbiol 2013;51:1305–6.
115. Langhendries JP. Early bacterial colonisation of the intestine: why it matters? Arch Pediatr 2006;13:1526–34.
116. Romero R, Korzeniewski SJ. Are infants born by elective cesarean delivery without labor at risk for developing immune disorders later in life? Am J Obstet Gynecol 2013;208:243–6.
117. Lorquet S, Melin P, Minon JM, et al. Group B streptococcus in the antenatal clinic and in the delivery room: a matter of systematic attitude. J Gynecol Obstet Biol Reprod 2005;34:115–27.
118. Håkansson S, Källén K. Impact and risk factors for early-onset group B streptococcal morbidity: analysis of a national, population-based cohort in Sweden 1997–2001. BJOG 2006;113:1452–8.
119. Telford JL, Barocchi MA, Margarit I, et al. Group B streptococcus in the antenatal clinic and in the delivery room: a matter of systematic attitude. J Gynecol Obstet Biol Reprod 2005;34:115–27.
120. 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.
121. Kenyon S, Pike K, Jones DR, et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labor: 7-year follow-up of the ORACLE II trial. Lancet 2008;372:1319–27.
122. Fossieck B, Parker RH. Neurotoxicity during intravenous infusion of penicillin. A review. J Clin Pharmacol 1974;14:504–12.
123. Bloom SL, Cox SM, Bawdon RE, Gilstrap LC. Amoxicillin for neonatal group B streptococcal prophylaxis: how rapidly can bactericidal concentrations be achieved? Am J Obstet Gynecol 1996;175:974–6.
124. Chow KM, Hui AC, Szeto CC. Neurotoxicity induced by beta-lactam antibiotics: from bench to bedside. Eur J Clin Microbiol Infect Dis 2005;24:649–53.
125. Colombo DF, Lew JL, Pedersen CA, et al. Optimal timing of ampicillin administration to pregnant women for establishing bactericidal levels in the prophylaxis of group B Streptococcus. Am J Obstet Gynecol 2006;194:466–70.
126. Bray RE, Roe RW, Johnson WL. Transfer of ampicillin into fetus and amniotic fluid from maternal plasma in late pregnancy. Am J Obstet Gynecol 1966;96:938–42.
127. Fiore Mitchell T, Pearlman MD, Chapman RL, et al. Maternal and transplacental pharmacokinetics of cefazolin. Obstet Gynecol 2001;98:1075–9.
128. Allegaert K, Van Mieghem T, Verbeesselt R, et al. Cefazolin pharmacokinetics in maternal plasma and amniotic fluid during pregnancy. Am J Obstet Gynecol 2009;200:170 e1–7.
129. de Cueto M, Sanchez MJ, Sampedro A, et al. Timing of intrapartum ampicillin and prevention of vertical transmission of group B Streptococcus. Obstet Gynecol 1998;91:112–14.
130. Lin FY, Brenner RA, Johnson YR, et al. The effectiveness of risk-based intrapartum chemoprophylaxis for the prevention of early-onset neonatal group B streptococcal disease. Am J Obstet Gynecol 2001;184:1204–10.
131. Illuzzi JL, Bracken MB. Duration of intrapartum prophylaxis for neonatal group B streptococcal disease: a systematic review. Obstet Gynecol 2006;108:1254–65.
132. Barber EL, Zhao G, Buhimschi IA, Illuzzi JL. Duration of intrapartum prophylaxis and concentration of penicillin G in fetal serum at delivery. Obstet Gynecol 2008;112:265–70.
133. Ramus R, McIntire D, Wendell GJ. Antibiotic chemoprophylaxis for group B strep is not necessary with elective cesaeran section. Am J Obstet Gynecol 2011;214:619–25.
134. Poncelet-Jasserand E, Forbes F, Varlet M-N, et al. Reduction of the use of antimicrobial drugs following the rapid detection of Streptococcus agalactiae in the vagina at delivery by real-time PCR assay. BJOG 2013;120:1098–108.