PREVENTION OF PERINATAL GROUP B STREPTOCOCCAL INFECTIONS

Guidelines from the Belgian Health Council, 2003

(SHC.7721)

FOREWORD

The recommendations reported below have been the matter of a consensus within the working group, they are based on the evidence available, on data from the literature and on the most recent results of epidemiologic investigations. Needless to say, they are likely to be affected by any change that may occur in the state of knowledge.

The main goal of these recommendations is to arrive at a decrease in the incidence of early-onset group B streptococcal infections in neonates.
The secondary objectives are to standardize the preventive strategies for the management of pregnant women, to optimize laboratory techniques for detecting GBS and to suggest an updated algorithm for the management of newborns.

SYMBOLS AND ABBREVIATIONS

CDC	Centers for Disease Control and Prevention, Atlanta, USA
CNA	Colistin-Nalidixic acid
CRP	C-reactive protein
CSF	Cerebrospinal fluid
EOD	Early-onset disease
FBC	Full blood cell count
GBS	Group B streptococcus
GBS EOD	Group B streptococcal early-onset disease
IAP	Intrapartum antimicrobial prophylaxis
ISP	Institut Scientifique de la Santé Publique, Bruxelles, Belgique
IV	Intra-venous
LIM	LIM broth (Todd-Hewitt broth with CNA)
LOD	Late-onset disease
OIA	Optical Immuno Assay
PPROM	Preterm (< 37 weeks gestation) premature (before the onset of labor) rupture of membranes
WIV	Wetenschappelijk Instituut voor Volksgezondheid, Brussel, België

1. INTRODUCTION

1.1. The issue of EARLY-ONSET GROUP B STREPTOCOCCAL DISEASE (GBS EOD)

Since the seventies, the incidence of neonatal group B streptococcal sepsis and meningitis has increased dramatically in all industrialized countries. Today, GBS is identified as the leading cause of invasive bacterial infections in neonates. The reported attack rates for the early-onset disease (EOD) (birth to age 7 days) range from 0.5 to 4 cases per 1,000 live births. As regards the late-onset form (LOD), which affects infants aged > 1 week, the attack rate is close to 0.5 per 1,000 live births.

The early-onset form of GBS disease typically occurs in the first 24 hours of life, with fulminant sepsis or pneumonia and less often with meningitis. Despite intensive supportive care, diagnostic and therapeutic progress, these infections have remained associated with high mortality (5 - 20 %) and morbidity; more than 30 % of infants recovering from meningitis present long term neurologic sequelae.

In perinatal infections or EOD, GBS is transmitted vertically to the newborn from the vagina of a *typically asymptomatic* colonized woman during labor and delivery. In addition to colonization with GBS, other factors increase the risk for GBS EOD. These include prematurity (gestation < 37 weeks), intrapartum fever (temperature >= 38°C), duration of amniotic membrane rupture >= 18 hours, previous delivery of an infant with invasive GBS disease and GBS bacteriuria during the current pregnancy. Furthermore, GBS also cause 15-25 % of the cases of postpartum febrile morbidity with or without bacteriemia and induce maternal complications and sterility succeeding *post-partum* endometritis.
Because of the continuing magnitude and severity of GBS disease, several preventive strategies have been evaluated. The reference recommendations were published by the CDC in 1996, and were reevaluated and updated in 2002. Maternal intrapartum antibioprophylaxis is currently considered to be the most effective strategy to decrease the incidence of EOD. However the cost of prenatal screening and antibioprophylaxis, as well as the selective pressure that antibiotics may have on the bacterial flora of mother and newborn still generate much controversy.

In Belgium, as in many European countries, no national guidelines for the prevention of GBS EOD are currently available. Nevertheless some hospitals have implemented strategies to decrease perinatal GBS infections and obstetric programs already include a GBS prevention policy.

1.2. Belgian background

1.2.1.Epidemiology

Belgium does not escape the endemic situation of GBS infections observed in most industrialized countries.

The main characteristics of GBS epidemiology and neonatal infections reported in Belgium are presented in Table 1. These data are based on different studies conducted by the Belgian reference laboratory for GBS in collaboration with the section of epidemiology of the ISP-WIV.

Table 1 : Characteristics of GBS epidemiology and neonatal infections in Belgium (1995-2001)

Early-onset disease		
	Attack rate in 1999	2 per 1,000 live births
	Mortality	> 14 %
	Meningitis	10 %
	Serotypes	III predominant (43 %), followed by II (20 %), Ia (16 %) and Ib (13 %) and V (9 %), very rare IV
	Obstetrical risk factors	presence in only 40 % of cases
Late-onset disease		
	Occurrence	about 1 case for 5 early-onset diseases
	Serotypes	III highly predominant (86 %)
Pregnant women		
	Rectovaginal colonization	13-25 %
Resistance to		
	Erythromycin	10-15 %
	(Erythromycin crossed-resistance with clindamycin 80 %)	

Between 1991 and 2001, GBS caused 37.9 % of early-onset sepsis and meningitis and no significant trend was demonstrated. The second most frequent cause of EOD was *E.coli* (11.4 %); a

decline in the rate of *E.coli* and other Gram negative bacilli infections has occurred. *Listeria monocytogenes,* another important neonatal pathogen, was identified in 3.9 % of EOD.

The rates of recto-vaginal colonization among pregnant woman range locally from 13 to 25 %, or even 35 %.

In 1999**,** the attack rate of GBS-EOD was 2‰ live births. Due to methods used for collecting these data, they are probably underestimated. Only 40 % of the cases were linked to at least one of the 5 additional risk factors.

1.2.2. Compliance to prevention policies

In 1998**,** a survey was directed to all gynaecologists and hospital biologists from the French-speaking Community. It showed that though 90,5 % of the departments of obstetrics complied to a prevention policy, only 66 % of them had a written protocol. Referring to the CDC guidelines, 30 % of the protocols in use recommended a preventive strategy of acceptable conformity. Individual practices of obstetricians were usually in agreement with the strategies suggested by hospitals. The best compliance to the CDC guidelines was reported among young obstetricians and in hospitals from the Brussels area.

In 1999**,** a similar study was conducted in the Flemish Community. It revealed that the Flemish attitudes were different from those observed in the French-speaking Community in the sense that the Flemish turned out to be less keen to apply the strategies endorsed by the CDC. While 84 % of obstetricians from the French-speaking Community had chosen the prenatal screening-based approach, in the Flemish Community, 38 % of obstetricians opted for a risk-based option.

As far as the antibioprophylaxis is concerned, both studies reported that the regimens recommended were often inadequate and the choice of antibiotics sometimes inappropriate.

1.2.3. Laboratory practice

The 1998 survey also evaluated the microbiological procedures used for GBS screening. Comparing once again existing practices with the CDC guidelines, it turned out that only 2% of laboratories used adequate prenatal screening methods. It should be stressed that one culture medium that was specifically recommended was not marketed in Belgium at that time. However, more than 60 % of the laboratories processed their specimens for GBS screening with acceptable culture and identification methods. The main problem with the culture methods was a lack of sensitivity to a prenatal screening.

All these observations clearly highlighted the need for promoting updated, widely accepted guidelines to reduce the perinatal GBS burden. The first step was to reach a consensus and then to issue national recommendations

2. RECOMMENDATIONS

2.1. PREVENTIVE STRATEGY

Several approaches have been proposed, mainly chemoprophylaxis and immunoprophylaxis.

Immunoprophylaxis is believed to be the most promising durable and cost-effective method for preventing EOD and LOD. However, this approach is not available yet, with different types of vaccines still being developed or tested on healthy subjects.

In the late 1980's clinical studies confirmed the fact that administering intrapartum penicillin G or ampicillin intravenously to GBS carriers led to a decrease in the transmission and incidence of the infection. This observation has led to a strategy with two options for the identification of mothers giving birth to a newborn at risk of developing GBS EOD. Intrapartum antibiotics could be recommended :

- either for women with recognized risk factors (**risk-based approach**),
- or for women with a positive prenatal screening for GBS vaginal colonization (**culture- or screening-based approach**).

Both penicillin G and ampicillin have been recommended, although the former is preferred for its narrower spectrum (other antibiotics must be given in case of penicillin-allergy).

A recent CDC-sponsored multistate study compared the two strategies and found that a screening-based approach was > 50% more effective than the risk-based approach in preventing perinatal GBS disease. The screening-based approach was more effective because it identifies women without additional maternal or intrapartum risk factors, and furthermore women with GBS positive screening were usually more likely to receive their prophylaxis than women with >= 1 risk factor when this option was chosen.

The implementation of these recommendations increases the use of antibiotics. Needless to say, the costs and risks they generate must be balanced against the benefits reaped. The main direct costs result from GBS prenatal screening cultures and antimicrobial prophylaxis. Among the risks are potential adverse effects (mainly allergic reactions); other unintended consequences of an increased use of antibiotics are the risk of emergence of GBS strains resistant to standard therapies but also the risk of a shift to serious infections caused by other pathogens including more resistant bacteria (enterobacteriaceae, ampicillin-resistant coliforms,…). So far, such a trend has not been unequivocally observed, but this should be monitored with great vigilance.

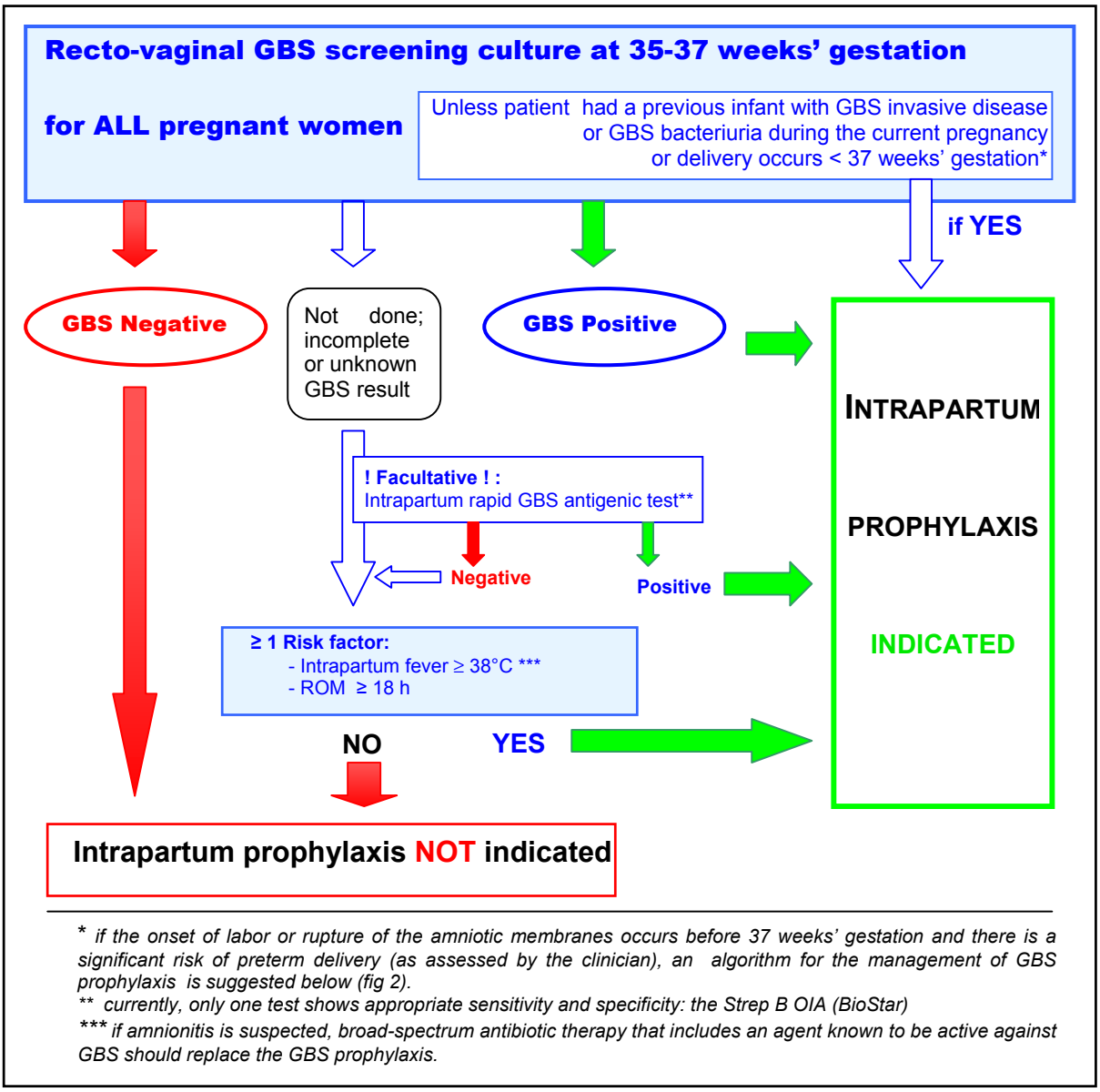
Recently intrapartum chlorhexidine vaginal flushing for all women admitted for delivery has been proposed under certain conditions. Preliminary results are encouraging but further studies are still needed.

The following recommendations for the prevention of perinatal GBS disease are, with some amendments, very close to the revised recommendations issued by the CDC in August 2002.

2.1.1. Practical recommendations

Obstetricians in conjunction with supporting laboratories and labor and delivery facilities should adopt the following strategy (Figure 1 or table 2).

Figure 1 : Strategy for the prevention of perinatal GBS disease



Objective of screening to detect GBS

- Screening to detect GBS colonization in each pregnancy will determine the need for intrapartum prophylaxis. At the time of labor or rupture of the membranes, intrapartum chemoprophylaxis should be given to all pregnant women identified as GBS carriers.

Meaning of GBS bacteriuria during pregnancy

- Women from whose urine GBS was isolated in any concentration during their current pregnancy should receive intrapartum chemoprophylaxis as they are usually heavily colonized with GBS and are at increased risk of delivering an infant with early-onset GBS disease.
    - Labels on urine specimens from prenatal patients should clearly state the patient's "pregnant" status to assist laboratory processing and reporting of results.
    - Prenatal culture-based screening at 35-37 weeks' gestation is not necessary for women with GBS bacteriuria.

- Women with a 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.

Other indications for intrapartum prophylaxis

- Women who have previously given birth to an infant with invasive GBS disease should receive intrapartum chemoprophylaxis; prenatal culture-based screening is not necessary for these women.
- If the result of the GBS culture is not known at the onset of labor, intrapartum chemoprophylaxis should be administered to women with any of the following risk factors (as in risk- based preventive strategy): gestation <37 weeks, duration of membrane rupture >=18 hours, or a temperature of >=38.0ºC. Women with known negative results from vaginal and rectal GBS screening cultures within 5 weeks of delivery do not require prophylaxis to prevent GBS disease even if any of the intrapartum risk factors should develop.

Table 2 : Summary of the strategy for prevention of perinatal GBS disease

- Vaginal and rectal GBS screening cultures at 35-37 weeks' gestation for ALL pregnant women (unless patient had GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease).

- Intrapartum prophylaxis IS INDICATED for women with:

- Previous infant with invasive GBS disease
- GBS bacteriuria during the current pregnancy
- Positive GBS screening culture during the current pregnancy (unless a planned cesarean delivery is performed in the absence of labor or amniotic membrane rupture)
- Positive GBS rapid screening antigenic test* – if performed – at the time of labor (unless a planned cesarean delivery is performed in the absence of labor or amniotic membrane rupture)
- Unknown GBS status (culture not done, incomplete, results unknown or negative GBS rapid screening antigenic test performed at the time of labor) **AND** any of the following:
  - Delivery at < 37 weeks' gestation**
  - Amniotic membrane rupture >= 18 hours
  - Intrapartum temperature >= 38°C***.

- Intrapartum prophylaxis IS NOT INDICATED for women with:

- Previous pregnancy with a positive GBS screening culture (unless a culture was also positive during the current pregnancy)
- Planned cesarean delivery performed in the absence of labor or amniotic membrane rupture (regardless of maternal GBS culture status)
- Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors.

** currently, only one test has appropriate sensitivity and specificity: the Strep B OIA (BioStar)*
***if the onset of labor or rupture of amniotic membranes occurs at <37 weeks' gestation and there is a significant risk for preterm delivery (as assessed by the clinician), an algorithm for the management of GBS prophylaxis is provided suggested below (fig. 2).*
**** if amnionitis is suspected, a broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace the GBS prophylaxis.*

Threatened preterm delivery

- Women with threatened preterm (<37 weeks' gestation) delivery should be assessed for the need for intrapartum prophylaxis to prevent perinatal GBS disease. An algorithm for the management of women with threatened preterm delivery is provided (Figure 2). Other management approaches developed by individual physicians or institutions may be appropriate.

Use of antimicrobial agents for GBS not recommended before labor and delivery

- In the absence of a GBS urinary tract infection, antimicrobial agents should not be used before the intrapartum period to treat GBS colonization. Such treatment is not effective in eliminating carriage or preventing neonatal disease and may cause adverse consequences.

GBS and planned cesarean delivery

- GBS colonized women who have a planned cesarean delivery performed before the rupture of the membranes and the onset of labor are at low risk for having an infant with early-onset GBS disease. These women should not routinely receive intrapartum chemoprophylaxis for perinatal GBS disease prevention, but should receive, if indicated, their regular cesarian-prophylaxis after clamping the umbilical cord.

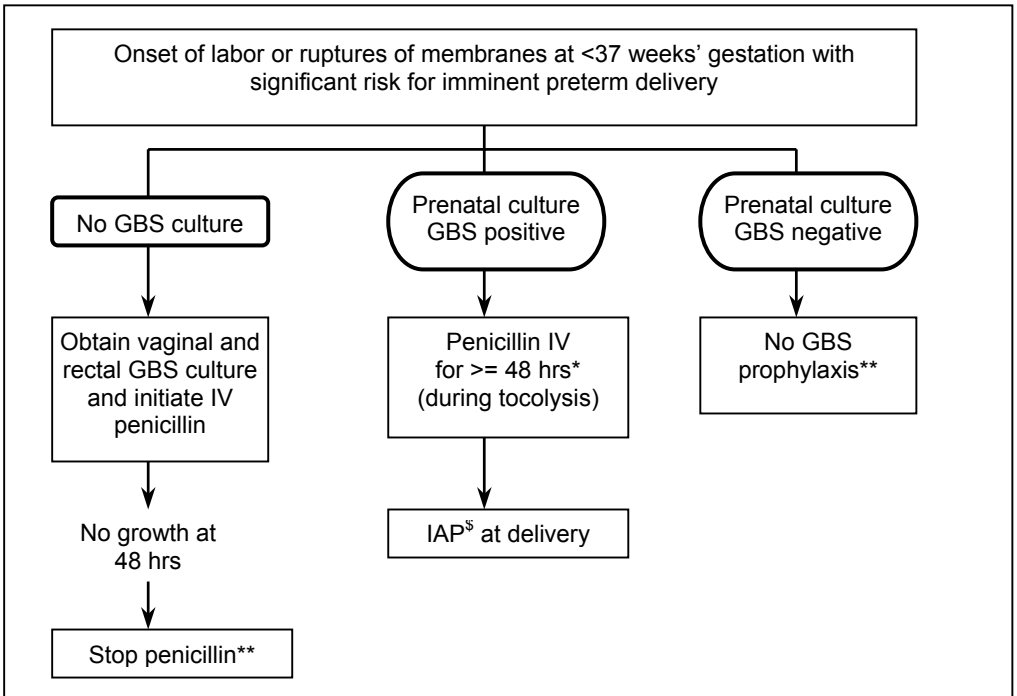
Rapid screening for GBS at time of labor and delivery

- For women with prenatal negative cultures for GBS, or of unknown status, a rapid screening test could be carried out with the Strep B OIA test; a positive result should be considered as a positive screening, whereas a “negative result” should be considered as “unknown result for GBS status”.

Newborns: routine use of an antimicrobial prophylaxis for GBS not recommended

- Routine use of an antimicrobial prophylaxis for newborns whose mothers received an intrapartum chemoprophylaxis for GBS infection is not recommended. However, therapeutic use of these agents is appropriate for infants with clinically suspected sepsis and for newborns at very high risk of developing an early-onset disease. An updated algorithm for the management of infants born to mothers who did or did not receive an intrapartum chemoprophylaxis for GBS infection is provided in figure 4. These algorithms are not exclusive approaches to the management of infants; variations that takes into account individual circumstances or institutional preferences may be appropriate.

Figure 2 *:* Sample algorithm for GBS prophylaxis for women with threatened preterm delivery. The algorithm is not an exclusive course of management. Variations that incorporate individual circumstances or institutional preferences may be appropriate (CDC, 2002).



* *Penicillin should be continued for a total of at least 48 hours, unless delivery occurs sooner. At the physician's discretion, an antibiotic prophylaxis may be continued beyond 48 hours when treating a woman with a positive GBS culture if delivery has not yet occurred. For women who are GBS positive, antibiotic prophylaxis should be reinitiated when labor likely to proceed to delivery occurs or recurs.*

** *If delivery has not occurred within 4 weeks, a vaginal and rectal GBS screening culture should be repeated and the patient should be managed as described, basing on the result of the repeat culture.*

2.1.2. Screening methods

2.1.2.1. Specimen collection and transport (table 3)

- Collection of specimens for culture may be conducted in the outpatient clinic setting by a health-care provider (or by the patient, with appropriate instruction). This involves swabbing the lower vagina and rectum (i.e., through the anal sphincter). Because lower vaginal as opposed to cervical cultures are recommended, cultures should not be collected by speculum examination.
- Specimens should be placed in a non-nutritive transport medium (e.g., Amies or Stuart's without charcoal). In these conditions, viability of GBS is guaranteed for at least 48 hours at room temperature or in a fridge (2 - 8°C).
- Specimen labels should clearly identify that the specimens are intended for group B streptococcal culture. Swabs should reach the lab within 48 hours of collection.

Table 3 Obstetrician's procedure for collecting clinical specimens for prenatal GBS screening cultures

PRENATAL GBS SCREENING	
WHEN	Collect specimen **at 35-37 weeks** of gestation.
WHO	**ALL pregnant women** at that time of pregnancy.
WHICH SPECIMEN	**Vaginal swab** : lower vagina **+ rectal swab** : through the anal sphincter
MATERIAL	**One (or two) swab(s) for both collection sites** placed in non-nutritive transport medium (e.g. Amies or Stuart's without charcoal)
STORAGE & TRANSPORT	Transfer specimens to the laboratory within the day. If any delay, refrigerate specimens (2 to 8°C), maximum 48 hours
REQUESTING FORM	**Clearly request** culture for "GBS Screening" **Communicate** the address of expected delivery facility

2.1.2.2 Laboratory procedures

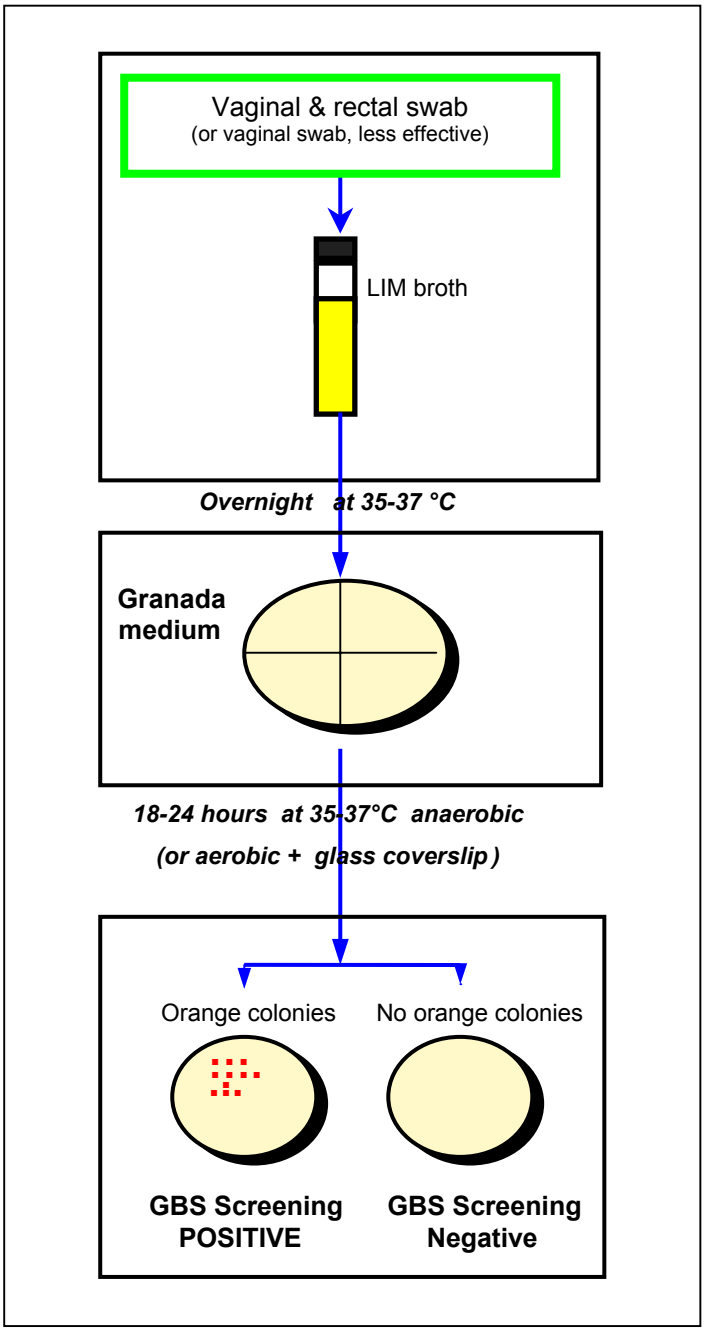
Culture procedures that maximize the likelihood of GBS recovery are required for prenatal screening (figure 3). They must therefore have the highest possible sensitivity.

- Upon reception, swabs for GBS prenatal screening cultures should be inoculated into a selective broth medium (Todd-Hewitt broth with colistin, 10mg/L and nalidixic acid, 15 mg/L = LIM broth), incubated overnight at 35-37°C, and subcultured onto Granada medium, or, should it be unavailable, on sheep blood agar. For Granada medium, a maximum of 4 specimens can be subcultured on the same plate, but a plate cannot be reused another day. Plates of Granada medium should be incubated anaerobically at 35-37°C, 18-24 hours; aerobic incubation is possible if a glass coverslip is placed over the inoculated surface (coverslips do not need to be sterile). Inspect and identify organisms suggestive of GBS. The development of orange or red colonies on Granada after 18-24 hours of incubation is specific (100%) to GBS. (On sheep blood, colonies suggestive of GBS should be specifically identified with a grouping latex agglutination test or other tests for GBS antigen detection).
- Laboratories should report a qualitative culture result for the recto-vaginal screening as "**GBS Prenatal screening POSITIVE, or negative**" at least to the anticipated site of delivery (when

known) and to the health-care provider who ordered the test (Important: the laboratory should not give a quantitative result).

- *Before inoculation in the selective enrichment broth, some laboratories may inoculate the swab onto CNA sheep blood agar or Granada medium plate. This should be done only in addition to (and not instead of) inoculation in selective broth. If this primary culture is positive for GBS, the broth can be discarded, thus shortening the delay before which the culture results are available.*
- **Health-care providers should inform women of their GBS screening test result and the recommended interventions.**

Figure 3 : Laboratory procedure for processing clinical specimens for GBS prenatal screening cultures



2.1.3. Regimens for antimicrobial prophylaxis

To date, all human isolates of GBS have remained uniformly susceptible to penicillin G. They are also susceptible to other β-lactams, cephalosporins, carbapenems and vancomycin.

Acquired resistance is observed for several antimicrobial agents : resistance rate to tetracyclines has reached nearly 90 % and more recently resistance to erythromycin and clindamycin is emerging. In Belgium, resistance to erythromycin and clindamycin currently occurs in about 15 % of isolates ; in some areas in North America this resistance can reach up to 30 %.

GBS are naturally resistant to bacitracin, nalidixic acid, trimethoprim-sulfamethoxazole, metronidazole and aminoglycosides. Nevertherless, when gentamicin is combined with either penicillin G or ampicillin, there is a synergistic killing.

Penicillin G is presented as the 1st choice, as a result of its narrower spectrum. Penicillin allergy is reported by 12 % of all pregnant women. However, skin tests show that only 10 – 20 % of those cases have a proven penicillin allergy.

In case of confirmed penicillin allergy, clindamycin is used, though its efficacy in reducing early-onset septicemia has not yet been investigated.

The different recommended options for intrapartum antimicrobial prophylaxis are summed up in table 4.

Table 4 : **Recommended regimens for intrapartum antimicrobial prophylaxis for perinatal GBS disease prevention**

1st choice	**Penicillin G, 5 million units IV initial dose; then 2.5 million units IV every 4 hours until delivery ***
In case of penicillin allergy : • ***at low risk for anaphylaxis***	• **Cefazolin, 2 g IV initial dose, followed by 1 g IV every 8 hours until delivery**
• ***at high risk for anaphylaxis***	• **Clindamycin, 900 mg IV every 8 hours until delivery** ***If GBS strain resistant to clindamycin : seek the advice of an infectiologist.***

- During prenatal care, the patient's history of penicillin allergy should be assessed to determine whether she is at high risk for anaphylaxis, i.e., has a history of immediate hyper-sensitivity reactions to penicillin (e.g., anaphylaxis, angioedema, or urticaria) or a history of asthma or other conditions that would increase the danger of anaphylaxis.
- Women who are not at high risk for anaphylaxis should be given cefazolin.
- For women at high risk for anaphylaxis, clindamycin and erythromycin susceptibility testing should be performed on isolates obtained during GBS prenatal carriage screening. Women with clindamycin-susceptible isolates should be given clindamycin, 900 mg intravenously every 8 hours until delivery.
- If the strain is resistant to clindamycin, an infectiologist's advice should be requested as soon as this information becomes available.

2.2. Management of the neonate at risk for early-onset Group B streptococcal disease (GBS EOD)

The majority (95%) of children with GBS EOD will become symptomatic within the first 24 hours after birth.

Though the management of symptomatic neonates and/or neonates at high risk of infection is well defined, the management of asymptomatic neonates is more problematic.

An approach for the empirical management of infants born to women who received or should have received IAP to prevent GBS EOD or to treat suspected chorioamnionitis, is provided (figure 4). One objective of developing an algorithm for the management of newborns was to minimize unnecessary evaluation and antimicrobial treatment of infants whose mothers received intrapartum prophylaxis.

2.2.1.Symptomatic newborn

A full diagnostic evaluation should be carried out for any infant with clinical signs of sepsis and empirical antibiotic therapy (ampicillin + aminoglycoside) should be started regardless of IAP, other obstetrical risk factors or maternal GBS status.

Because of sub-optimal sensitivity and specificity, and of poor predictive value for infection, routine use of urine antigen and cultures of mucous membranes or body surfaces cannot be recommended.

-***Clinical signs of sepsis****: infant with a combination of signs such as respiratory disturbance (apnea, grunting, tachypnea, cyanosis), cardiovascular (reduced capillary refill, hypotension, shock), central nervous system (lethargy, hypothermia, fever, seizures, apnoeic spells, irritability, bulging fontanel) or gastrointestinal (poor feeding, abdominal distension).*

-***Full diagnostic evaluation****: full blood cell count (FBC) and differential, CRP level, blood culture, lumbar puncture if indicated and feasable (CSF analysis and culture), chest X ray , endotracheal culture (in intubated infants or if respiratory distress or RX infiltrate).*
A lumbar puncture is indicated only in neonates with clinical signs of meningeal inflammation (seizures, apnoeic spells, irritability, bulging fontanel). In cases of clinical instability, antibiotic therapy should be administered and LP should be deferred and performed later for cell count, chemistry and culture.

2.2.2. Asymptomatic newborn

2.2.2.1. Neonates at high risk

Chorioamnionitis and PPROM (see 3.3.2) predispose to infection with Gram negative organisms and increase the risk of GBS infection in GBS colonized women. If a mother received intrapartum antibiotics for the treatment of suspected chorioamnionitis or in cases of PPROM, a full diagnostic evaluation should be carried out (see 2.2.1) and empiric antibiotic therapy (ampicillin + aminoglycoside) should be started in newborns regardless of the clinical condition at birth or other conditions.

2.2.2.2. Neonates at low risk

Routine use of antimicrobial prophylaxis for asymptomatic newborns whose mother received IAP is not recommended. An algorithm for the management of these newborns is suggested in figure 4.

If no maternal IAP for GBS is administered despite indication being present (see table 2), data are insufficient on which to recommend a single management strategy. In that case or if IAP is administered but its duration is < 4 hours or if gestational age is < 35 weeks, limited evaluation and observation should be undertaken.

- ***Limited evaluation****: serial measurements of CRP and full blood cell count repeated at least at 12 and 24 hours of life.*

Sepsis should be suspected based on repeated clinical and laboratory evaluations and if sepsis is suspected, a full diagnostic evaluation should be carried out (see 2.2.1.) and empiric antibiotic therapy should be started.

- ***Lower and upper limits of neutrophils count*** *vary with postnatal age. Sepsis should be suspected if leucopenia < 5000/mm^3 or if neutrophilia is out of range of Manroe criteria (table 5).*

Table 5. Manroe's criteria for lower and upper limits of neutrophils

Limits	0H	6H	12H	18H	24H
Low	1800	5400	8000	8000	7200
High	7000	13000	14400	13000	12500

- ***CRP****: the sensitivity of the test to predict a bacterial infection increases rapidly after birth but at least 6 to 12 hours after the onset of infection are necessary to reach an abnormal level. A significant increase between 2 serial dosages on samples taken over the first 8-48 hours of life has a sensitivity of almost 100% for an infectious status and normal levels for the 2 dosages have a negative predictive value of 90 to 100% for an infectious status. The normal upper level of CRP depends on the laboratory.*

Empiric antibiotic therapy should include antimicrobial agents active against GBS as well as other organisms that might cause neonatal sepsis (e.g. ampicillin + aminoglycoside). Dosage and regimen of antimicrobial agents depend on diagnosis, post-natal age and birth weight (see Sanford guide). IV immunoglobulins could be beneficial.

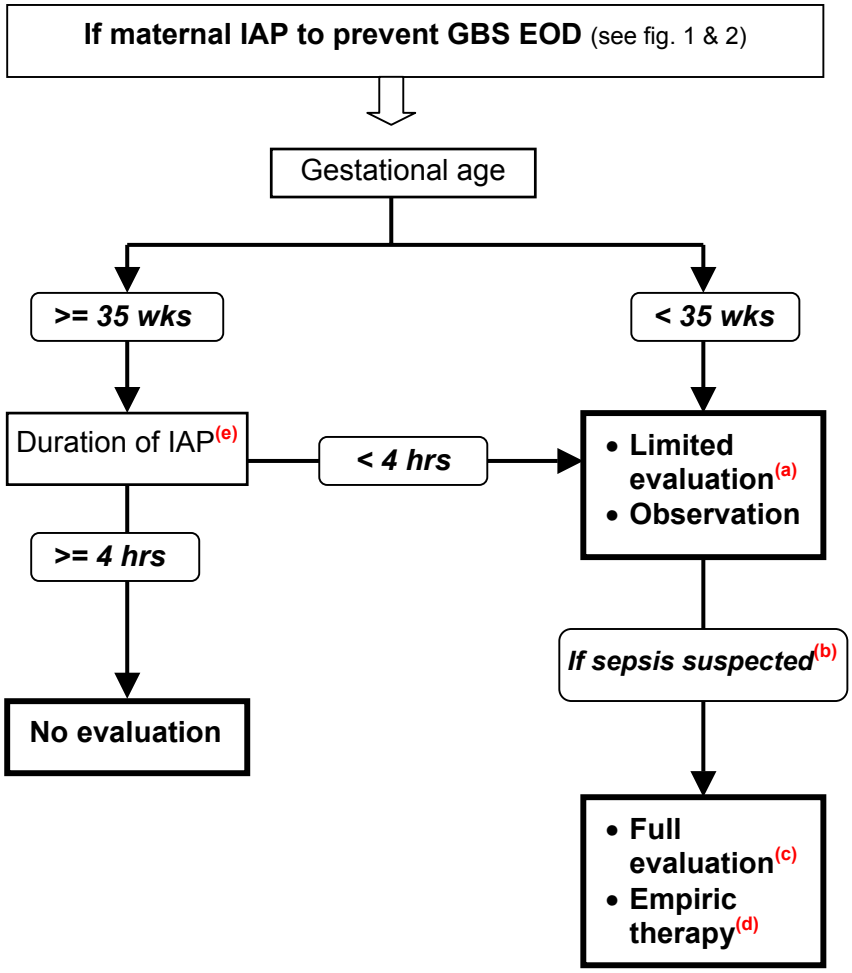
Duration of antibiotic therapy varies depending on the results of the cultures and on the clinical course of the infant (table 6): about 48 hours for suspected sepsis but without clinical, biological or bacteriological confirmation; 10 days for proven sepsis; 14 days minimum for meningitis; 28 days for ventriculitis or osteomyelitis. If GBS infection is confirmed by culture, ampicillin should be replaced by the narrower spectrum penicillin and aminoglycoside should be administered during 3 to 5 days.

Table 6 : Duration of antibiotic therapy

Focus of infection	Duration of therapy
Suspected sepsis not confirmed by clinical, biological or bacteriological results	48 hours
Proven sepsis	10 days
Meningitis	14 days minimum
Ventriculitis or osteomyelitis	28 days

Figure 4: **Sample approach for the management of an asymptomatic newborn whose mother received intrapartum antimicrobial agents**

1- ASYMPTOMATIC NEWBORN "AT LOW RISK"



2- ASYMPTOMATIC NEWBORN "AT HIGH RISK"

If maternal antibiotics for suspected chorioamnionitis or PPROM :
Full evaluation (c) & Empiric therapy (d)

(a) Includes serial full blood cell count and differential and CRP level
(b) sepsis should be suspected on repeated clinical and laboratory investigation. Abnormal laboratory values: leucopenia < 5000/mm^3, neutropenia or neutrophilia (see Manroe's criteria, table 5), increase CRP level on two separate samplings.
(c) Includes full blood cell count and differential, CRP level, blood culture, lumbar puncture if indicated (clinical signs of meningeal inflammation: seizures, apnoeic spells, irritability, bulging fontanel), chest Xray, endotracheal culture if intubated, respiratory distress or RX infiltrates
(d) ampicillin + aminoglycoside: duration varies depending on the culture results and on the clinical course of the infant (see table 6). If GBS infection is confirmed by cultures, ampicillin should be switched to a narrower spectrum penicillin. IV immunoglobulins could be beneficial.
(e) Applies only to penicillin, ampicillin or cefazolin and assumes recommended dosing regimens (table 4). For other agents used in penicillin-allergic patients, no data are available to suggest adequate durations for these regimens before delivery.

3. STATE OF THE ART

3.1. Streptococcus agalactiae : the bacteria

Streptococcus agalactiae, or Lancefield group B streptococci are Gram positive cocci, facultative aerobe, grown easily on a variety of bacteriological media. GBS may be further subdivided into serotypes based on type-specific capsular polysaccharide antigens. Currently nine serotypes are characterized : Ia, Ib, and II - VIII. A further classification is based on the presence of surface protein antigens c, R and X. Antibodies against type-specific polysaccharide antigens provide a good homologous passive protection.

3.2. Epidemiology and transmission

3.2.1. Asymptomatic colonization

The gastrointestinal tract is a natural reservoir for GBS and is the likely source of vaginal colonization. Vaginal colonization is unusual in childhood but becomes more common in late adolescence. Currently, the prevalence of recto-vaginal colonization among pregnant women ranges from 10 to 20 % in North Europe, 20 % in Belgium and from 20 to 30 % in North America. GBS colonization is dynamic, it can be continuous, transient or intermittent. The density of colonization also changes over time. Colonization is usually asymptomatic and carriers can only be identified by bacteriological testings.

3.2.2. Transmission to neonates

The rate of vertical transmission in neonates born to women colonized with GBS at the time of delivery ranges from 30 to 70 % (the mean being 50 %). Colonization of newborns results from vertical transmission of the organism from the mother, either in utero by ascending spread from the vagina or during passage through the birth canal. Transmission usually occurs after rupture of the membranes but can also occur through intact membranes. The likelihood of transmission is significantly influenced by the presence of a high genital inoculum at delivery. Maternal intrapartum GBS colonization is a major risk factor for early-onset disease in infants. However, colonization at an early stage of the pregnancy is not predictive of neonatal sepsis. Most newborns become colonized on the skin or mucous membranes but remain asymptomatic; among them, 1 to 4 % rapidly develop a clinical infection. Aspiration of infected amniotic fluid by the foetus can lead to stillbirth, neonatal pneumonia, or sepsis.

In addition to exposure at birth, horizontally acquired (nosocomial) colonization of the neonate is related to poor hygiene and poor handwashing.

3.3. Clinical manifestations

3.3.1. Neonatal infections

GBS invasive disease in neonates presents a bimodal distribution depending on their age at the onset of the infection. The syndromes of early- and late-onset disease (EOD and LOD) differ in clinical presentation, prognosis, epidemiological characteristics, and pathogenesis. (table 7)

EOD occurs during the first week of life, but nearly 90 % of patients have signs of systemic infection at birth or develop these within 12 hours. EOD accounts for approximately 80 % of GBS cases. The source is typically the presence of GBS in the mother's vaginal microflora. Most of the infants affected are full-term infants even if the attack rate is higher in premature and low weight neonates. Mortality rate is around 5-10 % in full-term neonates but can reach 40 % in premature neonates.

LOD infection can affect infants between 8 to 90 days of age, with a median onset of about 36 days, but LOD can occur up to 6 – 9 months of age. The acquisition of the GBS by the infants is more diverse and results more often from horizontal transmission. The attack rate ranges from 0.5 to 1. 5 per 1,000 live births.

Table 7 : Characteristics of Group B streptococcal Disease in infants

Feature	Early-onset	Late-onset	Late, late-onset
Age at onset (median)	<= 7 days (10 hours)	8 –90 days (36 days)	> 90 days
Infants affected	Birth after maternal obstetric complications, premature neonates	Term infants predominant	Premature <1500 g ; immune deficiency
Presentation	Respiratory distress, apnea, and hypotension common	Fever, nonspecific signs; occasionally fulminant	Fever, non specific signs
Site of infection	Bacteriemia (40-55 %) Pneumonia (30-45 %) Meningitis (6-15 %)	Bacteriemia without focus (55 %); meningitis (35 %)	Bacteriemia without focus; osteoarthritis (5 %); cellulitis/adenitis (2%)
Serotypes	All	Type III predominates	Type III predominates
Mortality	4 % - 15%	0 – 6 %	< 5 %

3.3.2. Additional risk factors for perinatal GBS disease

Vertical transmission is a pre-requisite for the development of invasive GBS EOD. Consequently, the **major determinant of risk** is of course the **presence of GBS in the birth canal at time of delivery** but other important factors are also the **absence of antibodies** homologous to the type of the colonizing strain and the **presence of other maternal risk factors** (Table 8)

Table 8 : Maternal risk factors for GBS EOD

- Chorioamnionitis or intrapartum fever (>= 38.0°C)
- Labor prior to 37 weeks' of gestation
- Prolonged rupture of membranes (>= 18 hours) before delivery
- GBS bacteriuria during current pregnancy
- Previous infant with invasive GBS infection

Intrapartum fever and Chorioamnionitis Infants born to women who have fever during labor (>= 38.0°C) are at increased risk of developing an invasive infection. In addition, clinical chorioamnionitis, evidenced by intrapartum fever accompanied by at least two additional clinical findings (foetal tachycardia, uterine tenderness, foul-smelling vaginal discharge, or maternal leukocytosis) is a marker of extremely high risk for the foetus, for sepsis in general as well as GBS EOD in particular.

Prematurity and low birth weight Smaller, less mature babies are at substantially higher risk than full-term infants, and the risk increases with decreasing gestational age and birth weight.

Prolonged or premature rupture of membranes Prolonged rupture of membranes for >= 18 hours before delivery (PROM) is associated with an increased risk of GBS EOD. Some have advocated considering PROM from 12 hours onwards. Preterm (< 37 weeks' gestation) premature (before the onset of labor) rupture of membranes (PPROM) in GBS colonized women is associated with an attack rate of EOD of 33-50 %.

Maternal GBS bacteriuria Some studies suggest that GBS bacteriuria during pregnancy may be associated with a higher neonatal GBS sepsis attack rate. It is a sign of maternal GBS colonization, perhaps with a more virulent strain or with a higher inoculum, but it is not an indicator of extreme risk.

Previous delivery of an infant with invasive GBS disease increases the risk of EOD in subsequent deliveries.

However, it is important to realize that more than half of the GBS EOD cases occur after a delivery without any of these risk factors (in Belgium: 60 % of the cases).

3.3.3. Pregnancy-related infections

GBS disease is also common in pregnant women. Clinical manifestations include urinary tract infection (usually asymptomatic bacteriuria), pyelonephritis, intra-amniotic infection (chorioamnionitis), wound infections associated with cesarean delivery or episiotomy, endometritis (often with bacteremia), puerperal sepsis and occasionally meningitis, septic thrombophlebitis, or other serious complications. In some instances, GBS cause stillbirth and the evidence increasingly points to a causative role for these organisms in amnionitis and preterm delivery.

3.4.Laboratory methods for detection of GBS

3.4.1. GBS culture-based screening methods

Using classical cultures, detection of GBS at the onset of labor is too slow; therefore GBS must be detected before the delivery. The earlier this detection is performed during the pregnancy, the lower the positive and negative predictive values for the presence/absence of GBS at time of delivery; the later this detection is performed, the higher the risk that results will not be available at the time of labor. As documented by numerous studies, the accuracy of prenatal screening cultures in identifying intrapartum colonization status can be enhanced by careful attention to the timing of the cultures, the anatomical sites swabbed and the precise microbiological methods used for the culture and detection of organisms. The most acceptable results are obtained by performing a culture between 35-37 weeks' gestation, by combining a vaginal and a rectal sampling, and by using a culture technique that can detect low numbers of organisms (enrichment in selective broth, or use of media that allow easy recognition of GBS based on the production of a carotenoid pigment (e.g. Granada medium).

3.4.2. Rapid testing methods to determine the GBS colonization status

Rapid tests detecting GBS colonization at the onset of labor or rupture of the amniotic membranes might obviate the need for prenatal culture-based screening if their sensitivity and specificity were comparable to culture in selective broth media and if they yielded results rapidly enough to allow the administration of adequate intrapartum antibiotic prophylaxis to women identified as carriers. An adequate rapid intrapartum test must be as sensitive as culture (minimally 85% compared with culture of vaginal and rectal swabs inoculated into selective broth media), rapid so that results are available to clinicians in time for an appropriate IAP before delivery, and convenient for integration into routine laboratory use. Even a highly sensitive rapid detection test would not be adequate if the results were not available to clinicians 24 hours a day, 7 days a week. A rapid intrapartum test possessing the attributes described above offers the advantage of ascertaining the GBS colonization status before delivery among women who have had no pre-natal care.

Currently, available rapid tests detect GBS antigen from swab specimens and are insufficiently sensitive to detect light colonization. As a result, they do not constitute an adequate replacement of culture-based prenatal screening. If they are used when culture results are unknown at the time of labor, a positive result should be considered as a positive carrier status for the pregnant woman but a negative result has no meaning.

In 2002, a highly sensitive real-time PCR test has become available in North America and is very promising for a rapid appropriate detection of GBS on vaginal swabs.

3.5.Preventive strategies

In the 1990s, perinatal GBS disease prevention made much progress. In 1996, the CDC, in collaboration with other agencies, published guidelines for the prevention of perinatal GBS disease. Two approaches were proposed: the risk-based and the screening-based approaches. In 2002, the CDC published new revised guidelines following the reevaluation of the prevention strategies based upon data collected after the publication of the 1996 guidelines and based on available evidence and expert opinion. Amongst the changes made, the key modification is the recommendation of a single approach: the screening-based approach.

3.5.1. Risk-based approach

A number of obstetrical factors have been associated with an increased likelihood of early-onset GBS disease in the newborn. These include premature deliveries, prolonged ruptures of the membranes, intrapartum fever. The incidence of GBS disease is also higher in mothers < 20 years of age. Also more likely to be infected are neonates born to mothers with a history of birth of an infant with GBS disease, heavy colonization such as seen in GBS bacteriuria and low levels of GBS antibody.

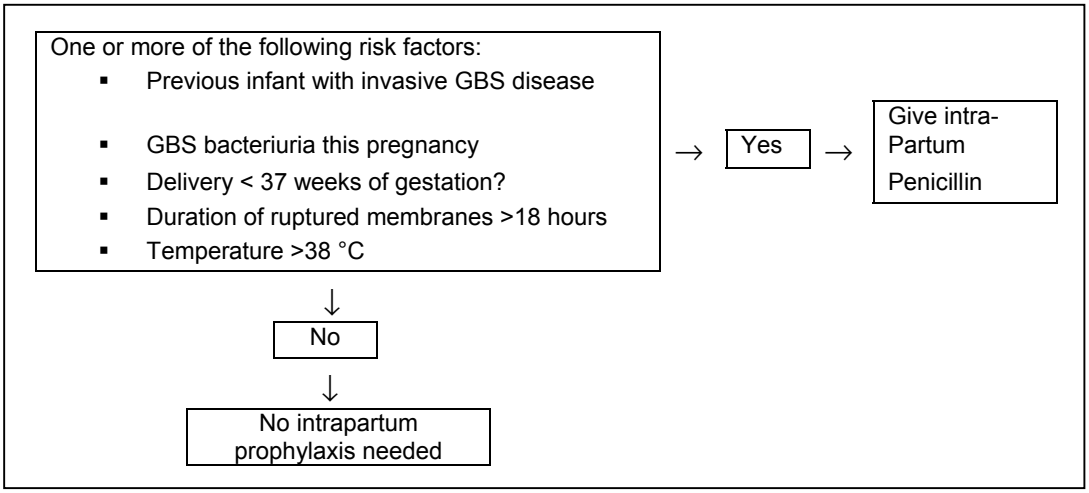
Based on these risk factors, the following risk-based preventive approach has been worked out (Figure 5): intrapartum antibiotic prophylaxis should be given to women with preterm labor (less than 37 weeks), preterm premature ruptures of the membranes, rupture of membranes > 18 hours, previous sibling with GBS disease, or women with intrapartum fever (≥ 38°C). Prior identification of GBS bacteriuria is also considered as an indication for IAP. Using a number of assumptions, a strategy based solely on intrapartum risk factors could result in intrapartum treatment of about 18 % of women and prevent up to 68 % of neonatal GBS EOD.

3.5.2. Prenatal screening-based approach

On this approach, maternal rectovaginal cultures should be performed at 35 to 37 weeks' gestation for all mothers without maternal risk factors (previous history of early-onset GBS disease in a sibling or maternal urinary tract infection with GBS). Culture techniques must be optimized to recover very small

numbers of GBS (subculture on sheep blood agar or Granada medium after a culture in a selective enrichment broth for instance). If the mother is GBS positive, she should be offered intrapartum antibioprophylaxis. This also holds if her GBS status is unknown, but she shows intrapartum risk factors. If none of these conditions are present, no prophylaxis is necessary.

Figure 5. Risk-based preventive strategy for early-onset group B streptococcal disease, CDC 1996



3.6. Impact and implementation of guidelines

Countries that have adopted perinatal GBS disease prevention guidelines similar to the United States have seen a decline in the incidence of early-onset disease of up to 70 %.

Furthermore, the incidence of invasive GBS infections among pregnant women in the United States declined by 21% from 0.29 per 1,000 live births in 1993 to 0.23 in 1998, suggesting that increased use of intrapartum antibiotics also prevented some cases of maternal GBS amnionitis and endometritis. In contrast, the rate of late-onset disease remained fairly constant throughout the 1990s, suggesting that this intervention, as expected, is not effective against late-onset disease.

With antimicrobial prophylaxis, potential adverse effects are expected :

- The first expected consequence is the risk of antibiotic allergies including anaphylaxis. Even though penicillin allergy and risk of anaphylaxis exist, very few allergic events have been reported since the release of the 1996 CDC guidelines.
- The second matter of concern is the potential rise of resistance in GBS. Among GBS isolates, no confirmed resistance to β-lactams has been observed to date and penicillin remains the agent of choice for IAP. Ampicillin is an acceptable alternative, but Pen should be preferred for its narrower spectrum and because it may be less likely to select for resistant organisms. Acquired resistance has been observed and is increasing for erythromycin and clindamycin. Currently, resistance to erythromycin and clindamycin occurs in about 15 % of isolates in Belgium; in some areas in North America this resistance can reach up to 30 %. In light of these increasing resistances, IAP regimens for penicillin allergic patients have been modified according to the level of risk for anaphylaxis and according to susceptibility results if available.
-The third potential unintended consequence of IAP is the increased incidence or resistance in non-GBS pathogens. A few studies reported an increase in non-GBS pathogens in perinatal infections, but it has not been confirmed by population-based multicenter studies, in which the incidence of non-GBS diseases has remained stable or is even decreasing during a period of increased use of IAP for the prevention of GBS EOD. Some single hospital studies have found an increased incidence of neonatal sepsis caused by *E coli* or ampicillin-resistant pathogens but these increases were limited to preterm or low birth weight infants. These data are not of sufficient magnitude to outweigh the benefits of IAP to prevent GBS EOD but continued surveillance of neonatal sepsis caused by organisms other than GBS is needed. In Belgium, a 10-year analysis of the data reported for perinatal sepsis or meningitis by a network of look-out laboratories shows a significant decrease in non-GBS Gram negative pathogens in recent years.

In 1998-1999, when no official guidelines were available in Belgium, two mail surveys were conducted to evaluate the Belgian practices for the prevention of GBS perinatal disease and to appraise methods used by microbiology laboratories to detect GBS. All Belgian obstetricians (Flemish-Fl and French-Fr Communities) had been invited to participate in one of these surveys, as were clinical microbiologists from the French Community. The guidelines issued by CDC in 1996 were considered as

the golden standard for the evaluation. The results of these surveys showed significant geographical differences in the obstetricians' clinical practice. Among the Fr. obstetricians, 90 % had chosen the prenatal screening approach, whereas Fl obstetricians preferred the risk-based approach. When the risk-based approach was or had to be considered for the decision to give an IAP, more than 90 % of the Fr obstetricians looked for intrapartum fever and prolonged rupture of membranes, and 58 % considered also prematurity as a risk factor. Among Fl obstetricians, respectively 57 %, 36 % and 36 % took the three most frequent risk factors into account to decide on an IAP. For their antibioprophylaxis, most obstetricians preferred amoxycilline to the recommended penicillin G. Furthermore, the regimen was often inadequate. On the microbiologists' side, less than 2% used the advised selective enrichment broth for the prenatal screening cultures, but at that time this medium was not commercially available in a ready-to-use form. Microbiologists also reported the usual lack of information on the requesting form, most of the time they did not know the prenatal status of the patient. Both surveys also pointed to a lot of room for improvements and the need for coordination between medical partners.

3.7. Effectiveness of a risk-based approach versus a screening-based approach

Though there might be some fear that the screening-based option will lead to more women being treated, the numbers will be the same for both strategies if all the risks are closely considered. The US experience indicates that compliance to the screening-based option (>90-95 %) is usually better than compliance to the risk-based option (45-88 %). A very important point in the screening-based approach is the good documentation of results and the organization to have these at hand at the time of labor. Of course, the expense is higher and is caused by the cost of the prenatal screening cultures, but overall cost savings due to more cases being prevented is in favor of the screening-based approach. No data are available or have been estimated for Belgium, but some projections are available for the US situation (table 7).

Table 7 : Comparison of some costs and effectiveness of the strategies proposed for the prevention of early-onset GBS infection (US simulation, W.E. Benitz 2001)

Prevention strategy	Risk-based	Prenatal Screening-based	Universal IAP
Screening for GBS	None	R+V, 35-37 weeks'	None
Criteria for IAP	< 37 w. or RF* +	GBS + or < 37 w. or RF* +	All parturients
Patients treated/1,000 births	171	307	1000
Patients treated/case prevented	106	136	415
% GBS cases prevented	53.8	75.1	80,2
Cost per case prevented (US $)	3,067	11.925	12,049

**RF = PROM > 18 hours or intrapartum maternal fever >= 38°C*

In table 7, "universal" IAP for all women is the most effective approach, but is not acceptable for other considerations, and is only mentioned for comparative purposes. It is important to keep in mind that no strategy will prevent 100 % of cases. In Belgium no maternal risk factors were found in 60 % of infected babies, which means that among these 60 %, not a single infection would have been prevented by the risk-based approach.

4. CONCLUSIONS

The recommendations presented develop the point of convergence between an extensive review of the literature and the opinions of the working group members.

This document aims at being a tool for improving the quality of the care given to the “mother-child” pair; it is not a constraining document, nor is it a legal reference text.

The recommended strategy for the prevention of perinatal GBS disease **is based on a universal prenatal screening-approach** with the integration of risk-based options when necessary.

Other strategies are still being investigated, such as strategies based on vaginal flushing with antiseptics or on the development of real-time PCR for the improvement of GBS screening. If the evaluation of those strategies demonstrates their relevance, the recommendations endorsed by this document could be affected accordingly.

The point is to implement these recommendations in the daily practice without this resulting in ill-considered overcosts or an excess of clinical work. Though the advice given to carry out both vaginal and anal sampling and to use a selective enrichment medium and an identification medium for GBS screening may seem maximalist, one should take into consideration that these conditions considerably improve screening efficiency.

Needless to say, the recommendations must be integrated in the standard follow-up of all pregnant women as well as in the perinatal management of newborns.

A crucial element of their success lies in the effective transmission of the prenatal GBS screening results to the delivery room. A narrow partnership between the obstetrician, the biologist and the pediatrician is also essential.

An obvious consequence of their implementation will be the frequent administration of a short-term and narrow-spectrum antibiotherapy (penicillin except in case of allergy). To date, no significant increase in the incidence of infections with bacteria resistant to prophylaxis has been demonstrated in countries where such a strategy has already been implemented.

Complying to these recommendations ensures a decline by 70% of the number of early neonatal GBS infections that occur in the absence of any intervention.

Nevertheless, it is not the ideal strategy because it exposes a large number of women to unnecessary antibiotherapy. Still, until effective vaccines have been licensed and become available, the recommended strategy is rational and effective.

Because of the potential unintended effects of chemoprophylaxis, it is necessary to monitor the incidence of serious neonatal infection, the occurrence of pathogens other than GBS and the potential emergence of GBS antimicrobial resistance as well as the prevalence of GBS recto-vaginal colonization among pregnant women while implementing this prevention strategy.

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6. APPENDIX

Specific microbiological media and tests

LIM Broth

- ***Composition*** : Todd-Hewitt broth + colistin (10 mg/L) + nalidixic acid (15 mg/L)
- ***Intended use*** : Lim broth is an enriched selective liquid medium used for the isolation of GBS, supporting rapid growth of Gram positive organisms while inhibiting the growth of numerous Gram negative organisms.
- ***Actual distributor in Belgium*** : Becton Dickinson

ESBM

- Not commercialized in Belgium at time of writing,
- Same use as LIM broth
- Potential future distributor in Belgium: International Medical

Granada (medium plate)

Granada agar

- ***Intended use*** : Granada medium allows the direct and easy identification of GBS colonies. The development of orange or red colonies is specific (100 %) to GBS.
- ***Producer*** : Biomedics, Madrid, Spain
- ***Presentation*** : ready to use agar plates or plastic containers with powdered medium to prepare 100 ml or 500 ml of Granada medium.
- ***Remark*** : if plates are prepared in-house, it is highly recommended to add 5 % of sterile serum and control of the pH is very important.
- ***Storage*** : Store in refrigerator and NOT at room temperature. Storage conditions are critical for the quality of the medium.
- ***Quality control*** : Frequently check the performance for production of red-orange colonies, with a known GBS strain.
- ***Actual distributor in Belgium*** : International Medical.

Group B Strep Differential agar

- ***Intended use*** : This medium is a variety of Granada medium and may be used instead of "Granada medium". It allows the direct and easy identification of GBS colonies. The development of orange or red colonies is specific (100 %) to GBS.
- ***Producer*** : Becton Dickinson, BD, Germany.
- ***Presentation*** : ready to use agar plates.
- ***Storage*** : Store in refrigerator and NOT at room temperature. Storage conditions are critical for the quality of the medium.
- ***Quality control*** : Frequently check the performance for production of red-orange colonies, with a known GBS strain.
- ***Actual distributor in Belgium*** : Becton Dickinson.

Strep B OIA

- ***Intended use*** : The Strep B OIA test is a qualitative optical ImmunoAssay (OIA) method for the rapid detection of GBS antigen directly from vaginal swabs of intrapartum maternity patients. The test is intended for use as an adjunct to culture, clinical observation and information available to the physician.
- ***Producer*** : Thermo-BioStar, Louisville, Colorado, USA
- ***Presentation*** : 30 tests/kit
- ***Remark*** : Each laboratory should verify and validate its own performance with the test.
- ***Actual distributor in Belgium*** : Forlab

7. COMPOSITION OF THE WORKING GROUP INVOLVED IN THE ELABORATION OF THE GUIDELINES

The following experts were involved in the elaboration of the guidelines :

- ALEXANDER Sophie
- BECKSTEDDE Inge
- CLAEYS Geert
- DE MOL Patrick
- DONDERS Gilbert
- FOULON Walter
- HUBINONT Corinne
- LEPAGE Philippe
- LEVY Jack
- MAHIEU Ludo
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- NAESSENS Anne
- POTVLIEGE Catherine
- TEMMERMAN Marleen
- TUERLINCKX David
- VAN ELDERE Johan

The working group was chaired by Prof. P.DE MOL and the scientific secretariat was carried out by Mr J.-J. DUBOIS.

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