Intrapartum antibiotics prophylaxis group B Streptococcus – strategies for prevention GBS disease

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Intrapartum antibiotic prophylaxis (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
  - How best to identify drawbacks of intrapartum administration of antibiotics

- 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
Why carry out screening and for what purpose?
Streptococcus agalactiae

✓ GBS has been recognized more than 3 decades

✓ As one of the most common causes of early neonatal sepsis (up to 7 days of life)

✓ To identify pregnant women at high risk for the development of neonatal GBS infection or chorioamnionitis
GBS disease in infants—Two clinical syndrome

• Are identified according to age at onset

• Early onset disease (EOD):
  – during first week of life (0-6 days)
  – presenting with mainly sepsis 79.4%; meningitis 11.8%; pneumonia 7.8%; focal infection 1%

• Late onset disease (LOD):
  – affecting infants aged >1week to three months old (7-90 days),
  – with mainly bacteremia and/or meningitis

GBS disease in infants - Two clinical syndrome

• 1. Early onset disease 0-6 days after birth
  – Incidence USA 1.7 per 1000 live births early 90s
  – decrease 0.34-0.37 per 1000 live births in 2003.
  – Mortality rate 4% / 50% early 1970s
    • A term infants 2-3%
    • Preterm infants 20%,
      – 30% preterm births below 33 weeks of gestation
      – surviving infants develop neurological abnormalities

• 2. Late-onset infection 7. days to 3 months after births
  – Incidence 0.5 per 1000 live births
  – Mortality 2.8%
    • Neurological sequele in survivors
Risk factors for EOD

1. Maternal GBS colonisation

In addition to maternal GBS colonization, other factors are associated to an increase risk for EOD in the newborn

a. mainly preterm labor and delivery prior to gestational age <37 weeks
b. duration of rupture of membranes 18 or more hours before delivery
c. intrapartum maternal fever greater than 38°C
d. GBS found in the urine at any time during the current pregnancy
e. Previous delivery of an infant with invasive GBS disease

Streptococcus agalactiae - GROUP B STREPTOCOCCUS

GBS carriage

- GBS is a human commensal of the gastrointestinal tract
- This natural reservoir is likely the source for vaginal colonization

- GBS carriage rate ranges approximately from 10 to 35% among pregnant women in the vaginal and rectal microbiota
GBS carriage

GBS colonization can be

• transient,
• intermittent,
• persistent

• and is commonly asymptomatic,

therefore the identification of carriers must be performed by bacteriological screening as close to delivery

Antenatal GBS screening between 35 and 37 weeks of gestation

- Based on Yancey’s study
- Antenatal GBS screening (vaginal-rectal) between 35 and 37 weeks of gestation (1-5 weeks before delivery)

- Has been used as a surrogate marker for GBS colonization at delivery and predictive values has been improved.
  
  - Sensitivity 95%
  - Specificity 96%.
  - Negative predictive values 95-98%

GBS carriage

• Large reported variations in colonization rates may be related to
  – age,
  – ethnicity,
  – body sites sampled
  – and microbiological procedures
The two alternative approaches to *intrapartum chemoprophylaxis*

- **Universal** antenatal culture-based GBS screening strategy
  - for maternal GBS colonization

- **Risk**-based strategy
• Some countries recommend
  – Either antenatal GBS screening strategy
  – Risk-based screening strategy
  – Any combination
• Other
  – Don't have national or any other kind of guidelines for prevention GBS neonatal disease

Universal antenatal culture-based screening strategy for maternal GBS colonization

• is based upon universal screening
  – for maternal GBS recto-vaginal colonization
  – at 35 to 37 weeks of gestation

• Followed by the administration of
  – intrapartum antibiotic prophylaxis at the time of labour to culture-positive women
Universal antenatal screening based approach

- It was estimated this screening based approach would result in intrapartum chemoprophylaxis of

- 26.7% of all deliveries

- 86% of EOD would be prevented

Intrapartum antibiotic prophylaxis is offered

- All identified pregnant women as GBS carriers
- Women with a previous neonate with GBS infection
- GBS bacteriuria during current pregnancy
- Delivering prior to 37 weeks of gestation
- Women with unknown carrier status
  - in the event of af intrapartum fever 38°C or higher
  - Rupture of membrane at 18 hours
Risk- based strategy

• Alternative prophylactic strategy

• Is based upon offering intrapartum chemoprophylaxis only in the presence of risk factors

  ➢ Previous infant with invasive GBS disease
  ➢ GBS bacteriuria current pregnancy
  ➢ Unknown GBS status
    ✤ Delivery prior to 37 weeks’
    ✤ Rupture of amniotic membrane ≥ 18 hours
    ✤ Intrapartum temperature ≥ 38°C
Risk-based factor approach

- 18.3% of pregnancies were estimated to merit antibiotic prophylaxis

- 68.8% of EOD would be potentially prevented
Drawbacks intrapartal antibiotics prophylaxis

Significant increase in the use of antibiotic

• Potential contribution to antibiotic resistance
  – Increasing resistance in GBS and other drug-resistant organisms
• Increase number of allergic reaction
Universal antenatal screening culture based strategy

• As in the USA since 2002, this strategy has **been recommended** by a number of countries (France, Belgium, Spain, Canada, Australia, New Zeland)

• and has resulted in a **decline in the incidence of neonatal GBS EOD**
Incidence of GBS early onset disease

after the widespread use of GBS antenatal screening and intrapartum antibiotic prophylaxis of all GBS carriers

- A more than 80% reduction in EOD

- The incidence of late onset has remained stable- unchanged
  - ranging from 0.25 to 0.5 per 1000 live births

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*Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC), Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC, 2010;19:59(RR-10):1-36*
The RCOG guidelines (2012) recommend

- **Do not currently recommend** routine screening for GBS at any stage during pregnancy.

- **At present, a risk-factor approach** is used in the National Health Service (NHS).

These are women who:

1. have previously had a baby with clinical GBS infection
2. have had a vaginal swab for GBS during their current pregnancy
3. when there had been a clinical indication of infection
4. have had GBS bacteriuria during their current pregnancy.

The following indications are also considered for offering broad-spectrum antibiotics, which should include activity against GBS:

- **✓** intrapartum fever (pyrexia >38°C)
- **✓** intra-amniotic infection (chorioamnionitis)

The RCOG guidelines (2012) recommend

*That women who are at increased risk for transmission of GBS are given intrapartum antibiotic prophylaxis during labour* to prevent colonisation of the baby.

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In screening-based strategies for prevention of perinatal GBS disease

Specimen collection and processing for GBS screening

- the main challenge is to identify accurately the pregnant women colonized with GBS in the genital tract at time of delivery

The crucial criteria impacting on accuracy are

- timing of screening,
- origin of collected specimen(s),
- transport conditions and microbiology
To increase sensitivity of the antenatal screening and to reduce false-negative results, several improvements have been proposed

- to use a flocked swab for collection of a vaginal-rectal specimen at 35–37 weeks of gestation,

- stored and transported in a selective enrichment broth/ Lim broth tube/ or non nutritient media, at room temperature as soon as possible within 4 days

- to subculture Lim broth to differential selective agars
  - as Granada like and/or specific GBS chromogenic media

Instructions for the collection of a genital swab for the detection of group B streptococcus (GBS)

1. Remove swab from packaging. Insert swab 2cm into vagina, (front passage). Do not touch cotton end with fingers.
2. Insert the same swab 1cm into anus, (back passage).
3. Remove cap from sterile tube.
4. Place swab into tube. Ensure cap fits firmly.
5. Make sure swab container is fully labelled with name, u.r. number, date and time of collection. Place swab container into transport bag and hand it to a staff member.

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
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.
– 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.
The Xpert GBS test

• is a rapid polymerase chain reaction (PCR) test

• for detecting group B streptococcus (GBS) colonisation in women who are about to give birth.
Rapid real-time PCR or other chosen NAAT testing for GBS should gather the following characteristics:

- Conditions to fulfil implementation of intrapartum screening:
  1. Sensitivity and specificity not inferior to 90% and 95% respectively.
  2. Fully automated processing with integrated internal controls, full traceability of the results and minimum maintenance.
  3. Easiness to perform and interpret results by delivery staff with a minimum of training.
  4. Short turnaround time not exceeding one hour.
  5. Availability 24 hours a day and seven days a week.
The main drawbacks of intrapartal rapid real time PCR testing

1. Delay in administration of antibiotics while waiting for the result

2. No antimicrobial susceptibility results for penicillin-allergic women

3. And their high costs.
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].

<table>
<thead>
<tr>
<th>Intrapartum GBS prophylaxis indicated</th>
<th>Intrapartum GBS prophylaxis non indicated</th>
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<tbody>
<tr>
<td>• Previous infant with GBS invasive disease</td>
<td>• GBS colonization during a previous pregnancy (unless an indication for GBS prophylaxis is present during the current pregnancy)</td>
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<tr>
<td>• GBS bacteriuria during any trimester of the current pregnancy1</td>
<td>• GBS bacteriuria during a previous pregnancy (unless an indication for GBS prophylaxis is present during the current pregnancy)</td>
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<tr>
<td>• Positive late antenatal GBS vaginal-rectal screening culture2 performed during the current pregnancy in the following cases:</td>
<td>• Negative intrapartum GBS vaginal screening with rapid real time PCR3 unless the duration of amniotic membrane rupture is 18 hours following PCR testing or if intrapartum temperature is 38˚C5</td>
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<tr>
<td>– If intrapartum PCR screening strategy3 is adopted and the patient is allergic to penicillin4</td>
<td>• Cesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age.</td>
</tr>
<tr>
<td>– If late antenatal vaginal-rectal GBS culture screening2 strategy is used for GBS EOD prevention.</td>
<td></td>
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<tr>
<td>• Positive intrapartum GBS vaginal screening with rapid real time PCR3</td>
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<td>– Amniotic membrane rupture 18 hours following the PCR testing</td>
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<tr>
<td>– Intrapartum temperature 38˚C5</td>
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<tr>
<td>• Unknown GBS status at the onset of labor (results indeterminate for intrapartum PCR or missed PCR testing4, missed antenatal culture screening or antenatal culture screening results not available3) and any of the following:</td>
<td></td>
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<tr>
<td>– Amniotic membrane rupture 18 hours</td>
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<td>– Intrapartum temperature 38˚C5</td>
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<tr>
<td>– Preterm labor &lt;37 weeks</td>
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• Cochrane review concluded that
  • Intrapartum antibiotic prophylaxis appeared to reduce EOGBSD,
    – but this result may well be due to bias as we found a high risk of bias for one or more key domains in the study methodology and execution.

• There is lack of evidence from well designed and conducted trials to recommend IAP to reduce neonatal EOGBSD.

• Ideally the effectiveness of IAP to reduce neonatal GBS infections should be studied in adequately sized double-blind controlled trials.

• The opportunity to conduct such trials has likely been lost,
  – as practice guidelines (albeit without good evidence) have been introduced in many jurisdictions.

Incidence of GBS neonatal disease

- Accurate population based data of incidence
- Are not available in some countries (in Croatia also)
- And hamper good effectiveness evaluation of prevention strategies
• **Croatian association for perinatal medicine** released and endorsed *National recommendations for antibiotic prophylaxis for early onset GBS disease* in 2010

• Unfortunately, until today, obstetricians have no coherent attitude or acceptance of these Recommendation

• Accurate population based data of incidence of GBS colonization are not available

• Data of effectiveness and feasibility our Recommendation are not recorded and available

• Potential adverse consequences of intrapartum antibiotic prophylaxis should be recorded as well:
  - emergence of bacterial antimicrobial resistance
  - or increase incidence or severity of non-GBS neonatal pathogens
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 angioedema 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 angioedema or respiratory distress or urticaria after receiving penicillin or a cephalosporin.
  - And GBS isolate susceptible to clindamycin *
- **Clindamycin 900 mg IV every 8 hours** until delivery
  - 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.

Vaccination

- **Immunisation during pregnancy** may offer protection against both early-onset and late-onset disease.
  
  - Several types of GBS vaccines have been developed and are currently undergoing clinical trials, including polysaccharide and polysaccharide-protein conjugate vaccines.

- **However, at the current time there are no commercially available GBS vaccines**
  
  - GBS immunisation during pregnancy activates the maternal immune system
  - However, it is still unclear whether immunisation prevents GBS infections in neonates

Conclusions

• There appears to be general agreement that Intrapartum Antibiotic Prophylaxis (IAP) is currently the recommended way to reduce the risk of neonatal GBS transmission and disease.

• but the main controversy that exists is the method used to select women „at risk“ to be given the IAP treatment.

• There seem to be two main approaches to selecting pregnant women requiring IAP treatment during labour.

Conclusions

The first approach to selecting women requiring the IAP treatment is

- **A prenatal culture-based screening test for all pregnant women at 35-37 weeks gestation**
  - is widely adopted in many countries including the USA, Australia, New Zealand, Germany, Italy, Spain and Canada
  - recommend the utilization of an enhanced culture program, including the improvements for sampling/transporting swabs and for culture procedure.

- **Proposed European guidelines recommend**

- **A universal intrapartum GBS screening strategy using a rapid real time testing**
  - intrapartum antimicrobial prophylaxis based on PCR-testing
    - 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
Conclusions

• The second, a risk-factor based approach is generally used as advocated by the Royal College of Obstetricians and Gynaecologists (RCOG)

• which recommends that IAP is offered to all pregnant women with recognised risk factors for early-onset GBS disease as,

  – “...there is still no clear evidence to show that screening all pregnant women (for GBS carriage) in the UK would be beneficial overall”.

  – BUT providers should beware of the high number of EOD infants, approximately 40–60%, presenting without risk factors.

And at the end some of my comments and remarks

• *It would be desirable that each country has data on its population*

• *Except for medical based evidences and data of incidences of EOD for each country,*

• *which of these strategies should or should not use*

• *it would be dependent of organization health care services and financial possibilities of health insurance in each country*
Other strategies to reduce maternal GBS colonization and vertical transmission

• 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**