Antibiotic therapy in time of labour – the Slovenian recommendations

Antibiotična terapia ob porodu – priporočila

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Abstract
Antibiotic agents are administered during the intrapartum period to prevent and treat maternal infection and to prevent neonatal disease. Short courses of antibiotics are used during labour to prevent such infections as group B streptococci (GBS) in newborns, postpartum endometritis and to treat chorioamnionitis. Many trials have evaluated the use of prophylactic antibiotics to prolong the pregnancy (and subsequently improve neonatal outcomes) after premature rupture of membranes (PROM).

Intravenous antibiotics recommended for women in active preterm labour are: Penicillin G: given initially as 3 g (or 5MU) intravenously and then 1.5 g (or 2.5MU) at 4-hour intervals until delivery. For women allergic to penicillin: provided a woman has not had severe allergy to penicillin, a cephalosporin should be used. If there is any evidence of severe allergy to penicillin, vancomycin should be used. For women allergic to penicillin, Clindamycin is no longer recommended as the current resistance rate is high.

Where infection of the membranes is diagnosed or suspected or where there is preterm prolonged rupture of membranes, broad-spectrum intravenous antibiotics should be given, which include adequate GBS cover (we recommend Cefazolin 2 g i.v and then 1 g at 8-hour intervals until delivery).

In PPROM we recommend as soon as possible after PPROM: ampicillin (2 g i.v. every 6 hours) for 48 hours plus azithromycin (1 g po in onetime administration), followed by amoxicillin (500 mg po every 8 hours) for 5 days unless delivery occurs.

Izvleček
Antibiotike v času poroda uporabljamo za preprečevanje in zdravljenje okužb pri materi ter za preprečevanje okužb pri novorojenčkih. Kratkotrajno zdravljenje med porodom se uporablja za preprečevanje okužb s streptokokom skupine B (SSB) pri novorojenčkih, poporodnega endometritis in za zdravljenje horioamnionitis. Številne raziskave so dokazale, da z uporabo profilaktičnih odmerkov antibiotikov lahko podaljšamo nosečnost (in nato izboljšamo rezultate obolevnosti in umrlosti novorojenčkov) po predčasničnem razpoku plodovih jajčnih ovojev (PPROM).

Pri nosečnicah z aktivnim prezgodnjim porodom priporočamo: penicilin G 3 g (ali 5 mE) intravensko, nato 1,5 g (ali 2,5 mE) intravensko v 4-urnih presledkih do poroda.

Pri nosečnicah, ki so alergične na penicilin, priporočamo naslednje: Pri ženski, ki je imela blago obliko alergije s kožnim izpuščajem, svetujemo uporabo cefalosporina. V primeru zabeležene hujše oblike alergije na penicilin svetujemo uporabo vankomicina. Zdravljenje s klindamicinom
1 Introduction

Antibiotic therapy is used during labour for three reasons:
• to prevent early-onset neonatal sepsis with group B streptococci;
• to prolong the pregnancy after preterm premature rupture of membranes (PPROM) before week 34 of pregnancy;
• to prevent infections in mothers (postpartum endometritis, amnionitis and chorioamnionitis).

These recommendations were presented and approved at the expert meeting of the Department of Infectious Diseases of the University Medical Centre Ljubljana on 28 March 2017, at the expert meeting of the Department of Perinatology, Division of Gynaecology and Obstetrics, University Medical Centre Ljubljana on 6 April 2017, at the expert meeting of the Slovenian Association of Perinatal Medicine Novakovi dnevi conference on 20 May 2017, and at the Extended Professional College for Gynaecology and Obstetrics on 13 June 2017, and adopted by the Board of Experts of the Slovenian Medical Association on 12 September 2017.

This paper presents primarily recommendations for the first two causes, since no clear recommendations on the topic have been available in Slovenia so far.

2 Antibiotic prophylaxis for group B streptococci (GBS)

Group B streptococci (GBS) is the leading infectious cause of neonatal morbidity and mortality. Timely identification of colonization in pregnant women and antibiotic prophylaxis during labour lower the risk of neonatal sepsis (1-4).

Asymptomatic colonization with GBS is present in around 15–30% of pregnant women. Colonisation can be proven with a urine test, or a vaginal and rectal swab (5).

GBS in neonates can cause early-onset neonatal sepsis, which occurs in the first week of life (most commonly within 24–48 hours of birth), or late-onset neonatal sepsis, which occurs after the first week up to 3 months of age. Antibiotic prophylaxis can only prevent early-onset sepsis. This is manifested as neonatal sepsis with respiratory distress, pneumonia or, less frequently, meningitis. The mortality rate from this infection dropped from 50% in the 1970s to 4-6% in the past years, which can be mostly attributed to better intensive care for neonates (1-5).

The mortality rate is higher, around 20%, for preterm neonates, and the highest, 30%, for neonates born before week 33 of pregnancy. The mortality rate for full-term neonates who are infected by GBS is
Preventive measures decreased the incidence of infection in neonates in the USA from 1.7/1,000 to 0.34–0.37/1,000 live births (6-8).

The foetus is colonized or infected during birth (50–75% of all neonates born to colonized mothers). Only 1–2% of colonized newborns fall ill. The infection is transmitted vertically, since the child is infected while passing through the birth canal. The infection usually occurs after the rupture of membranes, it can however also occur if these are intact. The foetus can inhale GBS into the lungs, which causes bacteremia, or is infected through mucosae (5-8).

Infections in neonates are more frequent in the following cases:
- when the membrane rupture over 18 hours before delivery;
- if bacteriuria was proven during pregnancy;
- if the parturient woman’s body temperature is above 38° C;
- if the woman already gave birth to a child who was infected by GBS;
- in preterm infants (born before week 37 of pregnancy).

### 3 Screening

Screening is done between weeks 35 and 37 of pregnancy. Swabs are taken from the lower third of the vagina (vaginal introitus) and rectum and sent to testing using Stuart’s transport medium. The final results are available in 48 hours. A fast PCR test is also available, where results are available in 3–4 hours, it is however quite more expensive, while its reliability is similar to that of the culture test. Currently not all Slovenian maternity hospitals can provide the test 24/7, so it is not used routinely. The negative predictive value for GBS cultures taken five weeks or less before the labour is 95–98%, and starts decreasing after that (1-8,11-12).

Pregnant women in whom GBS bacteriuria was proven during pregnancy do not need to be screened, since the bacteriuria is a sign of a significant vaginal and rectal colonization, and antibiotic prophylaxis is therefore recommended during labour. The same applies to pregnant women who already gave birth to a child who had early-onset neonatal sepsis with GBS (9-12).

Indications for antibiotic prophylaxis to prevent GBS sepsis (1-3,6-7,11-12):
- positive vaginal and/or rectal swab results;
- the woman already gave birth to a child who had GBS sepsis;
- GBS bacteriuria during pregnancy;
- active labour before week 37 of pregnancy.

In the event of preterm premature rupture of membranes (PPROM) over 12 hours before the delivery, or of signs of inflammation, we start antibiotic therapy (cefazolin 2 g IV, followed by cefazolin 1 g/8 h, for the next 24 hours) and not a prophylactic course.

When is antibiotic prophylaxis unnecessary (13-14)?
- in women positive for GBS delivering with cesarean section in any week of gestation, if the membranes are intact when the surgery starts;
- in pregnant women who were screened less than 5 weeks before the labour starts and tested negative for GBS;
- in pregnant women with elevated body temperature during labour (> 38 °C) or whose membranes ruptured over 12 hours before the delivery. These parturient women are given broad-spectrum antibiotics (we use Cefazolin) to treat the infection (e.g. suspected chorioamnionitis).

Antibiotic prophylaxis scheme

1. **Penicillin G** 5 million IU IV, followed by 2.5 million IU every 4 hours until delivery.
2. In the event of a mild allergic reaction to penicillin (only skin rashes, without hives, or an anaphylactic reaction) cef-
**fazolin** 2 g IV, followed after 8 hours by 1 g/8 h IV until delivery.

3. In the event of a severe allergic reaction to penicillin (anaphylactic reaction, angioedema, respiratory distress, generalized hives). Clindamycin 900 mg/8 hours IV until delivery.

- When using this treatment, a swab must be taken for antimicrobial susceptibility testing, since 15–20% of GBS strains are resistant to clindamycin and erythromycin.

4. Vancomycin 1 g/12 hours IV until delivery – in the event of clindamycin or erythromycin resistance.

Prophylaxis is the most effective when administered at least 4 hours before the delivery, with the penicillin's serum reaching high levels in 30 minutes from infusion. Since time until delivery cannot be determined precisely, the prophylaxis should start immediately upon admission to the delivery room, if we assess that the labour (active labour phase) has started (1-7,15-19).

With PPROM or spontaneous rupture of membranes (SRM), antibiotic prophylaxis should be introduced as soon as possible after the membrane rupture. If less than 12 hours have passed since the rupture of membranes, the antibiotic prophylaxis for GBS should be started immediately upon admission to the maternity hospital, and continued according to the scheme until the delivery (6,16-20).

We should be aware that about 30% of GBS strains are resistant to erythromycin, and some 15% to clindamycin, so it is important to be familiar with antimicrobial susceptibility test results for the GBS colonizing the pregnant woman when using clindamycin for antibiotic prophylaxis (15,20).

### 4 Antibiotic prophylaxis during preterm labour

Women who go into labour before week 37 of pregnancy have usually not been tested for GBS colonisation yet. A swab is taken from any woman at risk of preterm delivery or in labour and tested for GBS and other pathogenic bacteria, since premature newborns are at greater risk of neonatal GBS sepsis (6,15-20) (Figure 1).

If the preterm labour starts before week 37 of pregnancy, and we do not suspect an infection (amnionitis, chorioamnionitis), and less than 12 hours have passed since the rupture of membranes, the pregnant woman is given GBS prophylaxis to protect the neonate without performing a confirmatory vaginal and/or rectal swab test (6,18-20).

After starting the therapy with one antibiotic, we should not switch to another antibiotic during the labour without a reason (e.g. antimicrobial susceptibility testing)! Example: if we start with penicillin we do not switch to cefazolin 12 hours after the rupture of membranes (6,18).

**Recommendation: I A**

We recommend screening for GBS colonization in pregnant women between weeks 35 and 37 of pregnancy.

**Recommendation: II B**

Women with GBS bacteriuria during pregnancy require antibiotic prophylaxis during labour.

**Recommendation: II C**

Women who had a neonate with GBS sepsis in the previous pregnancy require antibiotic prophylaxis during labour.

**Recommendation: I A**

Women whose vaginal and/or rectal swab tested positive for GBS in the last 5 weeks before the delivery require antibiotic prophylaxis during labour.
Recommendation: I B
For women delivering with elective cesarean section without a prior SRM, who are colonized with GBS, antibiotic prophylaxis during labour is not necessary.

Recommendation: I B
Women in active labour before week 37 of pregnancy, whose GBS colonization status is unclear, require antibiotic prophylaxis during labour.

Recommendation: I A
Women colonized with GBS require antibiotic prophylaxis at least one hour before AROM or immediately after SRM.

5 Antibiotic therapy after preterm premature rupture of membranes (PPROM) before week 34 of pregnancy

Preterm premature rupture of the membranes (PPROM) means the rupture of the fetal membranes before week 37 of pregnancy, which occurs in about 3% of pregnancies. It is responsible for or related to approximately one third of preterm births (21).

The majority of pregnancies end within a week of the rupture of the fetal membranes (22).

When deliberating the postponement of birth when PPROM occurs before week 23 of pregnancy, we should keep in mind that lack of amniotic fluid can lead to severe complications in the development of fetus, especially lung tissue and the limbs (21–23).

Upon admission of the pregnant woman, a vaginal swab must be taken to prove or exclude the presence of pathogenic bacteria, and a blood test is required to exclude laboratory signs of inflammation (CBC, blood differential test, CRP, urine) (21,23).

The purpose of the antibiotic therapy for PPROM is to prolong the latency period before week 34 of pregnancy, to prevent early-onset neonatal sepsis caused by GBS, and to treat/prevent early stage amnionitis. Amnionitis can be the cause or result of PPROM. We may switch antibiotics during the therapy based on the pathogenic bacteria identified in the vaginal swab test (21–27).

An analysis of 22 studies on antibiotic therapy for PPROM before week 37 of pregnancy was published in the Cochrane Database in 2013. Compared to placebo, antibiotic therapy was linked to lower chorioamnionitis rate (RR 0.66), lower rate of labours started within 48 hours (RR 0.71) or within one week (RR 0.79), and lower rate of neonatal infections (RR 0.67), use of surfactants (RR 0.83), and neonatal CNS complications (RR 0.88). The analysis did not find any of the antibiotics to be superior to others in therapy. It however showed that using amoxicillin with clavulanic acid increases the probability of necrotizing enterocolitis in infants (22).

A meta-analysis published in 2008 reviewed antibiotic therapy for PPROM before week 34 of pregnancy and produced similar results (23).

Antibiotics should be administered for 7 days to all pregnant women who suffered PPROM before or in week 34 of pregnancy (21–26).

Antibiotic therapy requires a deliberation on the main pathogenic causes of pelvic organs infection, however the best scheme is not completely clear, since causes differ greatly on a case by case basis. We recommend a 7-day antibiotic prophylactic therapy for all pregnant women with PPROM before week 34 of pregnancy, regardless of whether they are prescribed maturation therapy with corticosteroids or have already received it (23–25).

Proposed treatment scheme:
- Ampicillin 2 g IV /6h, for 48 hours, followed by amoxicillin (500 mg PO, TID /8h) for another 5 days.
- We also recommend one dose of azith-
romycin (1 g PO) at the beginning of the antibiotic therapy.

Ampicillin is used to treat group B streptococcal infections, mostly aerobic, gram-negative, and some anaerobic bacteria. Azithromycin is used to treat Mycoplasma genitalium infection, which is a significant cause of chorioamnionitis, and also covers chlamydia, which is a significant cause of neonatal conjunctivitis and pneumonia (21-28,35-37).

In the event of a mild allergic reaction to penicillin (skin rash, hives, itching) we recommend (6,23,29-32):
- cefazolin 1 g IV /8h, for 48 hours, followed by ciprofloxacin (500 mg PO, /12h) for another 5 days.
- We also recommend one dose of azithromycin (1 g PO) at the beginning of the antibiotic therapy.

This covers two most common causes of early-onset neonatal sepsis, GBS and E. coli (19-20,21-23).

In the event of a severe allergic reaction to penicillin (anaphylactic reaction, angioedema, difficulty breathing) we recommend (6,30-35):
- clindamycin 900 g IV /8h, for 48 hours, followed by clindamycin 300 mg PO, /8h) for another 5 days, while also administering Gentamicin 7 mg/kg/24 h for 48 hours.
- We also recommend one dose of azithromycin (1 g PO) at the beginning of the antibiotic therapy.

Due to high clindamycin resistance of GBS, the treatment of pregnant women with PPROM must be adjusted based on the antimicrobial susceptibility test results for the GBS as soon as possible (15).

If GBS colonization is proven in the vaginal swab, the pregnant woman requires antibiotic prophylaxis for GBS at the start of the labour, if more than 72 hours have passed since the antibiotic therapy for PPROM was concluded (1-3,35).

If the pregnant woman has not yet received maturation therapy with corticosteroids, we recommend administering betamethasone (Flosteron’) 14 mg/24 hours IM in two doses. If the pregnant woman received maturation therapy before week 28 of pregnancy, we recommend assessment whether a one-time booster dose of 14 mg of betamethasone is required before the delivery prior to week 34 of pregnancy (28,35).

**Recommendation: I A**
Corticosteroids should be applied between weeks 23 and 34 of pregnancy.

**Recommendation: II B**
We recommend expectative management of pregnancy until week 34 for stable pregnancies with PPROM before week 34.

**Recommendation: I A**
We recommend maturation therapy with corticosteroids before week 34 of pregnancy.

**Recommendation: I A**
We recommend antibiotic prophylaxis before week 34 of pregnancy.

**Recommendation: I A**
The recommendation is 2 g of ampicillin IV /6h for 48 hours, followed by amoxicillin (500 mg PO, TID) for another 5 days. We also administer one dose of azithromycin (1 g PO) at the beginning of therapy.

**Recommendation: I A**
If a pregnant woman with signs of active labour is reexamined more than 72 hours after the prophylactic therapy, and GBS are present in her vaginal swab, we should prescribe Penicilin G 5 million IV, and after 4 hours 2.5 million /4 h during the active labour until the delivery.
Recommendation: II B

If a pregnant woman with signs of active labour is reexamined more than 72 hours after the prophylactic therapy and pathogenic bacteria have not been proven in her vaginal swab (not older than 5 weeks), we do not prescribe any antibiotic therapy during the active labour.

Recommendation: IA

If a pregnant woman with signs of active labour is reexamined more than 72 hours after the prophylactic therapy and pathogenic bacteria have not been proven in her vaginal swab (not older than 5 weeks), we do not prescribe any antibiotic therapy during the active labour.

Recommendation: II B

If a pregnant woman with signs of active labour is reexamined more than 72 hours after the prophylactic therapy and pathogenic bacteria have not been proven in her vaginal swab (not older than 5 weeks), we do not prescribe any antibiotic therapy during the active labour.

Recommendation: II B

In the event of proven vaginal GBS colonization and absence of bacteriuria, we recommend expectative management of the pregnancy until week 34.

Recommendation: IA

In the event of proven vaginal GBS colonization, and presence of bacteriuria without symptoms, we perform a qualitative urine test according to the Sanford guide. In the event of bacteriuria caused by GBS we prescribe antibiotic therapy with penicillin.

Recommendation: II B

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Recommendation: II B

In the event of proven vaginal GBS colonization and absence of bacteriuria, we recommend expectative management of the pregnancy until week 34.

6 Preventing maternal infections

In the event of:
- more than 12 hours passing since the rupture of membranes after week 34 of pregnancy, or
- elevated body temperature of the mother during labour, or
- clinical and/or laboratory signs of infection the parturient woman should be protected with a broad-spectrum antibiotic. She should be prescribed cefazolin 2 g IV, and after 8 hours cefazolin 1 g every 8 hours until the delivery. She should receive a least three doses. The duration of the cefazolin therapy is adjusted based on the clinical and laboratory signs of infection (30,36-37).

In the event of allergy, the parturient woman can be prescribed clindamycin 900 mg IV every 8 hours until the delivery or at least 3 doses in total (30).

In the event of a severe infection, we can use gentamicin 7 mg/kg/24 hours for 48–72 hours, and metronidazole 500 mg IV every 8 hours for 3–5 days (30).

The therapy must be adjusted based on microbiological test results, and the type of antibiotic and the duration (30).

7 Identifying and assessing evidence

The recommendations are based on the findings of studies done on the subject so far. We used the grading of recommendations as described in Table 1.

Table 1: Grading of recommendations.

<table>
<thead>
<tr>
<th>Degree of recommendation</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>The procedure or therapy is recommended.</td>
</tr>
<tr>
<td>II</td>
<td>Opinions on the procedure or therapy are not completely reliable – opposing facts exist.</td>
</tr>
<tr>
<td>II a</td>
<td>Benefit is more likely – reasonable to perform.</td>
</tr>
<tr>
<td>II b</td>
<td>Benefit is uncertain. No harm.</td>
</tr>
<tr>
<td>III</td>
<td>The procedure or therapy is harmful.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Multiple randomized trials or meta-analyses.</td>
</tr>
<tr>
<td>B</td>
<td>Single randomized clinical trial or several non-randomized studies.</td>
</tr>
<tr>
<td>C</td>
<td>Experts’ opinions, small trials and data from registers.</td>
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References


Figure 2: Antimicrobial therapy during labour.
References


