WHO recommendation on the prophylactic antibiotic of choice in women with preterm prelabour rupture of membranes

17 November 2015

Recommendation

Erythromycin is recommended as the antibiotic of choice for prophylaxis in women with preterm prelabour rupture of membranes

(Conditional recommendation based on moderate-quality evidence)

The use of a combination of amoxicillin and clavulanic acid ("co-amoxiclav") is not recommended for women with preterm prelabour rupture of membranes.

(Strong recommendation based on moderate-quality evidence).

Publication history

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Updated: No update planned

Assessed as up-to-date: November 2015

Remarks

- The GDG acknowledged the paucity of evidence from the subgroup analysis to demonstrate comparative effectiveness of different classes and regimens of antibiotics used for prophylaxis in women with preterm prelabour rupture of membranes (PPROM). However, the choice of erythromycin was based on the findings of a study (the ORACLE I trial) with over 2000 women, which showed that erythromycin lessens the risk of necrotizing enterocolitis (NEC) in the newborn compared to co-amoxiclav. The recommendation was made conditional because antibiotic choice may be dependent on local availability of the drug and sensitivities of prevalent organisms.

- For antibiotic prophylaxis in women with PPROM, oral erythromycin 250 mg four times a day for 10 days (or until delivery) should be used. The choice of this regimen was informed by the regimen used in the ORACLE I trial.

- The management of group B streptococcal colonization is outside the scope of this guideline. However, when considering colonization with group B streptococcus, management decisions should...
be taken based on adequate microbiological coverage and sensitivities.

- The recommendation was based on the increased risk of NEC with co-amoxiclav when compared with placebo and with erythromycin.
- Where organisms are sensitive to other antibiotics, it would seem sensible to avoid using co-amoxiclav during pregnancy.
- Penicillins (excluding amoxiclav) were used in the pooled trials that showed benefits of antibiotics in this context. Therefore, where erythromycin is not available, penicillin (such as amoxicillin) can be used.

**Background**

Preterm birth, defined as birth before 37 weeks of gestation, is the single most important determinant of adverse infant outcomes, in terms of survival and quality of life. (1) Globally, it is the leading cause of perinatal and neonatal mortality and morbidity. (2) Preterm infants are particularly vulnerable to complications due to impaired respiration, difficulty in feeding, poor body temperature regulation and high risk of infection. (3-5) With the increasing contribution of neonatal deaths to overall child mortality, it is critical to address the determinants of poor outcomes related to preterm birth to achieve further reductions in child mortality. (6-8)

Infant mortality and morbidity from preterm birth can be reduced through interventions delivered to the mother before or during pregnancy, and to the preterm infant after birth. (9) Interventions can be directed at all women for primary prevention and reduction of the risk of preterm birth (e.g. smoking cessation programme) or aimed at minimizing the risk in women with known risk factors (e.g. progestational agents, cervical cerclage). (10) However, the most beneficial set of maternal interventions are those that are aimed at improving outcomes for preterm infants when preterm birth is inevitable (e.g. antenatal corticosteroids, magnesium sulfate and antibiotic prophylaxis). (9) Special care of the preterm newborn to prevent and treat complications of prematurity is also critical to newborn survival. In high-income countries, reductions in mortality rates in infants that were born preterm have been driven largely by improved care and, more importantly, by appropriate policy changes.

**Methods**

The recommendations were developed using standard operating procedures in accordance with the process described in the WHO handbook for guideline development (11). Briefly, these included (i) identification of priority questions and critical outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of evidence, (iv) formulation of recommendations, and (v) planning for the dissemination, implementation, impact evaluation and updating of the guideline.

The scientific evidence underpinning the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (12). Up-to-date systematic reviews were used to prepare evidence profiles for the priority questions. WHO then convened a Technical Consultation in May 2014 where an international group of experts – the Guideline Development Group (GDG) – formulated and approved the recommendations based on the evidence profiles.

In November 2014, an online consultation of the GDG was conducted to review and revise the recommendations in the light of the findings of a large implementation trial of antenatal corticosteroids in low-resource countries.
Further information on procedures for developing this recommendation are available [here](#).

**Recommendation question**

For this recommendation, we aimed to answer the following question:

- Among pregnant women at risk of imminent preterm birth (P), is routine antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), effective in improving maternal and newborn outcomes (O)? If so:
  - Which population of women should be offered antenatal prophylactic antibiotics? (considering women with preterm rupture of membranes)
  - Which antibiotics (and regimens) should be used in eligible women?

**Evidence summary**

**Regimens of prophylactic antibiotics for women with PPROM**

The Cochrane review (13) also examined subgroups comparing different types of antibiotics:

- all penicillins (except co-amoxiclav) versus placebo
- beta-lactam antibiotics (including co-amoxiclav) versus placebo
- macrolide antibiotics (including erythromycin) versus placebo
- other antibiotics versus placebo
- erythromycin versus co-amoxiclav
- 3-day versus 7-day regimens of ampicillin.

*Perinatal death:* There was no statistically significant evidence that the type of antibiotic used had an impact on perinatal death compared with placebo (i.e. there were no significant differences between groups for any of the subgroups examined).

*Severe neonatal morbidity:* While there were no significant differences between groups for most types of antibiotics compared with placebo, risk of NEC was increased for those infants whose mothers had received beta-lactam antibiotics (including coamoxiclav) (RR 4.72, 95% CI 1.57–14.23; 2 studies, 1880 infants). The risk of other neonatal infections, including pneumonia, appeared to be reduced in the infants whose mothers received broad-spectrum penicillins (excluding co-amoxiclav) compared with placebo (RR 0.30, 95% CI 0.13–0.68; 5 studies, 521 infants), but differences were not significant for other subgroups. Similarly, all penicillins (excluding coamoxiclav) were associated with reduced occurrence of major cerebral abnormality on ultrasound, but the differences were not significant for other subgroups.

When erythromycin was compared with coamoxiclav in one study with data for more than 2000 women and infants, there were no significant differences for perinatal mortality or for the most serious neonatal morbidity outcomes (i.e. perinatal death, RDS, treatment with surfactant, major cerebral abnormality on ultrasound before discharge, NICU admission and serious childhood disability at 7 years). However, women in the erythromycin group were at slightly increased risk of birth within 48 hours of receiving the antibiotic (RR 1.14, 95% CI 1.02–1.28; 1 study, 2395 women). However, birth before 37 weeks of gestation was comparable between the erythromycin and co-amoxiclav groups. Infants whose mothers had received erythromycin rather than co-amoxiclav were at significantly reduced risk of NEC (RR 0.46, 95% CI 0.23–0.94; 1 study, 2395 women). One trial with data for 82 women compared 3- versus 7-day regimens. The study did not have sufficient statistical power to identify any significant differences for most outcomes.
The overall quality of the evidence varied across the subgroup comparisons. For comparisons of all penicillins (except co-amoxiclav) versus placebo, and for other antibiotics versus placebo, the quality of evidence was rated as low to high. The quality was rated as moderate for all outcomes reported in the comparison of macrolide antibiotics (including erythromycin) versus placebo and for most outcomes reported in the comparison of beta-lactam antibiotics (including co-amoxiclav) versus placebo. For the comparison between erythromycin versus co-amoxiclav, the quality of evidence was rated as moderate to high, while for 3- versus 7-day regimen comparisons, it was mostly rated as low.

Further information and considerations related to this recommendation can be found in the WHO guidelines, available at:

http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1
http://apps.who.int/iris/bitstream/handle/10665/183038/WHO_RHR_15.17_eng.pdf?sequence=1

**Implementation considerations**

- The successful introduction of this recommendation into national programmes and health-care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this recommendation.
- The recommendation should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner.
- A set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations, and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.
- In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged.

**Research implications**

The GDG identified that further research on the following high-priority question is needed:

- What is the appropriate dose and regimen that should be used for prophylaxis (particularly in relation to combination therapy with beta-lactam and macrolide)?

**Related links**

WHO recommendations on interventions to improve preterm birth outcomes (2015) –[full document](http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1) and evidence tables

Supporting systematic reviews:

Other links of interest

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors

Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice

WHO Programmes: Sexual and Reproductive health

Maternal Health

Infant, Newborn Health

References
