WHO recommendation on a simple regimen such as ampicillin and once-daily gentamicin as first-line antibiotics for the treatment of chorioamnionitis

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Recommendation

A simple regimen such as ampicillin and once-daily gentamicin is recommended as first-line antibiotics for the treatment of chorioamnionitis.

(Very low-quality evidence, conditional recommendation)

Publication history

First published: September 2015

Updated: no update planned

Assessed as up-to-date: September 2015

Remarks

- There is insufficient evidence to support the use of any antibiotic over another. Based on consensus, the GDG favoured a regimen that is simple, can be administered over a short duration and follows the principles of antibiotic use to reduce emergence of resistant strains of bacteria.
- Although there is no clear evidence as to whether antibiotics should be discontinued after birth or continued in the postpartum period, the GDG noted that women who remain symptomatic are likely to benefit from longer antibiotic treatment for at least 24 to 48 hours after the symptoms and signs of infection (e.g. fever, uterine tenderness) have subsided.

Background

Bacterial infections during labour and the puerperium are among the leading causes of maternal mortality worldwide, accounting for about one tenth of the global burden of maternal deaths. (1, 2) While the number of deaths arising from these infections has decreased considerably in high-income settings, the situation has not improved in resource-limited settings. Most of the estimated 75,000 maternal deaths occurring worldwide yearly as a result of infections are recorded in low-income countries. (3) Although the reported incidence in high-income countries is relatively low (between 0.1 and 0.6 per 1000 births), it is nonetheless an important direct cause of maternal mortality. (3, 4)

Apart from deaths and acute morbidities associated with infections during or following childbirth, long-term disabilities such as chronic pelvic pain, fallopian tube blockage and secondary infertility can also occur. Maternal infections around childbirth also have a considerable impact on newborn mortality, and an estimated 1 million newborn deaths are associated with such infections annually. (5, 6) In addition, infection-
related morbidities and prolonged hospitalization can interfere with mother–infant bonding in the first days after birth.

**Methods**

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, guided by the GRADE approach. Outcomes used for this recommendation were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of maternal peripartum infections (2015).

A cochrane review was conducted on the comparative effectiveness and safety of different antibiotics regimens for treatment of women diagnosed with intra-amniotic infection/chorioamnionitis. In the review, randomized controlled trials relevant to the key question were screened by review authors, and data on relevant outcomes and comparisons were extracted. Evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgments for each outcome, and the estimated risks.

WHO convened a Guideline Development Group (GDG) meeting on recommendations on prevention and treatment of maternal peripartum infections in September 2015, where this recommendation was developed. The GDG comprised of a group of independent experts, who used the evidence profiles to assess evidence on effects on the pre-specified outcomes. GDG members discussed the balance between desirable and undesirable effects, overall quality of supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity, to formulate the recommendation. Remarks were added to clarify the recommendation, and aid implementation.

**Recommendation question**

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

- Among women receiving antibiotic treatment for intra-amniotic infection/chorioamnionitis (P), is the use of a particular antibiotic regimen (I), compared with other regimens (C), more effective in improving maternal and neonatal outcomes (O)?

**Evidence Summary**

Evidence on comparative effectiveness and safety of different antibiotics regimens for treatment of women diagnosed with intra-amniotic infection/chorioamnionitis was extracted from a Cochrane systematic review of 11 trials involving 1296 women. All trials were conducted in the USA except one which was conducted in Italy.

The definition of chorioamnionitis varied between trials, but in all trials the definition included the presence of fever. Other conditions considered for diagnosis were maternal tachycardia, fetal tachycardia, uterine tenderness, purulent or foul amniotic fluid and maternal leucocytosis.

Women were followed up until discharge from hospital, and six trials reported follow-up between one and six weeks after discharge. Six trials included women who delivered by caesarean section. Four trials excluded women ≤34 weeks of gestation. Most of the trials excluded women who received antibiotics prior to delivery and those with other sources of infection.

Trials tested a range of IV antibiotics regimens, doses, frequency, duration of administration, combinations and timing of administration. Four trials compared antibiotics during labour, six trials compared antibiotics after birth, and one compared antibiotic administration before and after birth. The following antibiotics were used in the included trials: ampicillin, ampicillin/subactam, gentamicin, clindamycin and cefotetan.
**Intrapartum antibiotics (EB Table 19a)**

Ampicillin plus daily gentamicin versus ampicillin plus thrice-daily gentamicin (2 trials, 163 women)

- 2 g IV ampicillin six-hourly plus 5.1 mg/kg (every 24 hours) of gentamicin were compared with 2 g IV ampicillin six-hourly plus 80 mg of gentamicin eight-hourly.
- There were no differences between groups in the rates of endometritis (RR 0.86, 95% CI 0.27 to 2.70). One of the trials (125 women) reported no differences between groups in initial successful response to antibiotics (RR 1.05, 95% CI -0.45 to 1.25), maximum maternal temperature (MD 1.05, 95% CI 0.94 to 1.17) and maternal postpartum hospital stay (MD 0.00, 95% CI -0.43 to 0.43). No maternal death was reported in any of the treatment groups.
- There were no differences between groups for neonatal sepsis (RR 1.07, 95% CI 0.40 to 2.86). One of the trials (125 women) reported no differences between groups for respiratory distress syndrome (RR 1.69, 95% CI 0.42 to 6.78, 1 study, 125 neonates) or duration of neonatal antibiotic use (in days) (MD 0.20 days, 95% CI -0.37 to 0.77, 1 study, 125 neonates).

Dual-agent therapy (ampicillin/gentamicin) versus triple-agent therapy (ampicillin/gentamicin/ clindamycin) (1 trial, 133 women)

- There were no statistical differences between groups in the incidence of postpartum endometritis (RR 1.86, 95% CI 0.67 to 5.14), postpartum endometritis after vaginal delivery (RR 9.63, 95% CI 0.55 to 167.95; 73 women) or postpartum endometritis after caesarean section (RR 1.0, 95% CI 0.32 to 3.10; 60 women).
- There were no statistical differences for neonatal sepsis (RR 0.93, 95% CI 0.06 to 14.52), neonatal deaths (RR 1.39, 95% CI 0.24 to 8.06), intraventricular haemorrhage (RR 4.64, 95% CI 0.23 to 94.90), respiratory distress syndrome (RR 1.11, 95% CI 0.36 to 3.47; 125 neonates) or neonatal seizures (RR 0.93, 95% CI 0.06 to 14.52).

Ampicillin/sulbactam versus cefotetan (1 trial, 19 women)

- One small trial compared ampicillin/ sulbactam versus cefotetan and reported no failure of antibiotic treatment for women with chorioamnionitis and no maternal deaths.

**Postpartum antibiotics (EB Tables 19b–19e)**

Ampicillin during labour plus postpartum clindamycin/gentamicin versus no treatment during the postpartum period, 1 trial, 116 women

- No significant differences were observed for postpartum endometritis (RR 1.48, 95% CI 0.68 to 13.24), and wound infection (RR 0.37, 95% CI 0.04 to 3.45) between the postpartum treated and untreated groups.
- There were no differences in neonatal deaths (RR 3.32, 95% CI 0.14 to 79.88), neonatal sepsis (RR 1.11, 95% CI 0.23 to 5.27) or transient tachypnoea (RR 0.83, 95% CI 0.19 to 3.55).

Once daily versus thrice-daily gentamicin/ clindamycin in the postpartum (1 trial, 131 women)

- No differences were observed between groups in the rate of treatment failure, defined as elevated temperature after 72 hours treatment (RR 1.02, 95% CI 0.27 to 3.89), or length of antibiotic treatment (days) (MD -0.30 days, 95% CI -0.90 to 0.30). No cases of nephrotoxicity were observed.

Short versus long duration of treatment (2 trials, 401 women)

- Two trials compared continuation of intrapartum antibiotic administration with either a postpartum short-course or longer-course antibiotic treatment. In both trials women received ampicillin and
gentamicin when chorioamnionitis was diagnosed during labour. In one trial, there was no further treatment in the intervention arm after delivery, while in the control arm, the intrapartum schedule of ampicillin and gentamicin was continued postpartum until the women were afebrile and asymptomatic for 24 hours. In the second trial, women in the short-course arm received a single dose of cefotetan within one hour of delivery, while those in the long-course arm received cefotetan every 12 hours for a minimum of 48 hours.

- No significant differences were observed between the postpartum short- and long-course treatment in the overall rate of treatment failure (RR 1.31, 95% CI 0.42 to 4.02; 1 trial, 292 women) or after stratification by mode of delivery (vaginal delivery: RR 1.46, 95% CI 0.39 to 5.51; 2 trials, 284 women; caesarean delivery: RR 3.31, 95% CI 0.38 to 28.75; 1 trial, 117 women). There were no differences in the incidence of wound infection (RR 1.87, 95% CI 0.17 to 20.37; 1 trial, 292 women) or pelvic abscess (RR 2.80, 95% CI 0.12 to 68.24; 1 trial, 292 women). Mean duration of hospital stay (in days) was reduced in the shorter arm of treatment compared to the longer arm (MD -0.90 days, 95% CI -1.64 to -0.16; 1 trial, 292 women).

- Intrapartum versus postpartum ampicillin/ gentamicin (1 trial, 45 women)
- No differences were found between the group receiving antibiotics intrapartum versus postpartum in maternal bacteraemia (RR 2.19, 95% CI 0.25 to 19.48) or maximum maternal temperature postpartum (MD -0.50, 95% CI -1.08 to 0.08).
- Mothers and neonates in the intrapartum antibiotic group tended to have significantly shorter hospital stays (maternal postpartum hospital stay (days): MD -1.00 day, 95% CI -1.94 to -0.06; neonatal hospital stay: MD -1.90 days, 95% CI -3.31 to -0.49).
- There were no difference between groups in the incidence of early neonatal sepsis (RR 0.08, 95% CI 0.00 to 1.44) or sepsis and pneumonia combined (RR 0.06, 95% CI 0.00 to 0.95).

**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 did not identify further research priorities on this topic.

**Related Links**


References


Citation

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