WHO recommendation on a combination of clindamycin and gentamicin for the treatment of postpartum endometritis

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Recommendation

A combination of clindamycin and gentamicin is recommended for the treatment of postpartum endometritis.

(Very low - quality evidence, conditional recommendation)

Publication history

First published: September 2015

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Assessed as up-to-date: September 2015

Remarks

- The GDG acknowledged that availability and costs of clindamycin might be limiting factors in low-resource settings, and suggested the use of a penicillin class of drug as alternative treatment in such contexts.
- In the majority of studies that demonstrated benefits of clindamycin and gentamicin over other regimens, clindamycin was administered as 600 mg IV every six to eight hours, and gentamicin was administered as 1–1.5 mg/kg or 60–80 mg IV or IM every eight hours. Although the exact duration of the treatment was not specified in most cases, treatment was continued for as long as clinical symptoms and signs persisted. Similar to the remark regarding the treatment for chorioamnionitis, the GDG suggested that antibiotic treatment should continue for at least 24–48 hours after complete resolution of clinical signs and symptoms (e.g. fever, uterine tenderness, purulent lochia, leucocytosis).

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.\(^{(7)}\)

Outcomes used for this recommendation were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of maternal peripartum infections (2015).\(^{(8)}\)

A Cochrane review was conducted on the use of different antibiotics regimens to treat postpartum endometritis.\(^{(9)}\) 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 postpartum endometritis (P), is the use of a particular antibiotic regimen (I), compared with other regimen(s) (C), more effective in improving maternal outcomes (O)?

**Evidence Summary**

Evidence on the use of different antibiotics regimens to treat postpartum endometritis was extracted from a Cochrane systematic review. Forty-two trials including 4240 women were included (although 40 trials and 4240 women were included in the analysis).\(^{(9)}\) Trials were mostly conducted in high-income countries, particularly in the USA: 33 trials were conducted in the USA, two in Mexico, and one in each of Colombia, France, Italy and Peru. One study was a multi-centre study conducted in many countries including the USA.

Clinical criteria used to define endometritis were consistent across trials and included fever and uterine tenderness. Some trials also considered pelvic pain, purulent lochia, parametrial tenderness, leucocytosis, absence of other foci of infection or, in contrast, included women with chorioamnionitis or salpingitis or pelvic cellulitis after caesarean section. The definition of fever varied between trials in the criteria used for height of fever, intervals between febrile episodes and from the operative procedure. Some variations existed in the definition of serious morbidities, which included bacteraemia, pelvic thrombophlebitis, pelvic abscess and peritonitis.
Trials included women who developed endometritis within the six weeks following delivery, but the majority of women were enrolled about 48 hours post-delivery. In half of the trials, only women who developed endometritis after caesarean section were included, but in four trials information on the mode of delivery was not reported. Inclusion of women who delivered by caesarean section and received prophylactic antibiotics varied between trials. Cefazolin was the main prophylactic agent used except in one trial in which cefoxitin was used.

Antibiotic regimens were classified into 12 groups. In half of the trials (20 trials, 1918 women), the use of clindamycin plus an amino glycoside was compared with another regimen; in the others, different antibiotic regimens were compared.

No trial reported on maternal mortality. The review did not consider long-term complications such as subfertility or uterine adhesions.

**Clindamycin plus aminoglycoside versus other regimens (EB Table 20a)**

- Analyses of clindamycin plus an aminoglycoside (most often gentamicin) resulted in a significant reduction in the rate of treatment failure compared with penicillins (RR 0.65, 95% CI 0.46 to 0.90; 7 trials, 689 women) and cephalosprins (RR 0.69, 95% CI 0.49 to 0.99; 8 trials, 872 women).
  
  Concerning the other regimens tested, there were no significant differences observed between lincosamides when compared to quinolines (RR 0.72, 95% CI 0.38 to 1.37; 3 trials, 176 women) or monobactams (RR 2.25, 95% CI 0.60 to 8.43; 2 trials, 181 women), although the trials were much smaller. After antibiotic prophylaxis for caesarean section, there were no differences in treatment failure between lincosamides and penicillins (RR 1.12, 95% CI 0.63 to 1.98; 2 trials, 229 women).

- Analyses of severe complications showed no differences among the different subgroups: lincosamide versus cephalosporins (RR 2.40, 95% CI 0.30 to 19.19; 4 trials, 476 women), monobactams (no events; 1 trial, 62 women), penicillins (RR 0.33, 95% CI 0.09 to 1.18; 5 trials, 422 women) or quinolines (RR 2.89, 95% CI 0.31 to 27.20; 2 trials, 160 women).

- There was a decrease in wound infection with the use of clindamycin plus aminoglycoside compared with cephalosporins (RR 0.53, 95% CI 0.30 to 0.93; 4 trials, 500 women) and a trend towards reduction when compared to penicillins (RR 0.46, 95% CI 0.21 to 1.00; 3 trials, 339 women). No differences were shown within the other subgroups: lincosamides versus monobactams (RR 0.95, 95% CI 0.06 to 14.85; 1 trial, 119 women) or quinolones (RR 0.51, 95% CI 0.05 to 5.45; 1 trial, 97 women).

- No differences were found in side-effects among the various groups (diarrhoea, allergic reactions) or length of hospital stay.

**Aminoglycoside plus penicillin or ampicillin versus any other regimen (EB Table 20b)**

- Two trials compared gentamicin plus penicillin or ampicillin versus other regimens. These trials showed statistically significant heterogeneity (P = 0.03, I² = 78%) for treatment failure and were analysed separately. The trial (200 women) comparing gentamicin plus penicillin versus gentamicin/clindamycin showed significantly more treatment failures (RR 2.57, 95% CI 1.48 to 4.46) for those treated with gentamicin plus penicillin, but the trial comparing gentamicin plus ampicillin versus piperacillin/tazobactam showed no significant differences between groups (RR 0.56, 95% CI 0.15 to 2.03; 56 women).

- No differences were found when aminoglycoside plus penicillin were compared with gentamycin/clindamycin in the incidence of severe complications (RR 0.11, 95% CI 0.01 to 2.04; 1 trial, 200 women), wound infections (RR 0.50, 95% CI 0.22 to 1.12; 1 trial, 200 women), diarrhea (RR 5.00, 95% CI 0.24 to 102; 1 trial, 200 women) or allergic reactions (RR 1.00, 95% CI 0.14 to 6.96).

- No differences were found when aminoglycoside plus ampicillin were compared to piperacillin/tazobactam in the incidence of wound infection (RR 2.44, 95% CI 0.13 to 44.57; 1 trial, 56 women). No severe complications, diarrhea or allergic reactions were reported in this trial.
Penicillin plus beta-lactamase inhibitor versus any other regimen (EB Table 20c)

- Twelve trials including 1007 women compared penicillin plus beta-lactamase inhibitor with any other regimen. For all comparisons, no significant differences were observed in the incidence of treatment failure: penicillin plus beta-lactamase inhibitor versus lincomamides (RR 1.07, 95% CI 0.70 to 1.64; 6 trials, 495 women), versus cephalosporins (RR 1.08, 95% CI 0.39 to 43.93; 2 trials, 52 women), versus penicillins (RR 1.24, 95% CI 0.90 to 1.05; 2 trials, 155 women), versus carabapem (RR 0.97, 95% CI 0.90 to 1.05; 1 trial, 238 women) and versus nitroimidazoles (RR 1.09, 95% CI 0.24 to 5.04; 1 trial, 67 women).

- Two trials reported on severe complications. One compared penicillin plus beta-lactamase inhibitor versus lincomamides and found no differences between groups (RR 4.32, 95% CI 0.51 to 36.95; 3 trials, 160 women). No events were reported in a small trial comparing penicillin plus beta-lactamase inhibitor versus penicillin (56 women).

- Two small trials reported on wound infection. No differences were found when penicillin plus beta-lactamase inhibitor was compared to penicillins (RR 0.41, 95% CI 0.02 to 7.47; 1 study, 56 women). The other study (77 women) reported no events. For diarrhoea there were no differences between penicillin plus beta-lactamase inhibitor versus lincomamides (RR 1.08, 95% CI 0.29 to 4.01; 3 trials, 160 women) or penicillin plus beta-lactamase inhibitor versus cephalosporin (RR 0.54, 95% CI 0.06 to 5.26; 1 trial, 27 women). One small trial (56 women).

- Four trials reported on allergic reactions and reported no differences when comparing penicillin plus beta-lactamase inhibitor versus penicillins (RR 0.98, 95% CI 0.06 to 15.23; 2 trials, 155 women). The two trials comparing penicillin plus beta-lactamase inhibitor versus lincomamides reported no events. Length of hospital stay did not differ when a penicillin plus beta-lactamase inhibitor was compared to penicillin (MD 0.80, 95% CI -0.09 to 1.69; 1 trial, 99 women).

Aztreonam plus clindamycin versus any other regimen (EB Table 20d)

- Two trials each compared aztreonam plus clindamycin versus trospectomycin plus aztreonam or versus gentamicin plus clindamycin.

- No differences were found among subgroups in the incidence of treatment failure when aztreonam plus clindamycin was compared to trospectomycin plus aztreonam (RR 1.49, 95% CI 0.78 to 2.84; 2 trials, 422 women) or gentamicin plus clindamycin (RR 0.45, 95% CI 0.12 to 1.67; 2 trials, 181 women).

- There were no differences in the incidence of allergic reactions (RR 1.04, 95% CI 0.52 to 2.09; 2 trials, 181 women) in the aztreonam plus clindamycin group compared to gentamicin plus clindamycin. Only one trial comparing aztreonam plus clindamycin versus gentamicin plus clindamycin reported on other outcomes and found no difference in the incidence of wound infection (RR 1.09, 95% CI 0.07 to 17.00; 1 trial, 117 women), diarrhoea (RR 2.10, 95% CI 0.20 to 22.58; 1 trial, 119 women) or length of hospital stay (MD -0.45 days, 95% CI -1.15 to 0.25; one trial, 119 women). No cases of severe complications were reported.

Cephalosporin with longer half-life versus cephalosporin with shorter half-life (EB Table 20e)

- Two trials compared different half-life cephalosporins: cefoxitin administered every six hours was compared with either cefmetazole administered every eight hours or cefotetan administered every 12 hours.

- The rate of treatment failure was lower in the group treated with the longer half-life compared to the shorter half-life (RR 0.61, 95% CI 0.40 to 0.92; 2 trials, 484 women). For other outcomes, no differences were found between the groups for severe complication (RR 0.27, 95% CI 0.02 to 2.89; 1 trial, 355 women), wound infection (RR 0.70, 95% CI 0.13 to 3.68, 2 trials, 484 women), diarrhoea (RR 1.43, 95% CI 0.42 to 4.84; 1 trial, 129 women), allergic reaction (RR 0.78, 95% CI 0.22 to 2.72; 1 trial, 377 women) or length of hospital stay (MD -0.60 days, 95% CI -1.45 to 0.25; 1 trial, 129 women).
Metronidazole plus gentamicin versus penicillins (EB Table 20f)

- Only one trial (67 women) compared metronidazole plus gentamicin versus penicillins (ampicillin plus sulbactam). The study found no difference in the rate of treatment failure (RR 0.91, 95% CI 0.20 to 4.21).

Once-daily versus thrice-daily gentamicin (EB Table 20g)

- Four studies compared once-daily versus thrice-daily (eight-hourly) gentamicin. Once-daily gentamicin tended to reduce the likelihood of treatment failure compared with a thrice-daily regimen (RR 0.70, 95% CI 0.49 to 1.00; 4 trials, 463 women).
- There were no differences in antibiotic adverse effects reported (nephrotoxicity: RR 3.04, 95% CI 0.13 to 73.43; 3 trials, 353 women) or in the length of hospital stay (MD -0.73 days, 95% CI -1.27 to -0.20; 3 trials, 322 women).

Continued oral versus no treatment after intravenous antibiotic course (EB Table 20h)

- Three trials tested continued oral antibiotics (ampicillin, ampicillin/clavulanic or penicillin) versus no treatment after initial intravenous antibiotic course.
- No differences were found between treatment groups for treatment failure (RR 1.46, 95% CI 0.34 to 6.18; 1 trial, 109 women), wound infection (RR 3.38, 95% CI 0.14 to 80.70; 1 trial, 81 women), recurrence of endometritis (RR 2.91, 95% CI 0.12 to 68.81; 3 trials, 253 women) or length of hospital stay (MD -0.21 days, 95% CI -1.44 to 1.02; 1 trial, 63 women).

Poor activity against penicillin-resistant anaerobic bacteria versus good activity (EB Table 20i)

- Trials showed a significantly higher rate of treatment failure (RR 1.94, 95% CI 1.38 to 2.72; 7 trials, 774 women) and wound infection (RR 1.88, 95% CI 1.17 to 3.02; 6 trials, 740 women) in the group treated with antibiotic regimens with poor activity against penicillin-resistant anaerobic bacteria, compared with the good activity group (six out of the seven trials tested clindamycin/ gentamicin combination).
- No differences were found in the incidence of severe complications (RR 1.68, 95% CI 0.45 to 6.29; 5 trials, 671 women), diarrhoea (RR 0.29, 95% CI 0.08 to 1.04; 6 trials, 743 women), allergic reactions (RR 1.34, 95% CI 0.34 to 5.36; 5 trials, 628 women) or length of hospital stay (MD 0.37 days, 95% CI -1.44 to 0.73; two trials, 267 women).

Oral ofloxacin/clindamycin versus intravenous clindamycin/gentamicin (EB Table 20j)

- One small trial reported treatment failure when comparing oral ofloxacin/clindamycin versus intravenous clindamycin/gentamicin treatment. No difference was observed between the two groups (RR 0.67, 95% CI 0.15 to 2.98; 1 trial, 16 women).

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


Supporting systematic review:


References


Citation


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