WHO recommendation on antibiotic prophylaxis for caesarean section using a single dose of first generation cephalosporin or penicillin in preference to other classes of antibiotics

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Recommendation

For antibiotic prophylaxis for caesarean section, a single dose of first generation cephalosporin or penicillin should be used in preference to other classes of antibiotics.

(Very low - quality evidence, conditional recommendation)

Publication history

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Remarks

- The GDG noted that the available evidence on the effectiveness of antibiotics came largely from trials that tested first-generation cephalosporin or penicillin. Based on consensus, the group favoured these classes of antibiotics over other classes of antibiotics, as they have a broad spectrum of activities and are widely available in all settings.

- In acknowledgement of the lack of evidence on the comparative effectiveness of different classes of antibiotics, the GDG concluded that when the recommended antibiotic classes are not available, other classes of antibiotics may also be used. The group noted that the choice of such antibiotic class should be informed by the local bacteriologic patterns of postcaesarean infectious morbidity, the availability of such antibiotic class, the woman’s allergy history, the clinician’s experience with that particular class of antibiotics, and its cost.

- Due to the high risk of necrotizing enterocolitis among preterm babies, the use of “co-amoxiclav” for antibiotic prophylaxis should be avoided not only for caesarean delivery of preterm infants, but it might also be safer to avoid its use for caesarean delivery of term babies.

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 comparative effectiveness and safety of different classes of antibiotics to prevent infectious morbidity in women undergoing caesarean section.(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 routine antibiotic prophylaxis for caesarean section (P), is the use of a particular class of antibiotics (I), compared with other classes of antibiotics (C), more effective in preventing postoperative infectious morbidities (O)?

Evidence Summary

Evidence on the comparative effectiveness and safety of different classes of antibiotics to prevent infectious morbidity in women undergoing caesarean section was extracted from a Cochrane systematic review of 35 trials (with 31 trials providing data for 7697 women).(9)

Trials were conducted in low-, middle- and high-income countries: 12 studies in the USA, four in India, three in Italy, two in Thailand, and one each in the following countries: Argentina, Canada, Greece, Finland, the Netherlands, Malaysia, Mozambique, Rwanda, South Africa, Sudan, Switzerland, the UK, the United Arab Emirates and Zimbabwe.
The trials included women undergoing either elective or non-elective caesarean section. All but five trials administered prophylactic antibiotics after umbilical cord clamping. Antibiotics were administered preoperatively in four trials, and information about the timing of antibiotic administration was not available for one trial.

The comparisons considered in the review were those between two or more antibiotics of different classes. Comparisons of different drugs or drug regimens within the same class were excluded. The majority of the trials included compared cephalosporin with penicillin. The overall data for any cephalosporin versus any penicillin were not pooled but analysed according to the following subgroups: single cephalosporin versus single penicillin, single cephalosporin versus penicillin combination, cephalosporin combination versus single penicillin and cephalosporin combination versus penicillin combination. Three trials compared a cephalosporin or penicillin with another class of antibiotics. Few studies compared mixed antibiotic regimens (which do not include a cephalosporin or penicillin) with cephalosporin or penicillin.

**Cephalosporin versus penicillin (EB Tables 18a-18j)**

Single cephalosporin versus single penicillin (13 trials, 4010 women)

- There were no cases of maternal sepsis in 346 women involved in two trials.
- There were no significant differences between cephalosporin and penicillin regimens for endometritis (RR 1.11, 95% CI 0.81 to 1.52; 9 trials, 3130 women), maternal febrile morbidity (RR 0.89, 95% CI 0.61 to 1.30; 7 trials, 1344 women), wound infection (RR 0.83, 95% CI 0.38 to 1.81; 9 trials, 1497 women) or urinary tract infection (RR 1.48, 95% CI 0.89 to 2.48, 7 trials, 1120 women). There were no significant differences between antibiotic classes on a maternal composite of adverse effects (RR 2.02, 95% CI 0.18 to 21.96; 3 trials, 1902 women).
- No cases were reported in the two trials evaluating a composite outcome of maternal serious infectious morbidity.
- None of the included studies reported neonatal sepsis.

Single cephalosporin versus penicillin combination (12 trials, 2875 women)

- There were no significant differences between comparison groups for maternal sepsis (RR 2.37, 95% CI 0.10 to 56.41; 1 trial, 75 women), endometritis (RR 0.90, 95% CI 0.60 to 1.35, 10 trials, 2134 women), maternal febrile morbidity (RR 0.92, 95% CI 0.56 to 1.49; 6 trials, 1824 women), wound infection (RR 0.72, 95% CI 0.40 to 1.30; 7 trials, 1608 women) or maternal urinary tract infection (RR 0.66, 95% CI 0.17 to 2.55; 6 trials, 1361 women). There were no significant differences between antibiotic classes on maternal composite adverse effects (RR 0.96, 95% CI 0.09 to 10.50; 4 trials, 1333 women).
- None of the included studies reported neonatal sepsis.

Cephalosporin combination versus single penicillin (1 trial, 147 women)

- From one study involving 139 women, there were no differences observed between groups for endometritis (RR 2.70, 95% CI 0.63 to 11.55), maternal febrile morbidity (RR 2.36, 95% CI 0.84 to 6.62) or wound infection (RR 2.02, 95% CI 0.42 to 9.63). The other critical outcomes were either not reported by the study or there were no events.

Cephalosporin combination versus penicillin combination (2 trials, 363 women)

- There were no significant differences between groups in maternal sepsis (RR 3.21, 95% CI 0.34 to 30.45; 1 trial, 232 women), endometritis (RR 0.33, 95% CI 0.01 to 7.77; 1 trial, 83 women), maternal fever (RR 1.57, 95% CI 0.69 to 3.60; 2 trials, 315 women) or wound infection (RR 1.23, 95% CI 0.42 to 3.58; 2 trials, 315 women).
Cephalosporins versus penicillins: comparison by type of caesarean section (22 trials, 5788 women)

- Most of the trials included women undergoing either elective or emergency caesarean sections.
- There was no significant difference between women undergoing elective or emergency caesarean section for maternal sepsis (RR 2.91, 95% CI 0.47 to 18.10; 4 trials, 653 women).
- There was a significant difference between subgroups for endometritis ($I^2 = 61.4\%$). Penicillins showed a trend towards superior effectiveness compared with cephalosporins for reducing endometritis among women undergoing nonelective caesarean section (RR 1.33, 95% CI 1.01 to 1.75, 6 trials, 2362 women). The differences were not significant for elective caesarean section (RR 2.06, 95% CI 0.66 to 6.39; 3 trials, 461 women) or when type of caesarean section was not differentiated (RR 0.85, 95% CI 0.60 to 1.19; 11 trials, 2567 women).

Cephalosporins versus penicillins: comparison by timing of administration (22 trials, 5788 women)

- All but two trials administered antibiotics before umbilical cord clamping. Two trials did not report on the timing of antibiotic administration.
- There were no significant differences between antibiotics for maternal sepsis (RR 2.91, 95% CI 0.47 to 18.10; 4 trials, 653 women) or endometritis (RR 1.11, 95% CI 0.90 to 1.37; 20 trials, 5390 women).

Cephalosporins versus penicillins: comparison by route of administration (22 trials, 5788 women)

- Twenty trials compared antibiotics given intravenously. Two studies compared the antibiotics when administered as a lavage/irrigation during surgery.
- There were no significant differences between antibiotic classes for maternal sepsis (RR 2.90, 95% CI 0.46 to 18.17, 4 trials, 653 women) or endometritis (RR 1.12, 95% CI 0.92 to 1.37, 20 trials, 5390 women) in relation to the route of administration.

First-generation cephalosporins versus extended spectrum penicillins (2 trials, 822 women)

- Extended-spectrum penicillins were more efficient in preventing endometritis than first-generation cephalosporins (RR 2.18, 95% CI 1.30 to 3.66; 2 trials, 814 women). However, no differences were reported in maternal fever (RR 2.36, 95% CI 0.84 to 6.62; 1 trial, 139 women) or wound infection (RR 2.02, 95% CI 0.42 to 9.63; 1 trial, 139 women).

First-generation cephalosporins versus aminopenicillins (8 trials, 1882 women)

- There were no significant differences between groups for endometritis (RR 1.09, 95% CI 0.69 to 1.71; 7 trials, 1487 women), maternal febrile morbidity (RR 0.78, 95% CI 0.40 to 1.51; 5 trials, 883 women), wound infection (RR 0.85, 95% CI 0.36 to 2.01; 5 trials, 626 women) or urinary tract infections (average RR 1.41, 95% CI 0.54 to 3.70; 5 trials, 626 women).
- A reduction in the maternal length of hospital stay was observed in the group receiving cephalosporins compared to aminopenicillins (MD -1.50, 95% CI -2.46 to -0.54; 1 trial, 132 women).

Second-generation cephalosporins versus extended spectrum penicillins (6 trials, 2077 women)

- There were no significant differences between groups for endometritis (RR 1.10, 95% CI 0.78 to 1.54; 4 trials, 1334 women), maternal febrile morbidity (RR 1.08, 95% CI 0.79 to 1.47; 4 trials, 850 women), wound infection (RR 2.37, 95% CI 0.64 to 8.73; 2 trials, 438 women) or urinary tract infection (RR 1.43, 95% CI 0.67 to 3.07; 3 trials, 567 women). There were no reported events of maternal sepsis (1 trial, 287 women), post-discharge infections (3 trials, 305 women) or maternal composite adverse effects (RR 2.02, 95% CI 0.18 to 21.96; 2 trials, 1030 women).

Second-generation cephalosporins versus aminopenicillins (8 trials, 1921 women)
• There were no significant differences between groups in maternal sepsis (RR 2.37, 95% CI 0.10 to 56.41; 1 trial, 75 women), endometritis (RR 1.01, 95% CI 0.75 to 1.35; 8 trials, 1890 women), maternal febrile morbidity (RR 1.17, 95% CI 0.64 to 2.15; 3 trials, 387 women), wound infection (RR 1.14, 95% CI 0.47 to 2.78; 5 trials, 638 women), maternal urinary tract infection (RR 0.63, 95% CI 0.11 to 3.66; 4 trials, 462 women) or maternal composite of adverse effects (RR 1.92, 95% CI 0.18 to 20.82; 3 trials, 1130 women).

Third-generation cephalosporins versus extended-spectrum penicillins (2 trials, 359 women)

• Extended-spectrum penicillins were more efficient than third-generation cephalosporins in preventing endometritis (RR 2.14, 95% CI 1.14 to 4.00; 1 trial, 300 women). Other considered outcomes reported no events.

Third-generation cephalosporins versus aminopenicillins (7 trials, 1904 women)

• There were no significant differences between groups for endometritis (RR 1.47, 95% CI 0.89 to 2.42; 5 trials, 1472 women), maternal febrile morbidity (RR 1.12, 95% CI 0.69 to 1.83; 3 trials, 1060 women), maternal urinary tract infection (RR 0.52, 95% CI 0.10 to 2.80; 2 trials, 233 women) or length of maternal hospital stay (MD -0.03, 95% CI -0.14 to 0.08; 1 trial, 746 women).

• Wound infections were reduced in the group receiving third-generation cephalosporins (RR 0.49 95% CI 0.27 to 0.90; 6 trials, 1556 women).

Fluoroquinolones versus penicillin or cephalosporin (EB Tables 18k–18l)

• Two very small trials tested ciprofloxacin versus ampicillin/sulbactam (72 women) or cefotetan (81 women).

• No differences were found between these antibiotics regarding maternal sepsis, endometritis or wound infection.

Other antibiotic regimens versus penicillin or cephalosporins (EB Tables 18m-18n)

• There were other comparisons between other antibiotic class combinations versus penicillin or cephalosporin:
  ○ Lincosamide plus aminoglycoside versus penicillin (1 trial, 88 women)
  ○ Beta-lactam versus cephalosporin (2 trials, 118 women)
  ○ There were no differences observed between the comparison groups for the outcomes reported: wound infection and endometritis.

Aminoglycoside plus nitroimidazole versus standard antibiotic cocktail (EB Table 18o)

• One trial involving 241 women compared gentamicin (aminoglycoside) plus metronidazole (nitroimidazole) with a standard cocktail of antibiotics (containing penicillin, nitroimidazole and macrolide). There was no significant difference between the two groups with regard to endometritis (RR 0.81, 95% CI 0.29 to 2.26; 1 trial, 241 women), maternal fever (RR 1.12, 95% CI 0.69 to 1.83; 3 trials, 1060 women), wound infection (RR 3.23, 95% CI 0.34 to 30.64; 1 trial, 241 women) or maternal urinary tract infection (RR 1.08, 95% CI 0.07 to 17.03; 1 trial, 241 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

WHO recommendation on antibiotic prophylaxis for caesarean section using a single dose of first generation cephalosporin or penicillin in preference to other classes of antibiotics (September 2015). The WHO Reproductive Health Library; Geneva: World Health Organization.
