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Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy

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Abstract

Background—Asymptomatic bacteriuria occurs in 5% to 10% of pregnancies and, if left untreated, can lead to serious complications.

Objectives—To assess which antibiotic is most effective and least harmful as initial treatment for asymptomatic bacteriuria in pregnancy.

Search methods—We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2010) and reference lists of retrieved studies.

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CONTRIBUTIONS OF AUTHORS:

Dr Valerie T Guinto:

1. conceived the protocol;
2. designed the protocol; and
3. carried out analysis and drafted text for the protocol and the review

Professor Mario R Festin:

1. provided general advice on the protocol;
2. secured funding for the writing of the protocol; and
3. edited the protocol and commented on drafts of the review.

Professor Blanca C de Guia commented on drafts of the protocol and review.
Dr Therese Dowswell contributed to drafting the text and commented on drafts of the review.
All four authors were involved in assessing study eligibility and data extraction.

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Selection criteria—Randomized controlled trials comparing two antibiotic regimens for treating asymptomatic bacteriuria.

Data collection and analysis—Review authors independently screened the studies for inclusion and extracted data.

Main results—We included five studies involving 1140 women with asymptomatic bacteriuria. We did not perform meta-analysis; each trial examined different antibiotic regimens and so we were not able to pool results. In a study comparing a single dose of fosfomycin trometamol 3 g with a five-day course of cefuroxime, there was no significant difference in persistent infection (risk ratio (RR) 1.36, 95% confidence interval (CI) 0.24 to 7.75), shift to other antibiotics (RR 0.08, 95% CI 0.00 to 1.45), or in allergy or pruritus (RR 2.73, 95% CI 0.11 to 65.24). A comparison of seven-day courses of 400 mg pivmecillinam versus 500 mg ampicillin, both given four times daily, showed no significant difference in persistent infection at two weeks or recurrent infection, but there was an increase in vomiting (RR 4.57, 95% CI 1.40 to 14.90) and women were more likely to stop treatment early with pivmecillinam (RR 8.82, 95% CI 1.16 to 66.95). When cephalexin 1 g versus Miraxid® (pivmecillinam 200 mg and pivampicillin 250 mg) were given twice-daily for three days, there was no significant difference in persistent or recurrent infection. A one- versus seven-day course of nitrofurantoin resulted in more persistent infection with the shorter course (RR 1.76, 95% CI 1.29 to 2.40), but no significant difference in symptomatic infection at two weeks, nausea, or preterm birth. Comparing cycloserine with sulphadimidine, no significant differences in symptomatic, persistent, or recurrent infections were noted.

Authors' conclusions—We cannot draw any definite conclusion on the most effective and safest antibiotic regimen for the initial treatment of asymptomatic bacteriuria in pregnancy. One study showed advantages with a longer course of nitrofurantoin, and another showed better tolerability with ampicillin compared with pivmecillinam; otherwise, there was no significant difference demonstrated between groups treated with different antibiotics. Given this lack of conclusive evidence, it may be useful for clinicians to consider factors such as cost, local availability and side effects in the selection of the best treatment option.

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [* therapeutic use]; Bacteriuria [* drug therapy]; Pregnancy Complications, Infectious [* drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy

BACKGROUND

Description of the condition

The diagnosis of asymptomatic bacteriuria should be based on the culture of a urine specimen collected in a manner that minimizes contamination. It is defined as two consecutively voided urine specimens with isolation of the same bacterial strain in quantitative counts of at least 100,000 colony-forming units/ml. Counts as low as 100 colony-forming units/ml are also considered significant bacteriuria if the specimen is

catheterized urine (Hooton 2007; Macejko 2007). Bacteriuria occurs in 2% to 7% of pregnant women in the first trimester (Nicolle 2003).

Asymptomatic bacteriuria occurs in 5% to 10% of pregnancies, 20% to 30% of which progress to pyelonephritis if left untreated (Whalley 1967). Physiologic changes in pregnancy brought about by hormonal changes and uterine compression make the pregnant woman with asymptomatic bacteriuria particularly susceptible to the development of persistent and symptomatic urinary tract infection. The kidneys increase in length and filtration rate by 30% to 50%, increasing renal clearance of drugs and possibly decreasing the duration a drug stays in the urine. There is decreased peristalsis in the collecting systems and ureters and smooth muscle relaxation in the bladder, as well as mechanical obstruction by the enlarged uterus, promoting stasis of urine (Macejko 2007).

The US Preventative Task Force strongly recommends screening of pregnant women at 12 to 16 weeks' gestation (USPFTF 2004). Early detection of asymptomatic bacteriuria in pregnant women is of value, as bacteriuria is an established risk factor for serious complications including acute pyelonephritis, preterm delivery, and low birthweight. It has also been recently shown in a case-control study that untreated group B streptococcus bacteriuria was associated with chorioamnionitis, or infection in the placental tissues and amniotic fluid (adjusted odds ratio 7.2, 95% confidence interval (CI) 2.4 to 21.2) (Anderson 2007). The standard method for screening for asymptomatic bacteriuria is the urine culture (Lumbiganon 1998). A urine culture obtained at 12 to 16 weeks of pregnancy will identify 80% of women who will ultimately have asymptomatic bacteriuria in pregnancy, with an additional 1% to 2% identified by having repeated monthly screening (Stenqvist 1989). If a urine culture cannot be performed, any other available test, such as a microscopic examination of the urine sediment to look for more than 10 leukocytes per high power field or a dipstick positive for leukocyte esterase activity or presence of nitrates, could be performed. However, health workers should know that the most adequate and desirable test is a urine culture. Although considered the gold standard, urine culture is considered expensive for routine screening in settings with a low prevalence for this condition. Dipstick analysis and direct microscopy, which are the tests more commonly used in the primary care setting, have poor positive and negative predictive values (USPFTF 2004).

The isolates are usually gram-negative rods, but gram-positive organisms are also seen and may cause acute disease (Chapman 1986). The microbiology of bacteria in the urine are the same as the nonpregnant women. These are the enterobacters (*E coli*, Klebsiella and Enterobacter), other gram negatives (*P. mirabilis*, Pseudomonas, Citrobacter), gram positives (*Staphylococcus aureus*, Group B Streptococcus) and others (*Gardnerella vaginalis*, *Ureaplasma urealyticum*) (Macejko 2007).

Description of the intervention

Since virtually all chemotherapeutic agents are concentrated in the kidneys, a wide variety of agents are successful in treatment. Some agents may have theoretical and/or adverse fetal or neonatal side effects, but are still given in instances where the benefits are deemed to outweigh the risk of an adverse effect. Sulfonamides, for instance, confer some risk of neonatal jaundice if sufficient levels of the drug are present in the bloodstream at the time of

delivery. If trimethoprim is added, the therapeutic efficacy is greatly enhanced, but so is the possible hazard of inhibition of the production of folate in the fetus, a vitamin essential in cell division and in the prevention of fetal congenital anomalies. Quinolones are best avoided in pregnancy because of their renal toxicity to the fetus. Despite the emergence of resistance to ampicillin in vitro, it still demonstrates clinical effectiveness because it is highly concentrated in the urine. Semisynthetic penicillins remain the preferred agent for treating gram-positive urinary infections, partic ularly those caused by enterococcus. To circumvent resistance to ampicillin of B-lactamase producing *E. coli*, clavulanate, a B-lactamase inhibitor is added. Although there seems to be no contraindication to the use of the latter, it is still not extensively studied. Cephalosporins are an equally effective alternative, and cefazolin and cephalexin, first-generation derivatives, demonstrate effectiveness in vitro. Nitrofurantoin, which is very specific in the urinary tract and is found in very low levels in maternal serum and tissues and the fetal compartment, is also very effective against organisms found in urinary tract infections. Clinically, significant toxicity with premature breakdown of the red blood cells, however, can be seen in women with deficiency in an enzyme called glucose-6-phosphate dehydrogenase (Lucas 1993). Acquired resistance to nalidixic acid may readily occur; and, together with its derivatives the quinolones, are considered teratogenic and are therefore not recommended. Suggested first-line agents are ampicillin/amoxycillin, nitrofurantoin and oral cephalosporins because of their comparable cure rates, safety and high levels in the urine. Sulfonamides are best avoided in the third trimester because they may cause neonatal jaundice (Chapman 1986). Drugs with very high protein binding, such as ceftriaxone, may be inappropriate if given a day prior to parturition because of the possibility of displacement of bilirubin, a breakdown product found in bile, predisposing also to neonatal jaundice. Trimethoprim is avoided in the first trimester because it is a folic acid antagonist (Hooton 2007), increasing the risk of congenital defects in the brain and the spine.

Antibiotic preference differs in different countries. A recent survey of physicians in Denmark, Finland, Norway and Sweden confirms that B-lactam antibiotics (particularly pivmecillinan) and nitrofurantoin are their drugs of first choice. In the USA, amoxycillin use is common, whereas in Canada, trimethoprim and nitrofurantoin are preferred. In the UK, they advocate the use of penicillins and cephalosporins (Christensen 2000).

Other recommended antibiotic regimens are the following (Hooton 2007).

1. Sulfisoxazole 500 mg by mouth three times a day for three to seven days.
2. Amoxicillin 500 mg by mouth three times a day for three to seven days.
3. Amoxicilin-clavulanate 500 mg by mouth twice a day for three to seven days.
4. Nitrofurantoin 50 mg by mouth four times a day for three to seven days.
5. A cephalosporin such as cefpodoxime proxetil 100 mg by mouth every 12 hours for three to seven days.
6. Fosfomycin 3 g by mouth as single dose.

The duration of treatment varies, like the choice of the antimicrobial agents used. Single-dose therapy and shorter courses of three days were used with success in some studies. Treatment of more than 10 days seemed unnecessary (Lucas 1993). A more recent meta-analysis, however, demonstrated no significant difference between single dose and longer duration regimens in terms of their ability to cure asymptomatic bacteriuria and prevent its recurrence. Additional evidence is needed to determine whether a single dose is as effective as the longer duration regimen in preventing preterm births and pyelonephritis (Villar 2000). If recurrence or failure of initial therapy occurs, however, continuous suppressive therapy is considered for the duration of pregnancy. Symptomatic infection is likewise prevented by either frequent repeated screening or continuous antibiotic suppression (Lucas 1993).

How the intervention might work

Treatment of women who tested positive significantly reduces symptomatic urinary tract infections, low birthweight and preterm delivery (USPFTF 2004). A Cochrane meta-analysis of 14 studies showed treatment of asymptomatic bacteriuria, compared to placebo, effectively cleared infection (risk ratio (RR) 0.25, 95% CI 0.14 to 0.48), reduced pyelonephritis (RR 0.23, 95% CI 0.13 to 0.41) and reduced incidence of low birthweight babies (RR 0.66, 95% CI 0.49 to 0.89). No difference, however, was seen with the incidence of preterm deliveries. The review authors, however, assessed the studies included in this review to be of poor quality (Smaill 2007a).

Cost-effectiveness analysis of interventions for reducing maternal and perinatal deaths showed that screening and treatment of asymptomatic bacteriuria in pregnancy is highly cost-effective, especially if universal access to clinical services is provided as well (Adam 2005).

Why it is important to do this review

A search in the Cochrane Database of Systematic Reviews for reviews of urinary tract infection in pregnancy yielded three reviews (Smaill 2007a; Vazquez 2003; Villar 2000). The first review (Smaill 2007a) assessed the effects of antibiotic treatments for asymptomatic bacteriuria during pregnancy compared to placebo or no treatment on persistent bacteriuria during pregnancy, the development of pyelonephritis and the risk of low birthweight and preterm delivery. The second review (Villar 2000) investigated the effects of different durations of treatment for asymptomatic bacteriuria in pregnancy. Although they dealt with asymptomatic bacteriuria in pregnancy, both reviews did not aim to find out which agent is the most effective. The last review (Vazquez 2003) sets out to find the most effective agent, but only for symptomatic urinary tract infections. Vazquez 2003 failed to demonstrate the most effective agent against symptomatic urinary tract infections. It is likely that there would be a similar conclusion from a review on the best regimen for asymptomatic bacteriuria in pregnancy (Smaill 2007b). But until such a review is undertaken, a definite conclusion cannot be arrived at. There is no systematic review of which antibiotic is best for the treatment of asymptomatic bacteriuria in pregnancy (Smaill 2007b).

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OBJECTIVES

This review aims to determine from the best available evidence from randomized controlled trials which antibiotic agent is most effective and least harmful for the initial treatment of asymptomatic bacteriuria in pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies—We have included randomized controlled trials (RCTs) and quasi-RCTs comparing two different antibiotic regimens for the treatment of asymptomatic bacteriuria in pregnancy. For the purpose of analyzing which antibiotic regimen is most effective and safe, we have excluded studies with cross-overs, co-interventions and other studies comparing more than two antibiotics or regimens at the same time.

We planned to include studies published as abstracts provided there was sufficient information to allow us to assess study eligibility and risk of bias. If sufficient information was not available, the study would await assessment pending the publication of the full trial report, or the provision of further information by trial authors.

Types of participants—Pregnant women with asymptomatic bacteriuria, diagnosed by the authors using any method (whether by culture or other methods) at any stage of the pregnancy.

Types of interventions—We considered all studies comparing the effectiveness of macrolides, penicillins, cephalosporins, sulfonamides or any other antibiotics used in the first or initial treatment of asymptomatic bacteriuria in pregnancy in preventing its complications. We also planned to include studies comparing different routes of administration or different dosing schedules of these antibiotics.

Types of outcome measures

Primary outcomes:

1. Symptomatic infection, including pyelonephritis.
2. Persistent infection, defined as a repeat urine culture with the same organisms present after treatment.
3. Recurrent infection, defined as a repeat positive urine culture, after the first disease was judged adequately treated.
4. Shift to another antibiotic.
5. Adverse effects: nausea, vomiting, diarrhoea, allergy, prematurely stopping treatment.

Secondary outcomes:

1. Preterm delivery, defined as delivery before 37 completed weeks of gestation.

2. Preterm labor, as defined by the World Health Organization.
3. Neonatal infection.
4. Respiratory distress of the neonate.
5. Admission to neonatal intensive care unit.
6. Duration of ventilatory support of the neonate in days.

Search methods for identification of studies

Electronic searches—We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2010).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources—We also examined the reference lists of trials identified by the above search.

We did not apply any language restrictions.

Data collection and analysis

The methodology we used for data collection and analysis was based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

Selection of studies—Four authors (VT Guinto (VTG), MR Festin (MRF), BC dGuia (BCdG), T Dowswell (TD)) undertook the review. We used the search strategy described to obtain titles and abstracts of studies that might be relevant to the review. All authors independently screened the titles and abstracts and discarded studies that were not applicable; however, initially we retained studies and reviews that might include relevant data or information on trials. All authors independently assessed the retrieved abstracts and,

where necessary, the full text of these studies, to determine which studies satisfied the inclusion criteria. We resolved any disagreement through discussion or, if required, consulted an outside person.

Data extraction and management—We designed a form to extract data. At least two review authors extracted the data independently using the agreed standard data extraction forms. We arranged for the translation of studies reported in non-English journals before assessment. Where there was more than one publication for a trial, we have linked reports together in the reference list. We have highlighted any discrepancy between published reports. If necessary, we planned to write to request further information from trial authors and to include any relevant information provided in the review. We resolved discrepancies in data extraction through discussion. We used the Review Manager software (RevMan 2008) to enter data and double checked for accuracy.

One of the review authors (MRF) was involved in one of the included trials (Lumbiganon 2009) and was not involved in assessing eligibility for inclusion, or data extraction for this trial.

Assessment of risk of bias in included studies—We assessed risk of bias in included studies using The Cochrane Collaboration's tool for assessing risk of bias as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) and contained in RevMan (RevMan 2008). We did this by answering the following questions:

(I) Sequence generation (randomization): Was the allocation sequence adequately generated?

- Yes (e.g. random number table, computer random-number generator).
- No (systematic non-random approach, e.g. use of case record numbers, dates of birth, or days of the week).
- Unclear.

(II) Allocation concealment (selection bias): Was allocation adequately concealed?

- Yes (e.g. telephone or central randomization, consecutively numbered sealed opaque envelopes).
- No (e.g. open list of random number tables, alternation or rotation).
- Unclear.

(III) Blinding (checking for possible performance bias): Was knowledge of the allocated interventions adequately prevented in the study? If so, we have specified who were blinded (whether the study participants, or any of the key study personnel).

- Yes (participants and key study personnel were adequately blinded. If not blinded, the outcome and outcome measurement were not likely to be affected by lack of blinding of either the participants, key study personnel or both).

- No.
- Unclear.

(IV) Incomplete data collection (checking for possible attrition bias through withdrawals, dropouts, protocol violations): For each included study, and for each outcome and class of outcomes, we assessed completeness of data, including attrition and exclusions from the analysis. We have tried to address the following questions: were the rate of attrition and exclusions reported? How were the data due to attrition and exclusions treated in the analysis at each stage of the paper (compared with the total number of participants randomized)? What were the reasons for attrition and exclusions? How were the missing data related to the groups compared and how would they affect the outcome?

- Yes (missing outcome data adequately reported and addressed).
- No.
- Unclear.

Where sufficient information was reported or supplied by the trial authors, we have re-included missing data in the analysis (as an ITT analysis). We have discussed the size of the missing data and their impact on the outcomes of the study.

(V) Selective reporting bias: We have discussed for each included study how we examined the possibility of selective outcome reporting bias and what we found. Are the results of the study free from suggestions of selective outcome reporting?

- Yes (where the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported).
- No (where not all the study's pre-specified outcomes were reported; one or more reported outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would be expected to have been reported).
- Unclear.

(VI) Other sources of bias: We have described for each included study any important concerns we had about other sources of bias. We assessed whether each study was free of other problems that could put it at risk of bias (e.g. specific study design, trial stopped early, extreme baseline imbalances, study claimed to be fraudulent).

- Yes (free from other problems).
- No (not free from other problems).
- Unclear.

(VII) Overall risk of bias: We have made explicit judgements about whether studies are of high or low risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews and Interventions* with reference to (I) to (VI) above (Higgins 2008). We have presented assessments of the risk of bias as a table and as a graph, as shown in the

Cochrane Handbook for Systematic Reviews and Interventions (Higgins 2008), (*see* Figure 1 and Figure 2).

Measures of treatment effect—We have carried out statistical analysis using the Review Manager software (RevMan 2008).

In this version of the review we did not pool results from studies in meta-analysis because each study examined a different comparison. If more data become available in the future and we are able to carry out pooled analysis, in updates we will use fixed-effect meta-analysis for combining results from studies examining the same interventions.

Dichotomous data—For dichotomous data (symptomatic infection, including pyelonephritis, persistent infection, recurrent infection, need for change of antibiotic, premature rupture of membranes, side effects: nausea, vomiting, diarrhoea, allergy, prematurely stopping treatment, admission to neonatal intensive care unit), we present results as the summary risk ratio.

Continuous data—We have not included any continuous data in this version of the review. In updates of the review if such data do become available, we plan to use the mean difference for the analysis of continuous data (duration of ventilatory support) provided that outcomes are measured in the same way in different studies; if outcomes are not measured in the same way in different studies we will use the standardized mean difference.

Dealing with missing data—We have analyzed data on all participants with available data in the group to which they were allocated, regardless of whether or not they received the allocated intervention.

Assessment of heterogeneity—We did not pool results from studies in this version of the review, in updates of the review if more data become available and we are able to carry out meta-analysis, we plan to examine heterogeneity between trials by visual inspection of forest plots, and using the I^2 statistic to quantify heterogeneity. If we identify moderate or high levels of heterogeneity among the trials (I^2 exceeding 30%), we plan to explore it by pre-specified subgroup analysis, and by performing sensitivity analysis. We will use a random-effects meta-analysis if the values of I^2 and T^2 indicated heterogeneity.

Subgroup analyses: We were not able to carry out planned subgroup analysis in this version of the review. If more data are available when we update the review, we plan to conduct subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. We plan to carry out subgroup analyses for the following: according to types of bacterial isolates; and, whether single versus combination antibiotics were used.

Sensitivity analyses: In updates we plan sensitivity analysis based on trial quality, separating high-quality trials from those of low quality. For the purpose of this review, low-quality trials are those with high attrition rate (more than 20%) and with inadequate allocation concealment.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search—The search of the Cochrane Pregnancy and Childbirth Group's trials' register identified 23 reports representing 22 different studies for possible inclusion in the review. Using the eligibility criteria pre-specified in the protocol, we included five studies and excluded 17. Please refer to the section on Description of studies.

Included studies—We have included five studies examining different antibiotic regimens:

- Bayrak 2007 compared a single dose of fosfomycin trometamol 3 g with a five-day course of twice daily cefuroxime.
- In a study reported by Bint 1979, pivmecillinam 400 mg was compared with ampicillin 500 mg. Women in both arms of the trial had antibiotics four times each day for seven days.
- In the study by Campbell-Brown 1987, a three-day course of cephalexin 1 g twice-daily was compared with Miraxid® (pivmecillinam 200 mg and pivampicillin 250 mg) twice daily for three days.
- In the most recent and largest trial, a one-day versus a seven-day regimen of nitrofurantoin was compared (Lumbiganon 2009). Women received either nitrofurantoin 100 mg twice for one day (with placebo twice daily for the following six days) or a seven-day course of twice-daily nitrofurantoin.
- The study by Robertson 1968 compared cycloserine 250 mg given twice a day for 14 days with sulphadimidine 500 mg given for 14 days.

In all five studies women were recruited with bacteriuria (positive urine cultures) but without symptoms of infection.

Excluded studies—We excluded 17 studies identified by the search strategy. Some studies had more than one reason for exclusion. The main reasons for excluding studies was that the studies did not report findings from randomized trials, or did not report results by randomization group; we excluded eight studies for these reasons (Brumfitt 1973; Brumfitt 1982; Christopher 1969; De Cecco 1987; Harris 1982; McFadyen 1987; Reeves 1975; Whalley 1977); for example, in the study by Whalley 1977 looking at short-term versus continuous therapy using different antibiotics, results were not reported separately for different types of antibiotics.

In four studies, women participating in trials were not asymptomatic, or the trials included both women with and without symptoms and separate results were not available for those with asymptomatic bacteriuria (Pedler 1985; Stamatiou 2007; Zinner 1971; Zinner 1990). The trial by Davies 1975 included men, non-pregnant women, and pregnant women with and without symptoms; separate results were not presented for asymptomatic pregnant

women. The study reported by Sanderson 1984 focused on prophylaxis in women who had already been treated for bacteriuria.

In three studies the focus of the studies was not on comparing two different antibiotic regimens: Pathak 1969 compared antibiotic therapy with placebo, Pregazzi 1987 examined a range of dosing schedules in different antibiotics and results were not presented separately for different types of antibiotics. The study by Harris 1982 compared four antibiotic regimens at the same time and results were not presented by randomization group.

One study (Thoumsin 1990) was not finished, and only presented preliminary data. We could not find any publication with the final study results.

Risk of bias in included studies

Allocation

Sequence generation: In one of the included studies, the randomization sequence was generated using a computerized random number generator (Lumbiganon 2009). In the study by Robertson 1968, there was alternate allocation to study groups. In the remaining studies the method used to generate the sequence was not clear. Bayrak 2007 specifies that block randomization was used, but there were no further details on sequence generation, and in Bint 1979 andCampbell-Brown 1987 no information was provided.

Allocation concealment: In the Lumbiganon 2009, study randomization was carried out by an external randomization service and group allocations were concealed in opaque, numbered sealed envelopes. In the Bayrak 2007 trial, it was stated that randomization was carried out by a person not connected with the investigation. In the study by Robertson 1968, allocation was alternate and could be anticipated in advance. In the two remaining studies there was little information on methods and it was not clear what steps, if any, were taken to conceal allocation (Bint 1979; Campbell-Brown 1987).

Blinding—In the Lumbiganon 2009 trial, there was a placebo provided for women undergoing the shorter treatment regimen, and so women and staff were blind to treatment. In the study reported by Bint 1979, it was stated that outcome assessors were blind to treatment allocation, but it was not clear whether women and staff were blind. Campbell-Brown 1987 referred to a “double blind” method, but little information was provided on how this was achieved or whether blinding was successful. Finally, Bayrak 2007 and Robertson 1968 compared different treatment regimes and blinding may not have been practicable, and was not mentioned.

Incomplete outcome data—There were problems with attrition and missing data in all of the included studies. In the Bayrak 2007 study, 90 women were randomized and 84 were included in the analysis, although the overall rate of attrition was relatively low, the loss from treatment groups was not evenly balanced. In the fosfomycin group, one women was lost to follow up (from 45), whereas in the cefuroxime group five were lost (from 45). There was no intention-to-treat analysis. In the Bint 1979 study it was reported that 100 women were included, but that 24 were later excluded (before treatment commenced) after a second

urine analysis failed to confirm bacteriuria. It appeared that these exclusions took place after randomization. Of the 76 remaining, 11 women were lost to follow up; and data at two weeks were therefore available for 65 women. The numbers randomized and followed up were not clear in the Campbell-Brown 1987 trial. For those women receiving two different antibiotic treatments the follow up was described as complete; however, some women received other antibiotics, although it was not clear whether these women were randomized as part of the "double blind" study. In the Lumbiganon 2009 trial, loss to follow up and missing data were well described in a flow chart; here 778 women were randomized and 19 were lost to follow up, but there were some further missing data; at two weeks there were uncontaminated specimens from 741 women available for analysis. There were also missing data on six patients (out of the 160 women who received either cycloserine or sulphadimidine) in the study by Robertson 1968.

Other potential sources of bias—We were not able to formally assess outcome reporting bias as we relied on published study reports to assess risk of bias, and reporting bias is difficult to assess without access to the original study protocol. We did not look at possible publication bias as there was only one study for each of the comparisons in the review. Figure 1 and Figure 2 summarize risk of bias assessments for the five studies we included in the review.

Effects of interventions

From the included studies, there were five comparisons involving 1140 women. Only one study contributed data to each of the comparisons. We did not carry out meta-analyses, pooling results from more than one study, because each of the trials compared different antibiotics and regimens. In the results below, we have reported findings for primary and secondary outcomes together, as most of the studies reported on few of the review's pre-specified outcomes.

Comparing fosfomycin trometamol and cefuroxime in 84 women, Bayrak 2007 found no significant difference between groups in persistent infection (risk ratio (RR) 1.36, 95% confidence interval (CI) 0.24 to 7.75), shift to a different antibiotic (RR 0.08, 95% CI 0.00 to 1.45) and in allergy or pruritus (RR 2.73, 95% CI 0.11 to 65.24).

Likewise, when pivmecillinam and ampicillin were compared in a study by Bint 1979 including 65 women, there was no significant evidence of differences in persistent infection after two weeks (RR1.03, 95% CI 0.28 to 3.78) and after six weeks (RR 0.67, 95% CI 0.29 to 1.54), or in recurrent infection (RR 0.69, 95% CI 0.12 to 3.85). The numbers of women in the two groups reporting nausea (RR 0.98, 95% CI 0.30 to 3.17) and diarrhoea (RR 0.49, 95% CI 0.05 to 5.23) were not significantly different. There was, however, a statistically significant higher number of cases of vomiting with pivmecillinam compared with ampicillin (RR 4.57, 95% CI 1.40 to 14.90) and more women receiving pivmecillinam stopped treatment early (RR 8.82, 95% CI 1.16 to 66.95) although the CIs around these effect estimates are wide. When Lumbiganon 2009 compared short (one day) and long (seven days) courses of nitrofurantoin in 778 women, symptomatic infection was not significantly different two weeks after treatment (RR 0.71, 95% CI 0.23 to 2.22) and prior to

delivery (RR 0.82, 95% CI 0.36 to 1.88). There was, however, significantly more persistent infection encountered in the short course compared to the long course of nitrofurantoin (RR 1.76, 95% CI 1.29 to 2.40). Nausea (RR 0.72, 95% CI 0.43 to 1.20) and preterm delivery rates (RR 1.24, 95% CI 0.79 to 1.94) were not significantly different. Pivampicillin/ pivmecillinam (Miraxid®) resulted in no significant difference compared with cephalexin in persistent infection (RR 5.75, 95% CI 0.75 to 44.15) and in recurrent infection (RR 0.77, 95% CI 0.23 to 2.50) in the study by Campbell-Brown 1987, involving 47 women.

Comparing cycloserine and sulphadimidine in 160 women, Robertson 1968 found no significant difference in symptomatic (RR 0.62, 95% CI 0.33 to 1.16), persistent (RR 0.70, 95% CI 0.41 to 1.21) and recurrent infections (RR 0.89, 95% CI 0.47 to 1.68).

In this version of the review, we did not carry out planned subgroup and sensitivity analysis due to insufficient data.

DISCUSSION

Summary of main results

Except for the study by Lumbiganon 2009 where two dosing schedules of the same antibiotic were compared, the prevailing desire in the studies included in this review was to improve on the cure rates of the older antibiotics, since increasing resistance of the most common isolated organism, *E. coli*, against these antibiotics are now being observed.

The oldest study in this review, that of Robertson 1968, compared cycloserine, a newer drug commonly restricted for the treatment of multiple drug resistant tuberculosis (pregnancy category C), with sulphadimidine, a folate antagonist (pregnancy category B, but category D if given near term). Although symptomatic and recurrent infection were not significantly different, sulphadimidine had significantly more treatment failures, suggesting that cycloserine was a better choice between the two. Both of them however, as suggested by their pregnancy categories, are linked to congenital anomalies, and are therefore not commonly used in pregnancy nowadays.

Two studies (Bayrak 2007; Campbell-Brown 1987) compared cephalosporins (second-generation cefuroxime and first-generation cephalexin) with antibiotics less associated with *E. coli* resistant strains, fosfomycin trometamol and pivampicillin/pivmecillinam (Miraxid®), all of which belong to pregnancy category B. Both studies, however, failed to demonstrate any significant difference in efficacy between the cephalosporins and the latter two antibiotics.

One study (Bint 1979) compared two beta lactam antibiotics, ampicillin and pivmecillinam (both category B). Antibiotic resistance to ampicillin is increasing (Bayrak 2007). Pivmecillinam, despite belonging to the same family of antibiotics was able to retain its activity against *E. coli* (Bint 1979). In the study by Bint 1979, there were no clear differences between groups receiving pivmecillinam compared with ampicillin, although pivmecillinam was less tolerated, as shown by the higher incidence of vomiting in pregnant women given pivmecillinam. However, the lack of evidence of a difference between the two

treatment regimes in this small study may have been due to lack of statistical power. Lumbiganon and co-workers sought to find out if the dosing schedule of nitrofurantoin could be decreased from the traditional seven days of treatment to one day to increase compliance, while retaining its efficacy in the treatment of asymptomatic bacteriuria (Lumbiganon 2009). Nitrofurantoin was chosen because little or no bacterial resistance was demonstrated with its use, compared to the older antibiotics, like penicillins, trimethoprim-sulphamethoxazole, and first-generation cephalosporins. Although there were no significant differences in symptomatic infections, preterm deliveries and tolerance of subjects observed between the short and long dosing schedules, more treatment failures, however, were seen in the short-dosing schedule, suggesting the superiority of the traditional-dosing schedule.

Overall completeness and applicability of evidence

All five studies included in this review failed to demonstrate any newer antibiotic or regimen which would be better than the older antibiotics and the traditional regimen. As in an earlier published study by Vazquez 2003, where a search for the best antibiotic regimen for symptomatic bacteriuria in pregnancy was done, in this review we were not able to identify the best single initial antibiotic regimen for asymptomatic bacteriuria in pregnancy; rather, several antibiotics were seen to be equally useful for the initial treatment of this condition. Having said this, the fact that we were unable to detect statistically significant differences between groups for most of the outcomes measured does not necessarily indicate that there were no differences between groups. Several of the studies included in this review had relatively small sample sizes, and the wide confidence intervals for many of the outcomes measured suggest that studies may have lacked the statistical power to identify possible differences between groups.

Quality of the evidence

In one of the included studies (Lumbiganon 2009), the methods used in the study were well described; in the other included studies the methods were less clear and it was difficult to assess the quality of the evidence. One study used alternate allocation to study groups (Robertson 1968) and may be at high risk of bias.

Potential biases in the review process

There was potential for introducing bias at all stages in the reviewing process. We took a number of steps to try to minimize bias: at least two review authors assessed eligibility for inclusion, carried out data extraction and assessed risk of bias, and all data were checked after entry into Review Manager software (RevMan 2008).

Agreements and disagreements with other studies or reviews

There is little information in other reviews on the best antibiotic regimes to use to treat asymptomatic bacteriuria. In the UK, clinical practice guidelines recommend that women are offered screening for asymptomatic bacteriuria as part of routine antenatal care and that asymptomatic bacteriuria should be treated; however, there are no specific recommendations on the type of antibiotic clinicians should prescribe, and very little information on the best dosing regime (NICE 2008). Three related Cochrane reviews have examined bacteriuria in

pregnancy (Smaill 2007a; Vazquez 2003; Villar 2000). Smaill 2007a looked at antibiotic treatments for asymptomatic bacteriuria during pregnancy compared to placebo or no treatment, and concluded that antibiotic therapy reduced the risk of developing pyelonephritis and may reduce the risk of low birthweight babies. Vazquez 2003 was not able to identify the most effective agent against symptomatic urinary tract infections in pregnancy. Villar 2000 looked at different durations of treatment for asymptomatic bacteriuria in pregnancy and concluded that there was insufficient evidence on whether a single dose or longer treatment regimes are most effective. All of these reviews acknowledged the need for more research in this area.

AUTHORS' CONCLUSIONS

Implications for practice

Although there have been claims that the newer antibiotics and newer schedules were better than the older antibiotics, particularly ampicillin and cephalosporins, and more traditional longer seven-day treatment schedule, this review failed to show significant improvement in efficacy with the use of the newer antibiotics and a shorter treatment schedule. In the comparison between pivmecillinam and ampicillin, ampicillin was significantly better tolerated than pivmicillinam. In the case of sulphadimidine and cycloserine, although cycloserine was more effective against asymptomatic bacteriuria, both of them have higher pregnancy categories, being both associated with the risk of congenital anomalies. This limits their applicability in modern times where safer antibiotics are available.

Implications for research

Concerns exist regarding increasing resistance to penicillins and cephalosporins as well as failure of treatment due to inability of patients to stick to long traditional treatment schedules. However, as shown by this review, the antibiotics (fosfomycin trometamol, pivmicillinam and Miraxid®) and schedule (one-day regimen with nitrofurantoin) tested were not found to be superior. Additional studies need to be done investigating other antibiotics or antibiotic combinations and other shorter treatment schedules (three- or five-day regimens). Studies in different centers (high and low prevalence areas) should be conducted to investigate the usefulness of an antibiotic regimen in decreasing urinary tract infections and their sequelae.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies

Bayrak 2007

Methods	RCT with block randomization.
Participants	90 pregnant women attending the Department of Urology and antenatal clinics of the Obstetrics and Gynecology Department of Fatih University between the period of November 2004-May 2005 Women with no signs and symptoms of urinary tract infections, in the second trimester who screened positive for asymptomatic bacteriuria (defined as the presence of 2 consecutive clean-catch urine specimens yielding positive cultures (100,000 cfu/ml) of the same uropathogens in a patient without urinary symptoms) Women exhibiting leukocytosis, fever, urolithiasis, lower back pain, or with a history of previous urologic surgery and known abnormalities of the urinary tract were excluded from the study. 1100 pregnant women in the second trimester were screened, of which, 90 gravidas had at least 1 bacteria identified in 2 consecutive voided urine specimens The randomized groups were similar in terms of mean patient age and mean gestational age of pregnancy. *E. coli* was the most common initial isolated microorganism in the pretreated urine specimen. 93.2% of pathogens in the fosfomycin trometamol group and 95% in the cefuroxime axetyl group were *E. coli* (the difference is NS). Other enterobacteriaceae and some gram-positive cocci were also isolated in both groups. The proportion of isolated microorganisms did not differ statistically between the groups
Interventions	Group I: 45 women (mean age 25.4 ± 4.7 years and mean duration of pregnancy 16.0 ± 2.0 weeks (range 14-18 weeks)) received a single dose of 3 g fosfomycin trometamol Group II: 45 women (mean age 25.2 ± 4.7 years and mean duration of pregnancy 16.2 ± 2.4 weeks (range 14-20 weeks)) received 250 mg cefuroxime axetyl twice a day for 5 days
Outcomes	Primary outcomes: Symptomatic infection: not reported. Persistent infection: group 1: 3/44 (6.8%); group 2: 2/40 (5%) (P = 0.912). Recurrent infection: not reported. Shift to another antibiotic: not reported. Adverse effects: both regimens well-tolerated. Allergic skin rash: group 1: 1/44 (2.27%); vulvovaginal moniliasis: group 2: 2/40 (5%) Secondary outcomes: Preterm delivery: not reported. Preterm labor: not reported. Neonatal infection: not reported. RDS in the neonate: not reported. Admission to NICU: not reported. Duration of neonatal respiratory support: not reported.
Notes	Control cultures were mentioned in the results. But subjects were only randomized into 2 treatment groups at the start of the study (each group received either fosfomycin trometamol or cefuroxime axetyl)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Blocks were numbered. It was not stated whether the numbers came from a table of random numbers (p. 526)
Allocation concealment?	Yes	To ensure an equal number of patients in each group, a block randomization method was used. The blocks were numbered, placed into a bag, and a staff

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		member blinded to the research protocol selected the patients into the treatment groups. (p. 526)
Blinding? Participant	No	One treatment intervention was given single dose, the other was given as multiple doses
Blinding? Clinician	No	Same as above.
Blinding? Outcome assessor	Unclear	It was not mentioned.
Incomplete outcome data addressed? All outcomes	No	One woman in the fosfomycin trometamol group and 5 women in the cefuroxime axetyl group did not come to the scheduled follow-up visit by their physician and for a repeat urine analysis and urine culture 1 week after; therefore, they were excluded from the study. The remaining were 44 patients in the fosfomycin trometamol group and 40 patients in the cefuroxime axetyl group (dropout rate 2.2 and 11.1%, respectively). There was no intention-to-treat analysis.
Free of selective reporting?	Yes	All of the outcomes they planned to assess in the study were reported
Free of other bias?	Yes	

Bint 1979

Methods	RCT.
Participants	65 women included in the analysis (100 randomized, 24 excluded before treatment commenced, a further 11 were lost to follow up) Pregnant women consulting the hospital with at least 100,000 cfu/ml bacteria in urine culture were included The following women were excluded: (a) those with a known hypersensitivity to the penicillins; (b) those with infections caused by organisms resistant to the allocated drug; and (c) women already taking an antibiotic or who had taken one since providing the initial midstream urine
Interventions	Group 1: 400 mg of pivmecillinam 4 times daily for 7 days. Group 2: ampicillin 500 mg 4 times a day for 7 days.
Outcomes	Primary outcomes: Symptomatic infection: not reported. Persistent infection: at 2 weeks: group 1: 4/33 (12%); group 2: 4/32 (12.5%). Recurrent infection: at 2 weeks: group 1: 3/33 (9%); group 2: 2/32 (6.25%). Shift to another antibiotic: not reported. Adverse effects: those noted are: anorexia/vomiting, stopped treatment prematurely, diarrhea, headache, indigestion, pruritus ani, felt unwell, epigastric fullness, dizzy and light headed Secondary outcomes: Preterm delivery: not reported. Preterm labor: not reported. Neonatal infection: not reported. RDS in the neonate: not reported. Admission to NICU: not reported. Duration of neonatal respiratory support: not reported Other outcomes: Relapse (infection with the same organism): at 6 weeks: group 1:9/25 (36%); group 2: 7/29 (24,1%). Change in liver function tests: results are unclear since some of the women had deranged values before treatment
Notes	The study had a second part where in patients were given lower dose of pivmecillinam.

	Only the first part, where the patients were randomized between the 2 treatments, was included in this meta-analysis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Sequence generation was not described. "Randomized in equal numbers."
Allocation concealment?	Unclear	It was not described.
Blinding? Participant	Unclear	It was not stated.
Blinding? Clinician	Unclear	It was not stated whether the 1 administering the treatment was aware of the kind of treatment being given
Blinding? Outcome assessor	Yes	Patients were asked for their symptoms by doctors who were unaware of the treatment
Incomplete outcome data addressed? All outcomes	No	There were missing data from 11/76 patients who commenced treatment. (It appeared that 100 were randomized but that 24 were excluded before treatment commenced as bacteriuria was not confirmed from a second specimen)
Free of selective reporting?	Yes	All of the outcomes were reported.
Free of other bias?	Yes	

Campbell-Brown 1987

Methods	RCT.
Participants	47 women included in the analysis. Women who attended out patient clinics in 2 hospitals (Northwick Park Hospital and Aberdeen) who had bacteriuria of urine obtained through suprapubic aspiration or catheterization
Interventions	Group 1: three-day course of cephalexin 1 gram twice a day (23 women) Group 2: three-day course of pivmecillinam 200 mg and pivampicillin 250 mg (Miraxid®) twice daily (24 women)
Outcomes	Primary outcomes: Symptomatic infection: not reported. Persistent infection: group 1: 1/23; group 2: 6/24. Recurrent infection: group 1: 5/23; group 2: 4/24. Shift to another antibiotic: not reported. Adverse effects: not reported. Secondary outcomes: Preterm delivery: not reported. Preterm labor: not reported. Neonatal infection: not reported. RDS in the neonate: not reported. Admission to NICU: not reported. Duration of neonatal respiratory support: not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not mentioned.
Allocation concealment?	Unclear	Not mentioned.
Blinding? Participant	Yes	Described as double blind.

Blinding? Clinician	Yes	Described as double blind.
Blinding? Outcome assessor	No	
Incomplete outcome data addressed? All outcomes	Yes	Follow up described as complete.
Free of selective reporting?	Yes	Planned outcome to be analyzed were all reported.
Free of other bias?	Yes	

Lumbiganon 2009

Methods	RCT.
Participants	Pregnant women seeking antenatal care visits at the participating centers betweenMarch 2004 and March 2007 and capable of giving informed consent were recruited at gestational ages between 12 weeks and 32 weeks. 778 patients were recruited successfully for the study **Inclusion criteria:** **1** asymptomatic bacteriuria (> 100,000 cfu/ml); **2** microorganism sensitive to nitrofurantoin; **3** absence of symptoms suggesting UTI. **Exclusion criteria:** **1** history of treatment for UTI during the current pregnancy; **2** presence of an underlying disease that required continuous steroids and/or antibiotic.
Interventions	Group 1: 386 women were allocated to receive nitrofurantoin 100 mg twice a day on the first day plus placebo twice a day to complete 7 days Group 2: 392 women were allocated to receive nitrofurantoin 100 mg twice a day for 7 days
Outcomes	Primary outcomes: Symptomatic infection: at 2 weeks: group 1: 5/371 (1.3%); group 2: 7/370 (1.9%); in the following weeks before delivery: group 1: 10/354 (2.8%); group 2: 12/349 (3.4%). Persistent infection: at 2 weeks: group 1: 90/371 (24.3%); group 2: 51/370 (13.8%). Recurrent infection: not reported. Shift to another antibiotic: not reported. Adverse effects: Nausea: group 1: 23/375 (6.1%); group 2: 33/385 (8.6%). Headache: group 1: 17/375 (4.5%); group 2: 22/385 (5.7%). Flatulence: group 1: 15/375 (4.0%); group 2: 9/385 (2.3%). Others: group 1: 20/375 (5.3%); group 2: 26/385 (6.8%) Secondary outcomes: Preterm delivery: group 1: 39/353 (11%); group 2: 31/349 (8.9%) Preterm labor: not reported. Neonatal infection: not reported. RDS in the neonate: not reported. Admission to NICU: not reported. Duration of neonatal respiratory support: not reported Other outcomes: Low birthweight: group 1: 48/364 (13.2%); group 2: 28/350 (8%). Congenital malformations group 1: 5/364 (1.4%); 4/350 (1.1%). Mean birthweight: group 1: 3.059 g; group 2: 3.159 g. Mean birth gestational age: group 1: 38.4 weeks; group 2: 38.7 weeks
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization codes were independently generated for each study site by the statistical unit at the Department of Reproductive Health and Research, the World Health Organization, Geneva, Switzerland. The random allocation sequence was generated using computer-generated random numbers with randomly varying blocks of 6/8 (SAS software, SAS Institute, Inc., Cary, NC)
Allocation concealment?	Yes	The random allocation was concealed by using sealed, opaque treatment boxes numbered sequentially using the sequence described above
Blinding? Participant	Yes	Yes, placebo was used.
Blinding? Clinician	Yes	Yes, placebo was used.
Blinding? Outcome assessor	Yes	Yes, placebo was used.
Incomplete outcome data addressed? All outcomes	Yes	Low attrition. Sensitivity analysis was done where it was appropriate
Free of selective reporting?	Yes	All outcomes were presented.
Free of other bias?	Yes	

Robertson 1968

Methods	Quasi-randomized, alternate allocation.
Participants	160 pregnant women who consulted in Simpson Memorial Maternity Pavilion from January, 1963 to April 1966 with bacteriological counts of 100,000/ml of urine were included
Interventions	Group 1:cycloserine 250 mg twice a day for 14 days. Group 2: sulphadimidine 500 mg 4 times a day for 14 days.
Outcomes	Primary outcomes: Symptomatic infection: group 1: 13/82; group 2:20/78. Persistent infection: group 1: 17/82; group 2: 39/78. Recurrent infection: group 1: 15/82; group 2: 16/78. Shift to another antibiotic: not reported. Adverse effects: Nausea: not reported. Headache: not reported. Flatulence: not reported. Others: not reported. Secondary outcomes: Preterm delivery: not compared between Cycloserine and Sulphadimidine Preterm labor: not reported. Neonatal infection: not reported. RDS in the neonate: not reported. Admission to NICU: not reported. Duration of neonatal respiratory support: not reported. Other outcomes: none.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Alternate allocation was used.

Allocation concealment?	No	Alternate allocation was used.
Blinding? Participant	No	1 antibiotic was given twice and day and the other was given 4 times a day
Blinding? Clinician	No	The 2 antibiotics were administered in different ways.
Blinding? Outcome assessor	Unclear	Not stated.
Incomplete outcome data addressed? All outcomes	No	There were 160 patients included in the part of the study that compared cycloserine and sulphadimidine. The results of all 160 patientswere accounted for. However, therewas also mention of 6 patients who were treated but withdrawn in the study. The results in these 6 patients were not available
Free of selective reporting?	Yes	
Free of other bias?	Yes	

cfu: colony-forming units

NICU: neonatal intensive care unit

NS: not specified

RCT: randomized controlled trial

RDS: respiratory distress syndrome

UTI: urinary tract infection

Characteristics of excluded studies

Study	Reason for exclusion
Brumfitt 1973	This study presented data obtained from earlier studies. Original data were not presented. The data about treatment of asymptomatic bacteriuria were supposedly taken from a study by Leigh 1970. This study however, could not be retrieved.
Brumfitt 1982	Not a RCT.
Christopher 1969	It was a crossover study.
Davies 1975	Some of the subjects in the study were symptomatic.
De Cecco 1987	It was a crossover study which used only preliminary studies
Harris 1982	4 antibiotic regimens were compared at the same time and results were not presented by randomization group
McFadyen 1987	Only 1 subgroup was randomized. It was not clear why that subgroup was used for randomization
Pathak 1969	Nitrofurantoin was compared with placebo.
Pedler 1985	The subjects included symptomatic patients.
Pregazzi 1987	Single versus traditional dosing schedules of different antibiotics taken together were compared. Results from different antibiotics were presented together (i.e. single dose of penicillins, cephalosporins, and co-trimoxazole versus their traditional dosing schedules)
Reeves 1975	The study randomized only 1 subgroup. It was not clear why that subgroup was randomized
Sanderson 1984	This trial focused on prophylaxis in women who had already been treated for bacteriuria
Stamatiou 2007	It was not a randomized trial. Some of the subjects had symptomatic urinary tract infection
Thoumsin 1990	Only preliminary data were published.
Whalley 1977	Short-term therapy (of either 1 of 2 antibiotics) was compared with long therapy (of one of the antibiotics)
Zinner 1971	It was not for asymptomatic bacteriuria.

Zinner 1990	The study included symptomatic patients.

RCT: randomized controlled trial

DATA AND ANALYSES

Comparison 1
Fosfomycin trometamol versus cefuroxime

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Persistent infection	1	84	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.24, 7.75]
3 Recurrent infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Shift to another antibiotic	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.45]
5 Adverse effect: nausea	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Adverse effect: vomiting	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Adverse effect: diarrhea	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Adverse effect: allergy or pruritus	1	84	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.11, 65.24]
9 Adverse effect: prematurely stopping treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Preterm delivery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Preterm labor	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Neonatal Infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Neonatal respiratory distress	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Admission to the neonatal intensive care unit	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Duration of neonatal ventilatory support	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 2
Pivmecillinam versus ampicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Persistent infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 After two weeks	1	65	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.28, 3.78]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 After 6 weeks	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.29, 1.54]
3 Recurrent infection	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.12, 3.85]
4 Shift to another antibiotic	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Neonatal infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Adverse effect: nausea	1	65	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.33, 3.23]
7 Adverse effect: vomiting	1	65	Risk Ratio (M-H, Fixed, 95% CI)	4.81 [1.53, 15.17]
8 Adverse effect: diarrhea	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.41]
9 Adverse effect: allergy or pruritus	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Adverse effect: prematurely stopping treatment	1	65	Risk Ratio (M-H, Fixed, 95% CI)	9.28 [1.25, 69.13]
11 Preterm delivery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Preterm labor	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Neonatal respiratory distress	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Admission to the neonatal intensive care unit	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Duration of neonatal ventilatory support	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 3
1-day nitrofurantoin versus 7-day nitrofurantoin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Symptomatic infection at 2 weeks	1	741	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.23, 2.22]
1.2 Symptomatic infection prior to delivery	1	703	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.36, 1.88]
2 Persistent infection	1	741	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.29, 2.40]
3 Recurrent infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Shift to another antibiotic	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Adverse effect: nausea	1	760	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.43, 1.20]
6 Adverse effect: vomiting	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Adverse effect: diarrhea	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Adverse effect: allergy or pruritus	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Adverse effect: prematurely stopping treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Preterm delivery	1	703	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.79, 1.94]
11 Preterm labor	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Neonatal infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Neonatal respiratory distress	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Admission to the neonatal intensive care unit	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Duration of neonatal ventilatory support	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 4
Pivampicillin/pivmecillinam (Miraxid) versus cephalexin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Persistent infection	1	47	Risk Ratio (M-H, Fixed, 95% CI)	5.75 [0.75, 44.15]
3 Recurrent infection	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.23, 2.50]
4 Shift to another antibiotic	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Adverse effect: nausea	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Adverse effect: vomiting	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Adverse effect: diarrhea	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Adverse effect: allergy or pruritus	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Adverse effect: prematurely stopping treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Preterm delivery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Preterm labor	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Neonatal infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Neonatal respiratory distress	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Admission to the neonatal intensive care unit	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 Duration of neonatal ventilatory support	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 5
Cycloserine versus sulphadimidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic infection	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.33, 1.16]
2 Persistent infection	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.41, 1.21]
3 Recurrent infection	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.47, 1.68]
4 Shift to another antibiotic	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Adverse effect: nausea	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Adverse effect: vomiting	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Adverse effect: diarrhea	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Adverse effect: allergy or pruritus	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Adverse effect: prematurely stopping treatment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Preterm delivery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Preterm labor	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Neonatal infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Neonatal respiratory distress	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Admission to the neonatal intensive care unit	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Duration of neonatal ventilatory support	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 9, 2010

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* . Indicates the major publication for the study

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PLAIN LANGUAGE SUMMARY

Different antibiotic regimens for treating pregnant women with bacteria in their urine and without symptoms of urinary tract infection

Between 5% and 10% of pregnant women have bacteria in their urine without symptoms of infection (asymptomatic bacteriuria). If left untreated, women may go on to develop serious complications such as kidney infection or preterm birth. In this review we looked at studies comparing different antibiotic treatments for asymptomatic bacteriuria to see which antibiotics or which course of the same antibiotics (shorter versus longer courses) were most effective for reducing infection. We also looked at side effects such as vomiting. The studies included in this review failed to demonstrate any newer antibiotic or regimen which would be better than the older antibiotics and the traditional regimen.

We included five randomized controlled trials involving 1140 women with urine test results showing asymptomatic bacteriuria. Each of the five studies looked at different antibiotics; thus, we have not pooled the results. Four of the comparisons (fosfomycin versus cefuroxime; pivmecillinam versus ampicillin; cephalexin versus Miraxid® (pivmecillinam 200 mg and pivampicillin 250 mg); and cycloserine versus sulphadimidine) showed no definite advantage of one antibiotic over another for treating infection, side effects, or safety. Ampicillin compared with pivmecillinam resulted in less vomiting and was thus better tolerated by the women in one study. There was however no difference in curing present infection and preventing recurring infection in women who took ampicillin compared with those who took pivmecillinam. In another study comparing a one-day versus a seven-day course of nitrofurantoin, the longer course was better in treating bacteria in urine during pregnancy. Women receiving the shorter course had more persistent infection but no clear difference in symptomatic infection at two weeks, nausea or preterm birth.

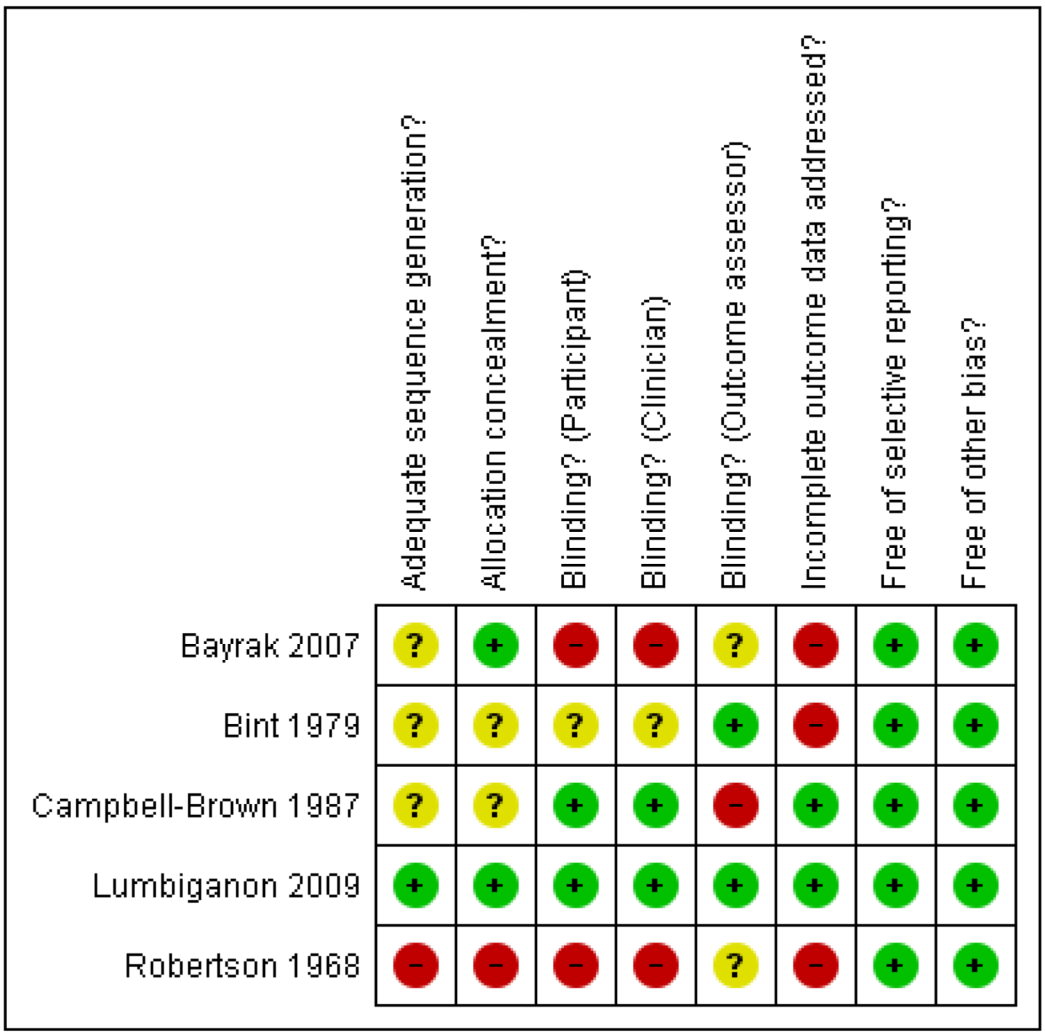

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

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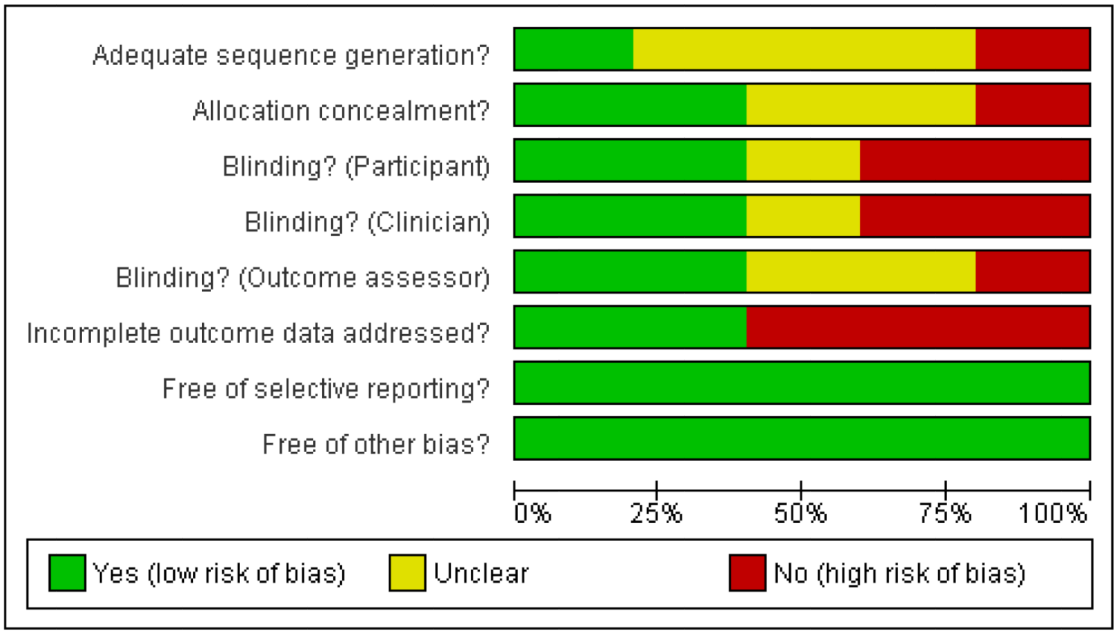

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

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