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# Antibiotics for acute pyelonephritis in adults (Protocol)

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[Intervention Protocol]

# Antibiotics for acute pyelonephritis in adults

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## ABSTRACT

### Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

This review aims to look at the benefits and harms of antibiotics used in the treatment of acute pyelonephritis in adults. The aspects of treatment that will be evaluated are:

1. Different routes of administration;
2. Different durations of the same antibiotic; and
3. Comparison of different antibiotic agents in the same population.

# BACKGROUND

## Description of the condition

Urinary tract infections (UTI) are considered an infection involving the urethra, urinary bladder, or the kidneys. Acute pyelonephritis denotes an infection of the renal pelvis and the kidney. It manifests with symptoms and signs of systemic inflammation and bladder inflammation. Those with anatomical abnormalities of the urinary tract, pregnant patients, patients with uncontrolled diabetes mellitus, kidney transplant recipients, acute kidney injury (AKI) or chronic kidney disease (CKD), immunocompromised patients, and those with hospital-acquired bacterial infections are considered to have complicated pyelonephritis. All others are considered to have uncomplicated pyelonephritis. Among adults, the incidence is highest among young women followed by adults over 65 years of age (Czaja 2007). The diagnostic criteria for acute pyelonephritis remain controversial and most studies include patients with a range of symptoms including fever, dysuria, and flank pain, along with bacteriuria with $10^5$ colony-forming units (CFU)/mL while a few have included CFU counts of $10^4$ in males (Piccoli 2006). Bacteriuria with colony counts ≥ $10^2$ CFU/mL is considered appropriate for diagnosis among samples collected by suprapubic aspiration or catheterization (Wilson 2004).

The epidemiology of organisms causing pyelonephritis has been starting to show an exponential increase in resistant organisms. While extended-spectrum beta-lactam (ESBL) producing bacteria are increasing, carbapenem resistance has increased from 1.2% in 2001 to 4.2% in 2011 (Golan 2015).

Most patients who are treated appropriately recover with no long-term renal consequences. Complications including obstruction, renal or perinephric abscess and emphysematous pyelonephritis are more common in patients with diabetes mellitus. Recurrent pyelonephritis and kidney failure are uncommon complications. The U.S. National Vital Statistics Reports for 2014 attributes 712 deaths to kidney infection (Johnson 2018).

## Description of the intervention

Many classes of antibiotics have been used to treat acute pyelonephritis in adults. These include trimethoprim-sulphamethoxazole, nitrofurantoin, quinolones, aminoglycosides, cephalosporins, extended penicillins (amoxicillin-clavulanic acid, piperacillin-tazobactam), carbapenems, and polymyxin group of antibiotics (Herness 2020). Some are oral, some oral and parenteral, while others are purely parenteral depending on how stable the patient is clinically as well as the antibiotic susceptibility. Parenteral antibiotics are required at least initially for severe pyelonephritis, underlying debilitating conditions, obstruction or when no oral formulations of sensitive antibiotics are available. The duration of treatment varies between five and 14 days, though it is often extended up to six weeks for kidney abscesses or emphysematous pyelonephritis.

## How the intervention might work

Antibiotics work by killing the bacteria responsible for pyelonephritis. They enter the bloodstream and concentrate in the urinary tract to have an effect. Given early in the course of pyelonephritis, they can prevent progression to renal abscesses, sepsis, septic shock, and potentially death. The choice of drug depends on the antimicrobial susceptibility pattern. As this may take a day or two the choice initially is empirically based on local knowledge of likely organisms and antimicrobial susceptibility patterns.

## Why it is important to do this review

Though antibiotics are the cornerstone for the treatment of acute pyelonephritis, the optimal drug, duration, and route of administration are still varied (Gupta 2011). A recent systematic review focused on long- versus short-course antibiotics for pyelonephritis (Berti 2018). However, they did not focus on complicated pyelonephritis or on pyelonephritis due to drug-resistant organisms.

Safely reducing the duration of antibiotics for acute pyelonephritis in adults would result in a reduced hospital stay, unnecessary extended use of antimicrobials, and potentially decrease antimicrobial resistance, adverse effects, and costs. This is especially important in the setting of emerging antimicrobial resistance across the globe.

Acute pyelonephritis can result in damage to the kidneys in the form of AKI and CKD if not treated appropriately. Hence it is essential to know the optimal antimicrobial therapy to prevent these long-term debilitating sequelae.

For patients with severe pyelonephritis or with underlying debilitating conditions or obstruction, most guidelines recommend parenteral antibiotics, while those who are clinically stable are managed with oral antibiotics. However, with increasing antimicrobial resistance many countries do not have oral antibiotics that are sensitive.

The cost of treatment is potentially large as a major part of hospital bills are expensive antibiotics and bed charges. The current recommendations for acute pyelonephritis range from five to 14 days. If shorter-duration antibiotics are as good as longer-duration, the overall cost to the health system could be reduced. These have not been documented in earlier reviews.

# OBJECTIVES

This review aims to look at the benefits and harms of antibiotics used in the treatment of acute pyelonephritis in adults. The aspects of treatment that will be evaluated are:

1. Different routes of administration;
2. Different durations of the same antibiotic; and
3. Comparison of different antibiotic agents in the same population.

# METHODS

## Criteria for considering studies for this review

### Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at conditions in which antibiotics were used in the treatment of adults (older than 16 years) with acute pyelonephritis will be included. Where studies included both adults with acute pyelonephritis and those with cystitis, these will be

included if data for participants with acute pyelonephritis could be extracted separately; otherwise, these studies will be excluded.

### Types of participants

#### *Inclusion criteria*

- Adults, 16 years or older with acute pyelonephritis who are treated either as inpatients or as outpatients with antibiotics.
- The diagnosis of acute pyelonephritis require UTI (generally requiring a bacterial growth on urine culture > $10^5$ CFU/mL with at least one symptom or sign of systemic illness such as fever, loin pain or toxicity. Acute pyelonephritis defined by any alternative diagnostic criteria as defined by the authors will also be included. Lower counts (1000 to 9999 CFU/mL) especially in men and pregnant women will be included.
- Those with diagnosed urinary tract abnormalities including mechanical obstruction such as stones, enlarged prostate, pelvic organ prolapsed or non-mechanical such as neurological involvement affecting the bladder will be included.
- We will also include those with a history of previous UTIs, pregnant women, kidney transplant recipients and those who are catheterised.

#### *Exclusion criteria*

Patients considered to have asymptomatic bacteriuria or cystitis (UTI as defined in inclusions with no symptom or sign of systemic illness) will be excluded.

### Types of interventions

- Different durations of the same antibiotic
- Comparison of different antibiotic agents in the same population
- Different routes of administration

### Types of outcome measures

#### *Primary outcomes*

- Efficacy: recurrence of UTI, readmission for UTI treatment, duration of symptoms
- Adverse effects of treatment: minor (e.g. vomiting, discomfort from IV cannula) and major (e.g. anaphylaxis, hearing impairment)
- Costs
- Length of hospital stay

#### *Secondary outcomes*

- Long-term outcomes: CKD, kidney damage identified by imaging; kidney failure
- Death

## Search methods for identification of studies

### Electronic searches

We will search the Cochrane Kidney and Transplant Register of Studies through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Searches of kidney and transplant journals, and the proceedings and abstracts from major kidney and transplant conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of hand-searched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website.

See Appendix 1 for search terms used in strategies for this review.

### Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Contacting relevant individuals/organisations seeking information about unpublished or incomplete studies.
3. Grey literature sources (e.g. abstracts, dissertations and theses), in addition to those already included in the Cochrane Kidney and Transplant Register of Studies, will be searched.

## Data collection and analysis

### Selection of studies

The search strategy described in Appendix 1 will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors (VKC, TG) who will discard studies that are not applicable, however, studies and reviews that might include relevant data or information on trials will be retained initially. The two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Disagreements will be resolved in consultation with a third author (SA).

### Data extraction and management

Data extraction will be carried out independently by two authors (VKC, TG) using standard data extraction forms. Disagreements will be resolved in consultation with a third author (RDS). Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted.

### Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2020) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?

- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

### Measures of treatment effect

For dichotomous outcomes (persistent bacteriuria, recurrent UTI, kidney damage, readmission, death) results will be expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (duration of symptoms, length of hospital stay, length of hospital stay, duration of inotropic agents, economic costs) the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

### Unit of analysis issues

We don't anticipate to find any cluster or cross-over studies. Therefore, the unit of analysis will be individuals who are assigned to intervention arms.

### Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing the corresponding author) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients, as well as intention-to-treat, as-treated and per-protocol population, will be carefully performed. Attrition rates (e.g. drop-outs, losses to follow-up and withdrawals) will be investigated. Issues of missing data and imputation methods (e.g. last-observation-carried-forward) will be critically appraised (Higgins 2020).

### Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. We will quantify statistical heterogeneity using the $I^2$ statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of $I^2$ values will be as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of $I^2$ depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the $Chi^2$ test, or a CI for $I^2$) (Higgins 2020).

### Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2020).

### Data synthesis

Data will be pooled using the random-effects model but the fixed-effect model will also be used to ensure the robustness of the model chosen and susceptibility to outliers. For dichotomous data Mantel-Haenszel method of pooling will be done whereas for continuous data Inverse-variance approach of pooling will be performed. Data from cluster and cross-over design are anticipated to be not available. Nevertheless, if we have identified these studies we will combine the data in a meta-analysis using the generic variance approach.

### Subgroup analysis and investigation of heterogeneity

Heterogeneity among participants could be related to gender and the organism characteristics (e.g. pyelonephritis in males are likely to be more complicated than in females; catheter-associated pyelonephritis is likely to be caused by resistant pathogens requiring a longer duration of treatment and high risk of recurrence; bacteraemic infections likely require prolonged antibiotic course; ESBL organisms are considered to require a longer duration of treatment with limited oral antibiotic options). Heterogeneity in treatments could be related to a prior agent used, and the agent's dose and duration of therapy (e.g. higher dose of antibiotics like fluoroquinolones and aminoglycoside are more likely to require a shorter duration of treatment; longer duration of treatment possibly results in lower risk of recurrence). The following subgroup analysis will be used to explore possible sources of heterogeneity.

- Bacteraemic versus non-bacteraemic
- Males versus females
- Catheter-associated UTI versus non-catheter-associated UTI
- ESBL versus non-ESBL organisms
- Hospital administered versus home administered antibiotics
- Studies with a low risk of bias
- Published versus unpublished studies
- The studies will be categorized into small or large studies:
  - Number of study participants (< 50, 50 to 100, 100 to 500, > 500);
  - Classifying the studies into four quarters based on the number of participants;
  - Power of the study (power less than and greater than 50).

Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference (RD) with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

### Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the missing data and imputed data on effect size. We will also perform sensitivity analysis by:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis excluding any very large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

### Summary of findings and assessment of the certainty of the evidence

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2020a). The 'Summary of findings' tables also includes an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the certainty of a body of evidence as to the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. This will be assessed by two authors. The certainty of a body of evidence involves consideration of the within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates and risk of publication bias (Schunemann 2020b). We plan to present the following outcomes in the 'Summary of findings' tables.

- Recurrence of UTI
- Duration of symptoms
- Length of hospital stay
- Cost of treatment
- Readmission for UTI
- Adverse effects of treatment including minor and major (anaphylaxis, thrombophlebitis, hearing loss, kidney failure)
- Death

## ACKNOWLEDGEMENTS

The Methods section of this protocol is based on a standard template used by Cochrane Kidney and Transplant.

The authors are grateful to the following peer reviewers for their time and comments: Bryan N Becker, MD (JPS Health Network) and Neil Boudville (Medical School, University of Western Australia).

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## Additional references

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**Czaja 2007**

Czaja CA, Scholes D, Hooton TM, Stamm WE.Population-based epidemiologic analysis of acute pyelonephritis. *Clinical Infectious Diseases* 2007;**45**(3):273-80. [MEDLINE: 17599303]

**Golan 2015**

Golan Y.Empiric therapy for hospital-acquired, Gram-negative complicated intra-abdominal infection and complicated urinary tract infections: a systematic literature review of current and emerging treatment options. *BMC Infectious Diseases* 2015;**15**:313. [MEDLINE: 26243291]

**GRADE 2008**

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al.GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [MEDLINE: 18436948]

**GRADE 2011**

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al.GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [MEDLINE: 21195583]

**Gupta 2011**

Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al.International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical Infectious Diseases* 2011;**52**(5):e103-20. [MEDLINE: 21292654]

**Herness 2020**

Herness J, Buttolph A, Hammer NC.Acute pyelonephritis in adults: rapid evidence review. *American Family Physician* 2020;**102**(3):173-80. [MEDLINE: 32735433]

**Higgins 2003**

Higgins JP, Thompson SG, Deeks JJ, Altman DG.Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

**Higgins 2020**

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al.Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

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**Piccoli 2006**

Piccoli GB, Consiglio V, Colla L, Mesiano P, Magnano A, Burdese M, et al.Antibiotic treatment for acute 'uncomplicated' or 'primary' pyelonephritis: a systematic, 'semantic revision'. *International Journal of Antimicrobial Agents* 2006;**28 Suppl 1**:S49-63. [MEDLINE: 16854569]

**Schunemann 2020a**

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al.Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

**Schunemann 2020b**

Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al.Chapter 15: Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

**Wilson 2004**

Wilson ML, Gaido L.Laboratory diagnosis of urinary tract infections in adult patients. *Clinical Infectious Diseases* 2004;**38**(8):1150-8. [MEDLINE: 15095222]

# APPENDICES

## Appendix 1. Electronic search strategies

| Database | Search terms |
|---|---|
| CENTRAL | 1. pyelonephritis:ti,ab,kw<br>2. ((urinary next tract next infection*) near/2 (upper or febrile or fever or complicated or severe)):ti,ab,kw |

*(Continued)*

| | |
|---|---|
| | 3. ((upper next urinary next tract) near/2 infection*):ti,ab,kw<br>4. (acute next lobar next nephronia):ti,ab,kw<br>5. {or #1-#4} in Trials |
| MEDLINE | 1. Pyelonephritis/<br>2. pyelonephritis.tw.<br>3. (urinary tract infection* adj2 (upper or febrile or fever or complicated or severe)).tw.<br>4. (upper urinary tract adj2 infection*).tw.<br>5. acute lobar nephronia.tw.<br>6. or/1-5 |
| EMBASE | 1. Pyelonephritis/<br>2. Acute Pyelonephritis/<br>3. pyelonephritis.tw.<br>4. (urinary tract infection* adj2 (upper or febrile or fever or complicated or severe)).tw.<br>5. (upper urinary tract adj2 infection*).tw.<br>6. acute lobar nephronia.tw.<br>7. or/1-6 |

## Appendix 2. Risk of bias assessment tool

| Potential source of bias | Assessment criteria |
|---|---|
| **Random sequence generation**<br><br>Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence | *Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random). |
| | *High risk of bias:* Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention. |
| | *Unclear:* Insufficient information about the sequence generation process to permit judgement. |
| **Allocation concealment**<br><br>Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment | *Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes). |
| | *High risk of bias:* Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure. |
| | *Unclear*: Randomisation stated but no information on method used is available. |
| **Blinding of participants and personnel**<br><br>Performance bias due to knowledge of the allocated interventions by participants | *Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. |

*(Continued)*

| | |
|---|---|
| and personnel during the study | *High risk of bias*: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. |
| | *Unclear*: Insufficient information to permit judgement |
| **Blinding of outcome assessment**<br><br>Detection bias due to knowledge of the allocated interventions by outcome assessors. | *Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. |
| | *High risk of bias:* No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding. |
| | *Unclear:* Insufficient information to permit judgement |
| **Incomplete outcome data**<br><br>Attrition bias due to amount, nature or handling of incomplete outcome data. | *Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods. |
| | *High risk of bias:* Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation. |
| | *Unclear:* Insufficient information to permit judgement |
| **Selective reporting**<br><br>Reporting bias due to selective outcome reporting | *Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). |
| | *High risk of bias:* Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study. |
| | *Unclear:* Insufficient information to permit judgement |
| **Other bias**<br><br>Bias due to problems not covered elsewhere in the table | *Low risk of bias:* The study appears to be free of other sources of bias. |
| | *High risk of bias:* Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem. |

(Continued)

| | |
|---|---|
| | *Unclear:* Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias. |

## CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: RDS, SA, VKC, TG, TDS, PT
2. Study selection: JPBE, VKC, TG, VPT, SA, TDS, PT. VKC and TG will screen titles and abstracts independently and SA will resolve any disagreements
3. Extract data from studies: VKC, SA, TG, RDS, VPT, TDS, PT. VKC and TG will extract data from studies independently and RDS will resolve any disagreements
4. Enter data into RevMan: RK, RDS, TG, VPT, VKC
5. Carry out the analysis: RK, VKC, PT
6. Interpret the analysis: RK, VKC, TDS, PT
7. Draft the final review: RDS, VKC, SA
8. Disagreement resolution: TDS, PT
9. Update the review: VKC, TDS

## DECLARATIONS OF INTEREST

Vignesh Kumar Chandiraseharan, Vijay Prakash Turaka, Rani Diana Sahni, and Thambu David Sudarsanam are co-investigators of an RCT on seven versus 14-day antibiotic treatment for acute pyelonephritis awaiting publication.

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### Internal sources

- Christian Medical College, Vellore, India

  The authors RDS, SA, VKC,TG, TDS, TVP, RK and JPBE are employed in this institution

### External sources

- No sources of support provided