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Antibiotics for asymptomatic bacteriuria in kidney transplant recipients (Review)

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[Intervention Review]

Antibiotics for asymptomatic bacteriuria in kidney transplant recipients

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ABSTRACT

Background

Asymptomatic bacteriuria, defined as bacteriuria without signs or symptoms of urinary tract infection (UTI), occurs in 17% to 51% of kidney transplant recipients and is thought to increase the risk for a subsequent UTI. No consensus exists on the role of antibiotics for asymptomatic bacteriuria in kidney transplantation.

Objectives

To assess the benefits and harms of treating asymptomatic bacteriuria in kidney transplant recipients with antimicrobial agents to prevent symptomatic UTI, all-cause mortality and the indirect effects of UTI (acute rejection, graft loss, worsening of graft function).

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 1 September 2017 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal, and ClinicalTrials.gov.

Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs in any language assessing treatment of asymptomatic bacteriuria in kidney transplant recipients at any time-point after transplantation.

Data collection and analysis

Two authors independently determined study eligibility, assessed quality and extracted data. Primary outcomes were incidence of symptomatic UTI and incidence of antimicrobial resistance. Other outcomes included incidences of all-cause mortality, graft loss, graft rejection, graft function, hospitalisation for UTI, adverse reactions to antimicrobial agents and relapse or persistence of asymptomatic bacteriuria. We expressed dichotomous outcomes as absolute risk difference (RD) or risk ratio (RR) with 95% confidence intervals (CI) and continuous data as mean differences (MD) with 95% CI. Data were pooled using the random effects model.

Main results

We included two studies (212 participants) comparing antibiotics versus no treatment, and identified three on-going studies. Overall, incidence of symptomatic UTI varied between 19% and 31% in the groups not treated for asymptomatic bacteriuria. Antibiotic treatment had uncertain effects on preventing symptomatic UTI (2 studies, 200 participants: RR 0.86, 95% CI 0.51 to 1.45). Risk for selecting multidrug-resistant organisms was uncertain with antibiotic treatment (1 study, 112 participants: RR 1.21, 95% CI 0.60 to 2.41). Persistence of asymptomatic bacteriuria was high regardless of treatment. Antibiotics also have uncertain effects on other important patient and graft outcomes, for instance on all-cause mortality (1 study, 112 participants: RR 2.23, 95% CI 0.21 to 23.86), graft loss (1 study, 112 participants: RR 1.11, 95% CI 0.07 to 17.36), acute rejection (1 study, 112 participants: RR 0.93, 95% CI 0.44 to 1.97), hospitalisation for UTI (1 study, 112 participants: RR 0.74, 95% CI 0.13 to 4.27), graft function (2 studies, 200 participants, MD in serum creatinine concentration -0.06 mg/dL, 95% CI -0.19 to 0.08) and adverse reactions (1 study, 112 participants: no severe adverse event attributable to the antibiotic treatment). Evidence quality was low for all outcomes.

Authors' conclusions

Currently, there is insufficient evidence to support routinely treating kidney transplant recipients with antibiotics in case of asymptomatic bacteriuria after transplantation, but data are scarce. Further studies assessing routine antibiotic treatment would inform practice and we await the results of three ongoing randomised studies, which may help resolve existing uncertainties.

PLAIN LANGUAGE SUMMARY

Antibiotics for bacterial infection in the urine in kidney transplant recipients when there are no symptoms

What is the issue?

Bacteria in the urine in kidney transplant recipients when there are no symptoms of urine infection is called asymptomatic bacteriuria. Up to one in two people with a kidney transplant will develop a bacterial infection of the urine (bacteriuria) at some point after transplantation. Bacteriuria with symptoms like fever, chills, painful urination, abdominal pain and blood in urine is a urinary tract infection (UTI). Bacteriuria often occurs without symptoms and it is frequently treated with antibiotics with the idea this might help avoid subsequent UTI. Avoiding UTI might improve patient and transplant survival. However, it is unclear how many people with asymptomatic bacteriuria go on to develop UTI symptoms; whether treatment with antibiotics truly avoids UTI; or whether treatment when asymptomatic improves survival of both patient and kidney. Also, there can be downsides to taking antibiotics. Taking regular antibiotics might mean that bacteria resistant to antibiotics are encouraged, and taking antibiotics might cause diarrhoea and other adverse events. There are also antibiotic costs to consider. This review looked at whether treating with antibiotics is beneficial of harmful.

What did we do?

We searched the literature up to September 2017 and identified two studies (212 participants) that were evaluated in this review. These studies compared antibiotics versus no treatment.

What did we find?

The bacterial infection of the urine often persisted, whether antibiotics were given or not. It was uncertain whether antibiotics prevented symptomatic urinary infection or increased the risk of selecting bacteria resistant to antibiotics, because there were too few data and several limitations in the included studies. Also, it was unclear whether the use of antibiotics in case of urinary infection without symptoms reduced the risks of graft rejection, need for hospitalisation due to symptoms of urinary infection, or mortality, or whether antibiotics improved the function of the kidney transplant. One study with 112 participants suggested there were no severe harmful reactions caused by the antibiotic treatment, and non-severe adverse events appeared to be rare.

Conclusions

It is uncertain whether antibiotics are beneficial in kidney transplant recipients with bacteria in their urine but no symptoms. In one study, participants were assigned to antibiotics or no therapy by a method that was not random (i.e. according to patients' transplant code). In both studies, participants knew which treatment they were receiving (i.e. antibiotics or no therapy), which may have influenced the results. Last, we had not enough data to estimate with precision some effects of antibiotics. More research is needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotics versus no treatment for asymptomatic bacteriuria in kidney transplant recipients

Patient or population: adult kidney transplant recipients
Intervention: antibiotics[1]
Comparison: no treatment[1]

Outcomes (follow-up period)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with no treatment	Risk with antibiotics			
Symptomatic UTI Follow-up: 12 to 22 months	240 per 1,000	207 per 1 000 (123 to 349)	RR 0.86 (0.51 to 1.45)	200 [2] (2 studies)	Low [3] ⊕⊕◯◯
Antimicrobial resistance Mean follow-up: 16.9 months	203 per 1,000	245 per 1,000 (123 to 490)	RR 1.21 (0.60 to 2.41)	112 (1 study)	Low [4] ⊕⊕◯◯
All-cause mortality Mean follow-up: 16.9 months	17 per 1,000	38 per 1,000 (4 to 404)	RR 2.23 (0.21, 23.86)	112 (1 study)	Low [5] ⊕⊕◯◯
Graft loss Mean follow-up: 16.9 months	17 per 1,000	19 per 1,000 (1 to 294)	RR 1.11 (0.07 to 17.36)	112 (1 study)	Low [5] ⊕⊕◯◯
Acute graft rejection Mean follow-up: 16.9 months	203 per 1,000	189 per 1,000 (89 to 401)	RR 0.93 (0.44 to 1.97)	112 (1 study)	Low [6] ⊕⊕◯◯
Hospitalisation for UTI Mean follow-up: 16.9 months	51 per 1,000	38 per 1,000 (7 to 217)	RR 0.74 (0.13 to 4.27)	112 (1 study)	Low [5] ⊕⊕◯◯

Graft function (creatinine at end of study) Follow-up: 12 to 22 months	Mean serum creatinine in the treatment group was 0.06 mg/dL lower (0.19 mg/dL lower to 0.08 mg/dL higher) than the control group	200 [2] (2 studies)	Low [7,8] ⊕⊕◯◯

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RD:** risk difference; **RR:** risk ratio; **UTI:** urinary tract infection

[1] The two included studies compared antibiotics versus no treatment, with choice of antibiotics depending on antimicrobial susceptibility testing results. As participants could have had multiple episodes of asymptomatic bacteriuria during the follow-up period, participants from the intervention group were retreated with antibiotics if asymptomatic bacteriuria recurred during the follow-up period in both studies. Duration of antibiotics therapy ranged from 3 to 10 days for the first episode of asymptomatic bacteriuria

[2] 212 participants included but data provided for 200 participants

[3] Neither study attempted to blind participants, personnel or data analysts. As symptoms of UTI are partly subjective, we anticipated this would put the results at risk of being biased in favour of antibiotic treatment

[4] Samples could be collected both in case of symptoms of UTI or as part of routine screening

[5] The confidence interval crosses the line of no effect but does not rule out a significant effect of antibiotics on mortality and/or graft loss

[6] No systematic graft biopsy performed during the study follow-up. Not all episodes of allograft rejection were biopsy-proven

[7] Graft function was evaluated using creatinine at end of study, despite different values between groups at time of inclusion. We were unable to pool the data for change in graft function from baseline to end of study (data missing for one study)

[8] No significant effect of antibiotics on change in graft function from baseline to end of study in both studies

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

BACKGROUND

Description of the condition

Asymptomatic bacteriuria is generally defined as bacteriuria without signs or symptoms of urinary tract infection (UTI; e.g. dysuria, frequency, suprapubic pain or fever). The Infectious Diseases Society of America (IDSA) defines bacteriuria in men as one bacterial species isolated from a single, clean-catch voided urine specimen in a quantitative count $\geq 10^5$ colony forming units (CFU)/mL (Nicolle 2005). In asymptomatic women, diagnosis of bacteriuria requires a second urine specimen with isolation of the same bacterial strain in a quantitative count $\geq 10^5$ CFU/mL. If a urine sample is collected through catheterization, a single urine specimen with isolation of a single bacterial species in a quantitative count $\geq$ 100 CFU/mL is enough to identify bacteriuria in women or men.

Observational studies from the 1970s and 1980s reported high incidences of asymptomatic bacteriuria in kidney transplant recipients, especially in the first six months after transplantation (Nicolle 2005). Many patients also developed symptomatic UTI with subsequent ramifications for graft function (Tolkoff-Rubin 1982). This prompted many clinicians to screen for asymptomatic bacteriuria and treat with antibiotics on the presumption it would reduce the incidence of symptomatic episodes and improve graft and patient outcomes in the longer term (Abbott 2004).

The past two decades have seen several changes in the management of transplant recipients including the introduction of routine perioperative antibiotic prophylaxis, earlier removal of indwelling urethral catheters, and long-term antibiotic prophylaxis for preventing *Pneumocystis jirovecii* pneumonia and other opportunistic infections (KDIGO 2009; Nicolle 2005). These interventions are also expected to prevent UTI and asymptomatic bacteriuria.

At present, asymptomatic bacteriuria is estimated to occur in 17% to 51% of kidney transplant recipients, estimates largely depending on definition of asymptomatic bacteriuria, follow-up period, and frequency of urine sampling (El Amari 2011; Fiorante 2010; Green 2013). The limited retrospective data available seem to indicate that few asymptomatic episodes lead to symptomatic or severe UTI, and that graft function is not affected (El Amari 2011; Green 2013). Most transplant physicians still, however, treat asymptomatic bacteriuria after transplantation. Reasons include the possibility that denervation of the kidney graft and the use of immunosuppressive medications mask the clinical features of UTI, and the fear that kidney transplant recipients may be at higher risk for developing severe infections (Parasuraman 2013).

Description of the intervention

Treatment of asymptomatic bacteriuria involves the detection of bacteria in urine through routine processing of urine cultures. Once diagnosis of asymptomatic bacteriuria has been established, treatment with antibiotics may be started with the aim to prevent progression to symptomatic UTI (e.g. acute graft pyelonephritis).

How the intervention might work

Antibiotics are given under the assumption they are effective in improving individual patient outcomes by eliminating infection, reducing recurrence and preventing long-term kidney damage.

Why it is important to do this review

Screening for and treatment of asymptomatic bacteriuria may be beneficial if asymptomatic bacteriuria has negative effects that could be reduced with antibiotics. There is consensus that the benefits of screening and treatment outweigh the harms in patients awaiting transurethral resection of the prostate (Nicolle 2005; Zani 2011). In the general population though, the available data do not support the use of antibiotics to treat asymptomatic bacteriuria. In pregnant women, the routine screen-treat-policy for asymptomatic bacteriuria has recently been called into question (Kazemier 2015; Smaill 2015). In healthy, non-pregnant young women it may even increase the risk of symptomatic UTI (Cai 2012).

No consensus exists on the role of antibiotics for asymptomatic bacteriuria in kidney transplantation (Nicolle 2014a). The 2005 IDSA guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults refrained from making a recommendation in kidney transplant recipients for want of evidence (Nicolle 2005). In 2013, the American Society of Transplantation Infectious Diseases Community of Practice suggested not treating asymptomatic bacteriuria that occurs beyond three months after kidney transplantation, unless in case of an accompanying rise in serum creatinine (SCr) concentration (Parasuraman 2013). However, the authors underlined that the recommendation was not based on randomised controlled studies (RCTs) and that general adoption of such a strategy could lead to over-treatment and selection of resistant micro-organisms. Indeed, there is some concern that treating kidney transplant recipients with asymptomatic bacteriuria with antibiotics leads to selection of resistant strains (El Amari 2011). Aside from the possible consequences for the individual, there may be ramifications for society at large (Goossens 2005). In addition, treatment may have direct and very harmful side-effects (e.g. fluoroquinolone-induced Achilles tendon rupture), cause severe allergic complications (Chang 2012) and promote *Clostridium difficile*-associated diarrhoea (Shah 2013).

OBJECTIVES

To assess the benefits and harms of treating asymptomatic bacteriuria in kidney transplant recipients with antimicrobial agents

to prevent symptomatic UTI, all-cause mortality and the indirect effects of UTI (acute rejection, graft loss, worsening of graft function).

METHODS

Criteria for considering studies for this review

Types of studies

All 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 treatment of asymptomatic bacteriuria in kidney transplant recipients.

Types of participants

Inclusion criteria

- Adults and children with end-stage kidney disease, who are recipients of a first or subsequent cadaveric or living donor kidney transplant, including combined grafts (e.g. kidney-pancreas).
- Asymptomatic bacteriuria defined according to the IDSA definitions or as defined by the authors, at any time-point after transplantation.

IDSA definition of asymptomatic bacteriuria:

- In men: a single, clean-catch voided urine specimen with one bacterial species isolated in a quantitative count $\geq 10^5$ CFU/mL in the absence of symptoms or signs of UTI.
- In women: two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts $\geq 10^5$ CFU/mL in the absence of symptoms or signs of UTI.
- A single catheterized urine specimen with one bacterial species isolated in a quantitative count $\geq$ 100 CFU/mL identifies bacteriuria in women or men.

Exclusion criteria

- Pregnant women, as antibiotic treatment of asymptomatic bacteriuria in pregnancy effectively reduces the risk of pyelonephritis in the mother and possibly reduces the chance a baby will be born too early or have a low birthweight. This question has been addressed in a Cochrane review (Smaill 2015).
- Transplant recipients awaiting transurethral resection of the prostate or any other urologic procedure during which mucosal bleeding is anticipated, as antibiotic treatment of asymptomatic bacteriuria is recommended in this setting (Nicolle 2005).

Types of interventions

We included studies of any antibiotic medication and investigated the following comparisons:

- Any antibiotic medication versus placebo or no treatment
- Any antibiotic medication versus any other antibiotic medication
- Low dose versus high dose of the same antibiotic medication
- Short-course versus long-course antibiotic therapy
- Oral versus intravenous (IV) administration of the same or different antibiotic medication.

Types of outcome measures

Primary outcomes

- Incidence of symptomatic UTI (isolation of a bacterial species from a patient with signs or symptoms of UTI, i.e. cystitis, pyelonephritis, prostatitis)
- Incidence of antimicrobial resistance (isolation of multidrug-resistant bacteria, with multidrug-resistance being defined as non-susceptibility to at least one agent in three or more antimicrobial categories).

Secondary outcomes

- All-cause mortality
- Graft loss including death with a functioning graft
- Graft rejection (classified as clinically suspected and treated, or biopsy proven)
- Graft function as measured by SCr concentration, estimated or measured glomerular filtration rate
- Hospitalisation for UTI
- Adverse reactions to antimicrobial agents (i.e. allergic reactions, toxicity)
- Relapse or persistent asymptomatic bacteriuria.

Relapsing and persistent asymptomatic bacteriuria were defined as follows:

- Relapsing asymptomatic bacteriuria: recurrence of asymptomatic bacteriuria after clearance of the initial isolate
- Persistent asymptomatic bacteriuria: persistence of an organism similar to the initial isolate (same species with similar antimicrobial-susceptibility profile).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 1 September 2017 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. Handsearching of kidney and transplant-related journals and the proceedings of 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 search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the "Specialised Register" section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies possibly relevant to the review. The titles and abstracts were screened independently by two authors who discarded studies that were not applicable. However, studies and reviews that possibly included relevant data or information on studies were retained initially. The same two authors independently assessed retrieved abstracts, and if necessary the full text of these studies, to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions these data were used.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (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 a risk of bias?

Measures of treatment effect

For dichotomous outcomes (symptomatic UTI, death, graft loss, allograft rejection, hospitalisation for UTI, adverse reactions to antimicrobial agents, asymptomatic bacteriuria relapse and persistence, antimicrobial resistance), results were expressed as absolute risk difference (RD) or risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (graft function), the mean difference (MD) was used.

Unit of analysis issues

The unit of analysis within each study was the individual patient. All the studies included used a simple parallel group design.

Dealing with missing data

Any further information required from the original author were requested by written correspondence (e.g. emailing corresponding author) and any relevant information obtained in this manner were 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 were carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (e.g. last-observation-carried-forward) were critically appraised (Higgins 2011).

Assessment of heterogeneity

We planned to assess the heterogeneity by visual inspection of the forest plot. Heterogeneity was then analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). A guide to the interpretation of I^2 values is 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 confidence interval for I^2) (Higgins 2011). Lack of data prevented informative formal heterogeneity analysis.

Assessment of reporting biases

We planned to assess the possibility of publication bias for every outcome studied, but there were too few studies to allow meaningful evaluation.

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analysis to explore possible sources of heterogeneity.
Heterogeneity among participants could be related to age, sex, time from transplantation to asymptomatic bacteriuria, and possible presence of a ureteric stent. Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of antibiotic therapy.
Heterogeneity among bacterial strains could be related to the following conditions:

- species involved (*Escherichia coli* versus other strains),
- degree of resistance (multidrug-resistant strains versus non-multidrug-resistant, with multidrug-resistance being defined as non-susceptibility to at least one agent in three or more antimicrobial categories)

The paucity of data precluded us from assessing heterogeneity.

Sensitivity analysis

We planned to perform sensitivity analysis in order to examine the stability of the results in relation to the quality of the included studies. As only two studies with available results were included in the review, it was not feasible to perform a sensitivity analysis

'Summary of findings' tables

We presented the main results of the review in the 'Summary of findings' table. This table presents key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' table 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). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We presented the following outcomes in the 'Summary of findings' table.

- Symptomatic UTI
- Antimicrobial resistance
- All-cause mortality
- Graft loss
- Acute graft rejection
- Hospitalisation for UTI
- Graft function

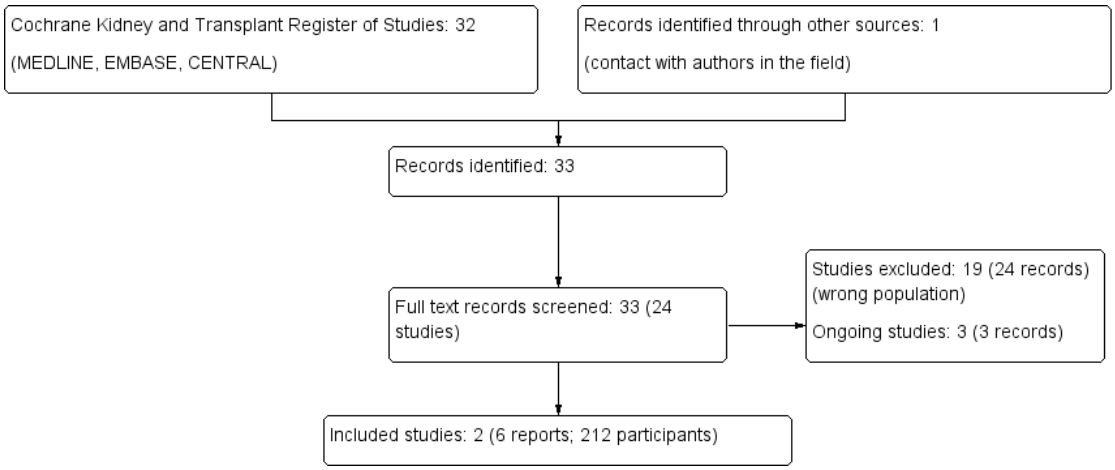
RESULTS

Description of studies

Results of the search

We identified 32 reports through electronic searches. We added one additional report by contacting authors of an identified study (Origuen 2016). We reviewed these 33 reports in detail and identified 24 studies. Two studies (six reports) were included and 19 studies (24 reports) were excluded. Three ongoing studies were identified and will be assessed in a future update of this review (NCT01771432; BiRT Study 2013; NCT02113774) (Figure 1).

Figure 1. Study flow diagram.



Included studies

The two studies (212 participants enrolled, data provided for 200 participants) compared antibiotics versus no treatment, with the choice of antibiotics depending on antimicrobial susceptibility testing results (Moradi 2005; Origuen 2016). In both studies, participants from the intervention group were retreated with antibiotics if asymptomatic bacteriuria recurred during the follow-up period. In Moradi 2005, participants took oral antibiotics for 10 days; we were unable to obtain details regarding choice of antibiotics or dosing. In Origuen 2016, participants received antibiotics for three to seven days during the first episode of asymptomatic bacteriuria, and for two and six weeks during the second and subsequent episodes. The choice of antibiotic, dosing and route of administration were left to the discretion of the treating physician (protocol not provided). In 94% of cases, participants took one of eight different antibiotics orally; IV antibiotics were given when considered appropriate by the treating physician.

Both studies exclusively enrolled adult kidney transplant recipients.

Moradi 2005 enrolled 100 participants with asymptomatic bacteriuria occurring at least one year after transplantation, who did not have ureteral stents, indwelling urethral catheters and/or a Proteus species isolated from the urine culture. Asymptomatic bacteriuria was defined as the joint presence of pyuria and bacteriuria in urinalysis; a colony count greater than 100,000 CFU/mL of a single organism after urine culture; and the absence of irritative voiding symptoms, fever, or chills. Specific strategies to obtain good quality urine samples were not mentioned. Half the participants were women (50/100), aged 45 ± 13 years. *E. coli* was the most common isolate (65%, 57/88 episodes); there was no information on the level of antimicrobial resistance regarding baseline episodes of bacteriuria. The investigators reported outcomes up to 9 to 12 months after randomisation.

Origuen 2016 enrolled 112 outpatients with asymptomatic bacteriuria occurring at least two months after transplantation. They excluded people with a simultaneous kidney-pancreas transplant, a ureteral stent, an indwelling urethral catheter, pregnant women, or people who had lost the graft during the first two months after transplantation. Also, patients who had at least one episode of asymptomatic bacteriuria between the end of the second month after transplantation and the trial screening were excluded (n = 30). Asymptomatic bacteriuria was defined according to IDSA guidelines (Nicolle 2005) and dedicated nurses educated patients in order to obtain good quality urine samples. Participants were about 10 years older than in Moradi 2005 (mean age 54 ± 15 years), just under half were women (53/112; 47%). *E. coli* was the most commonly isolated micro-organism (43% of episodes); there was no information on the level of antimicrobial resistance regarding baseline episodes of bacteriuria. Of the participants enrolled, 92% were within the first year after transplantation, with a median time from transplantation to study inclusion of 83 days. Outcomes were recorded until two years after transplantation or until acute pyelonephritis, graft loss or death occurred during the study period. Median duration of follow-up was 16.9 months (range 0.43 to 22).

Both studies evaluated the incidences of symptomatic UTI and persistent asymptomatic bacteriuria, as well as graft function (Origuen 2016, Moradi 2005). Origuen and co-workers also evaluated the incidences of acute pyelonephritis (which was selected as their primary outcome), lower UTI, hospital admission due to UTI, antimicrobial resistance, *C. difficile*-associated diarrhoea, acute allograft rejection, graft loss, adverse events and all-cause mortality (Origuen 2016).

Excluded studies

We excluded 19 studies. All studies enrolled kidney transplant recipients but participants were included independently of the presence or absence of asymptomatic bacteriuria. Nine studies evaluated the effect of pre- or perioperative antimicrobial prophylaxis (Castelao 1993; Cohen 1988; Ferreira 1990; Matteucci 1998; Robles 1990; Salehipour 2010; Salmela 1990; Townsend 1980; Wilms 1986), nine studies evaluated the role of antimicrobial prophylaxis of bacterial infection after transplantation (Fox 1990; Hibberd 1992; Khosroshahi 2006; Maddux 1989; Melchor 1996; Moyses-Neto 1997; NCT01820897; Tegzess 1986; Tolkoff 1982) and one study evaluated the safety of cotrimoxazole in kidney transplant recipients treated with azathioprine (Hall 1974).

Risk of bias in included studies

See Characteristics of included studies, Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

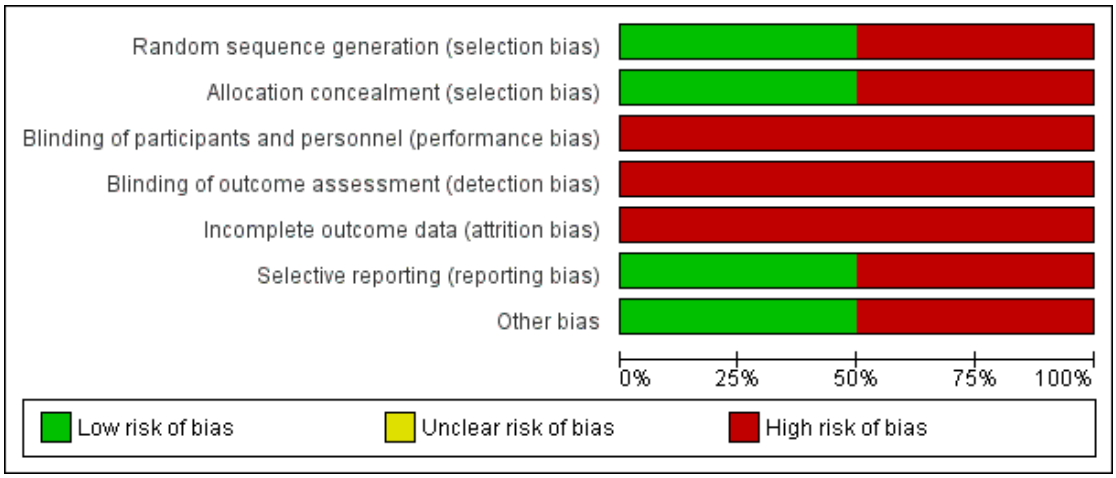
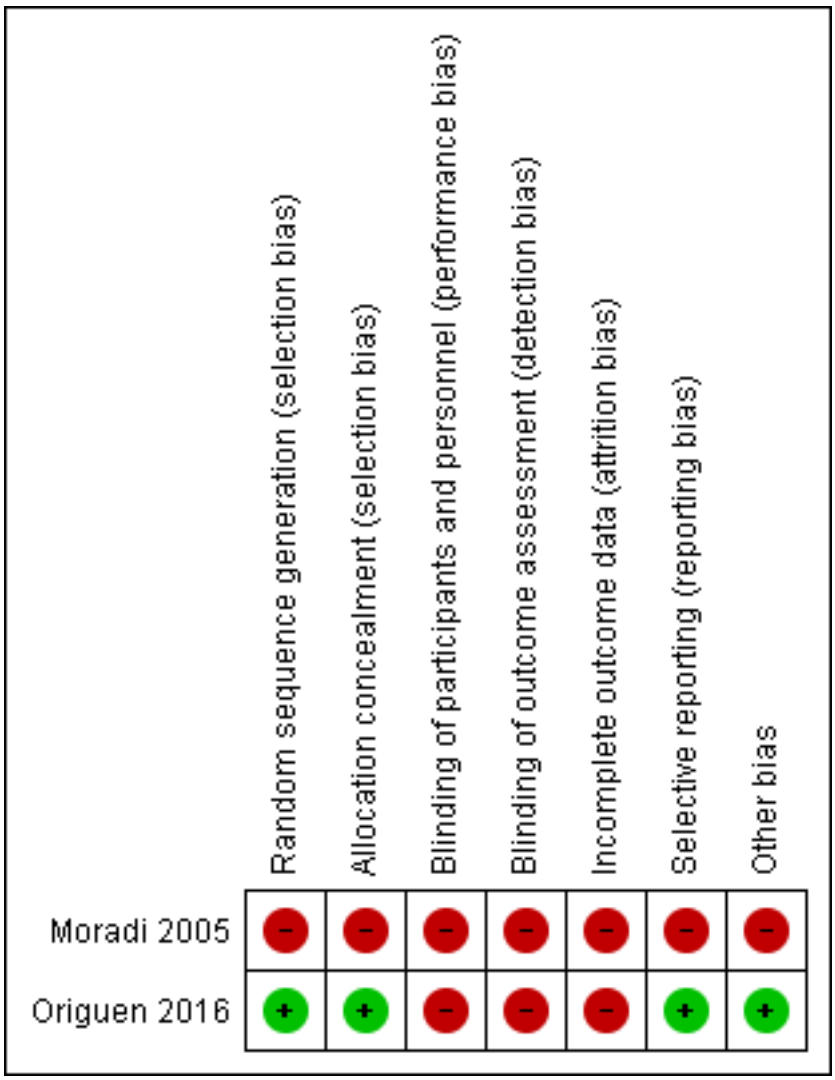


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Origuen 2016 used a computer to generate the randomisation sequence and consecutively numbered sealed envelopes to mask the allocation such that we considered the risk of selection bias to be low. Moradi 2005 used the transplantation code to determine the allocation sequence, entailing a high risk of selection bias.

Blinding

Neither study attempted to blind participants, personnel or data analysts. As symptoms of UTI are partly subjective, we anticipated this would put the results at risk of being biased in favour of antibiotic treatment. Moreover, there were differences between groups in how persistence of asymptomatic bacteriuria was determined in Origuen 2016. In the antibiotics group, investigators asked the participants to do a urinalysis two weeks after completing the antimicrobial therapy. In the control group, no systematic urinalysis occurred at two weeks but subsequent cultures were used to evaluate this outcome.

Incomplete outcome data

We considered both studies to be at high risk of attrition bias. Moradi 2005 excluded 12/100 participants from the analysis after loss to follow-up (11) or the occurrence of acute graft pyelonephritis (1). Baseline characteristics and outcomes were only reported for the remaining 88 participants. Origuen 2016 included all 112 participants into the intention-to-treat analyses. However, little more than half reached the end of the two year study period (54.5%, 61/112 patients). This is partly attributed to the fact that participants were withdrawn after they developed acute pyelonephritis (9) or graft loss (2), which could have biased results for the other outcomes.

Selective reporting

Origuen 2016 had a registered protocol which was published on Clinicaltrials.gov after the end of the recruitment period. That said, the authors reported all expected outcomes related to both benefits and harms and we considered the risk of reporting bias to be low. Moradi 2005 failed to report outcomes such as incidence of pyelonephritis, antimicrobial resistance, graft rejection and graft loss, all-cause mortality, hospitalisation for UTI, and adverse reactions to antimicrobial agents. As such, we considered it at high risk of reporting bias.

Other potential sources of bias

Moradi 2005 did not provide a specific definition of the term "symptomatic UTI" and there were no details on the episodes of symptomatic UTI. Attempts to contact the corresponding author were unsuccessful. Because the incidence of symptomatic UTI was one of our primary outcomes, we considered it at high risk of bias. We considered the risk of sponsorship bias to be low due to the nature of the research question.

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotics versus no treatment for asymptomatic bacteriuria in kidney transplant recipients

Symptomatic UTI

Overall, incidence of symptomatic UTI varied between 19% and 31% in the groups not treated for asymptomatic bacteriuria. Antibiotics had uncertain effects on the subsequent occurrence of symptomatic UTI (Analysis 1.1 (2 studies, 200 participants): RR 0.86, 95% CI 0.51 to 1.45; I^2 = 0%). Origuen 2016 distinguished pyelonephritis from symptomatic UTI and found no little or no difference between the ones who were treated for asymptomatic bacteriuria and those who were not (1 study, 112 participants: RD -0.01, 95% CI -0.12 to 0.10).

Antimicrobial resistance

Origuen 2016 assessed the incidence of antimicrobial resistance as the number of study participants in whom bacteria with acquired non-susceptibility to at least one agent in three or more antimicrobial categories were isolated during follow up. Samples could be collected both in case of symptoms of UTI or as part of routine screening. Even if numerically more people had a multidrug-resistant bacteria in the treatment group as compared with the group not treated for asymptomatic bacteriuria (13/53 versus 12/59), the results were very uncertain (1 study, 112 participants: RR 1.21, 95% CI 0.60 to 2.41).

Secondary outcomes

All-cause mortality, graft loss, (mostly) biopsy-proven acute rejection, and hospitalisation for UTI were only reported by Origuen 2016. In the group not treated for asymptomatic bacteriuria, 1 of the 59 participants died (1.7%), graft loss occurred in 1/59 participants (1.7%) and acute rejection in 12/59 participants (20.3%). There was hospitalisation for UTI in 3 of the 59 untreated participants (5.1%). Overall the investigators reported little or no difference between the two groups for any of these outcomes (Analysis 1.3).

Graft function

Both included studies assessed the effect of antibiotics on graft function. Antibiotics had uncertain effects on graft function, as measured by SCr (Analysis 1.4 (2 studies, 200 participants): MD -0.08 mg/dL, 95% CI -0.35 to 0.18; I^2 = 70%).

Also, there was no significant effect of antibiotics on change in graft function from baseline to end of study. In Moradi 2005, mean plasma creatinine concentrations rose during the study period from 1.16 ± 0.27 mg/dL to 1.2 ± 0.55 mg/dL in the antibiotics group versus 1.42 ± 0.67 mg/dL to 1.43 ± 0.56 mg/dL in the no treatment group. In Origuen 2016, mean change in eGFR from baseline to end of study was 0.53 ± 7.6 mL/min/1.73 m^2 in the antibiotics group (data available for 26/53 participants, 49.1%), as compared with 0.11 ± 15.8 mL/min/1.73 m^2 in the untreated group (data available for 37/59 participants, 62.7%)

Persistence or relapse of asymptomatic bacteriuria

Both studies noted high frequencies of persisting asymptomatic bacteriuria in both groups.

In Moradi 2005, bacteriuria recurred in 25/43 treated participants (58.1%) and 33/45 untreated participants (73.3%). The difference was not statistically significant (RD -0.15, 95% CI -0.33 to 0.05). Of note, the authors did not provide a specific definition of the term "recurrence". Attempts to contact the corresponding author were unsuccessful.

In Origuen 2016, investigators took a sample for urinalysis in the patients treated with antibiotics, two weeks after completing

the treatment. Analysis of data obtained from 90% of the participants revealed that persisting asymptomatic bacteriuria (as defined in our systematic review) was common despite the use of antibiotics, occurring in 46/131 episodes (35.1%). In addition, a different uropathogen was cultured in 18 episodes (13.7%). As a consequence, microbiological cure was achieved in 51.1% (67/131) of the episodes treated with antibiotics. In the control group, no systematic urinalysis occurred at two weeks, but subsequent cultures were used to evaluate the outcome. Under these conditions, asymptomatic bacteriuria persisted after 59% (175/296) of the untreated episodes, and more frequently in the control group (RD -0.24, 95% CI -0.33 to -0.14).

Adverse reactions to antimicrobial agents

Only Origuen 2016 assessed incidence of adverse reactions to antimicrobial agents. The investigators did not compare the incidence of adverse events between the two study groups. However, there was no severe adverse event attributable to the use of antibiotics and non-severe adverse events appeared to be rare (two patients experienced mild diarrhoea in relation with a course of amoxicillin-clavulanate and one patient experienced nausea).

Other outcomes

Additionally, one study evaluated incidence of *C. difficile*-associated diarrhoea (Origuen 2016). In this study, *C. difficile*-associated diarrhoea occurred in 3/53 participants from the antibiotics group (5.7%) and 5/59 participants from the control group (8.5%). There was no statistically significant difference between the two groups (RD -0.03, 95% CI -0.13 to 0.08).

DISCUSSION

Summary of main results

Based on two studies treating kidney transplant recipients with asymptomatic bacteriuria had uncertain effects on preventing symptomatic UTI, and entailed uncertain risks for selecting resistant strains. Persistence of asymptomatic bacteriuria was high regardless of treatment and although the available data were limited, so far, there is no evidence to suggest antibiotic treatment of asymptomatic bacteriuria would improve patient and graft outcomes such as all-cause mortality, graft loss, acute rejection, hospitalisation for UTI or graft function. Data on adverse reactions were very limited, but there seemed to have been no severe adverse event attributable to the antibiotic treatment, and non-severe adverse events appeared to be rare.

Overall completeness and applicability of evidence

The two studies contributing to this review included both male and female adult kidney transplant recipients.

As kidney transplant recipients with asymptomatic bacteriuria in the first few months after transplantation (> two months in Origuen 2016, > one year in Moradi 2005) were not included in these studies, the applicability of our findings to the early post-transplant phase is unclear. First, these exclusions may reflect the belief that asymptomatic bacteriuria increases susceptibility to subsequent UTI specifically in the first few months after transplantation due to the degree of immunosuppression, urologic manipulations and mucosal bleeding, compelling physicians to start antibiotics even when kidney transplant recipients are asymptomatic. Second, establishing the diagnosis of UTI may be difficult early after transplantation, with typical signs and symptoms of UTI being both common and often due to non-infectious causes. Third, the incidence of asymptomatic bacteriuria and UTI is highest in the first months after transplantation (Parasuraman 2013). Despite these specificities, the usefulness of screening for and treating asymptomatic bacteriuria in the early post-transplant period have not been evaluated in a RCT and this should be subject to further study.

We need to be careful when extrapolating the results of this review to patients with ureteral stents or indwelling urethral catheters, as the two included studies excluded these patients. People with urinary devices develop symptomatic UTI more frequently than non-catheterized people in the general population (Hooton 2010). The use of such devices is associated with biofilm formation, where asymptomatic bacteriuria is universal and persistent (Nicolle 2014b). While screening for and treatment of catheter associated-asymptomatic bacteriuria is not recommended in the general population, very little is known about what to do in kidney transplant recipients with urinary devices.

Because both studies exclusively enrolled kidney transplant recipients, caution is required when managing people with combined transplants (e.g. kidney and pancreas). Even if very little is known on the effect of asymptomatic bacteriuria in combined transplant recipients, there is no reason to assume antimicrobial agents would be more effective for asymptomatic bacteriuria in these patients, as compared with kidney transplant recipients. To the best of our knowledge, there is no evidence to support strategies of screening for and treatment of asymptomatic bacteriuria in recipients of non-kidney organ transplants (Parasuraman 2013).

Last, Origuen 2016 excluded pregnant patients. Screening for and treatment of asymptomatic bacteriuria have historically been considered to effectively reduce the risk of pyelonephritis in the mother and possibly complications in the child (Smaill 2015). Even if this approach has recently been questioned (Kazemier 2015), our systematic review does not provide any additional information as pregnant women were excluded from the review.

Quality of the evidence

First, the estimates of the effect of antibiotics for preventing symptomatic UTI were very imprecise, and consistent with either important benefits or harms (Analysis 1.1 (2 studies, 200 participants): RR 0.86, 95% CI 0.51 to 1.45; I^2= 0%). Regarding the absence of significant difference between study groups, we estimated that these two studies lacked power to detect a potential effect of antibiotics for preventing symptomatic UTI. In fact, neither study had an adequate sample size calculation. No sample size calculation was reported in Moradi 2005. In Origuen 2016, a sample size calculation was conducted based on the assumption of a risk reduction of pyelonephritis from 23% in the control group to 3% in the antibiotics group. Under these conditions, the study investigators estimated that 55 patients per arm were required to have a 90% chance of detecting the risk reduction expected between study groups, as significant at the 5% level. However, the incidence of pyelonephritis was much lower in the control group than expected (8.4% versus 23%) and we estimated that the sample size calculation was based on an overly optimistic effect of antimicrobial agents.

Secondly, the included studies were at high risk of bias from various sources. Regrettably, neither of the included studies attempted to blind participants, personnel or data analysts. As symptoms of UTI are partly subjective, we anticipated this would put the results at risk of being biased in favour of antibiotic treatment. As a consequence however, chances are slim that blinding would have been associated with greater effect of antibiotics on the incidence of symptomatic UTI. Nonetheless, the studies were also considered at high risk of attrition bias (Moradi 2005; Origuen 2016), selection bias, and reporting bias (Moradi 2005).

These limitations suggest that additional studies are likely to change our confidence in the effect estimates (GRADE 2008).

Potential biases in the review process

Although this review was conducted by two or more independent authors, used a comprehensive search of the published and unpublished research designed by a specialist librarian, and examined all potentially relevant clinical outcomes, potential biases exist in the review process. The single most important reservation is that four authors of this systematic review are involved in an investigator-led multicentre ongoing RCT comparing antibiotics versus no treatment for asymptomatic bacteriuria in kidney transplant recipients (BiRT Study 2013). No results were available at the time this systematic review was written, and as a consequence no results were included in this review. None of the authors have any commercial conflict of interest related to this review, and although every care was taken to interpret the data as objective as possible, it is difficult to rule out a subconscious intellectual conflict that may have influenced the conclusions.

Agreements and disagreements with other studies or reviews

To the best of our knowledge, there has been no previous attempt to specifically and systematically review the evidence for treating asymptomatic bacteriuria in kidney transplant recipients with antibiotics. In 2005, the IDSA guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults refrained from making a recommendation in kidney transplant recipients for want of evidence (Nicolle 2005). In 2013, the American Society of Transplantation Infectious Diseases Community of Practice suggested not treating asymptomatic bacteriuria that occurs beyond three months after kidney transplantation, unless in case of an accompanying rise in SCr concentration (Parasuraman 2013). However, this recommendation was not based on a systematic review but on expert opinion, and this group of expert acknowledged that such a strategy may be too aggressive and lead to emergence of antimicrobial resistance. Based on the evidence currently available, our review do not support treating asymptomatic bacteriuria before or after three months post-transplantation.

AUTHORS' CONCLUSIONS

Implications for practice

Based on currently available data, there is insufficient evidence to support routinely treating kidney transplant recipients with antibiotics in case of asymptomatic bacteriuria after transplantation, but data are scarce. Because the usefulness of antibiotics has not been demonstrated in kidney transplant recipients with asymptomatic bacteriuria, it is not clear whether a strategy of screening for asymptomatic bacteriuria with urine cultures should be performed. Screening cultures could provide information on the level of antimicrobial resistance in case of asymptomatic bacteriuria, but the effect of such findings regarding the choice of empirical therapy in case of subsequent symptomatic UTI has to be determined.

Implications for research

Further studies assessing routine antibiotic treatment would inform practice and we eagerly await the results of three ongoing randomised studies, which may help resolve existing uncertainties. Our review is limited by the lack of information on baseline level of antimicrobial resistance and the effect of antibiotics given for asymptomatic bacteriuria after transplantation on the risk of promoting antimicrobial resistance, both in the urine and in the gut, which is the reservoir of resistant organisms. We would urge future research to include information on both baseline level of antimicrobial resistance and change in drug resistance after antibiotic treatment, using appropriate samples (e.g. rectal swab and urine specimens) and systematic methodology.

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Coussement J, Scemla A, Abramowicz D, Nagler EV, Webster AC. Antibiotics for asymptomatic bacteriuria in kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2014, Issue 10. [DOI: 10.1002/14651858.CD011357

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Moradi 2005

Methods	• Study design: parallel quasi-RCT • Recruitment period: March 2002 to February 2003 • Duration of follow-up: 9 to 12 months
Participants	• Country: Iran • Setting: Single centre • Inclusion criteria: men and women kidney transplant recipients ≥ 18 years with a diagnosis of asymptomatic bacteriuria (defined as the as the joint presence of pyuria and bacteriuria in urine analysis, with a positive culture with colony count > 100,000 of one organism and the absence of irritative voiding symptoms, fever and chills); at least one year post-transplantation ○ Main causes of underlying disease: hypertension (43.1%), diabetes mellitus (14.8%), glomerulonephritis (12.5%), urolithiasis (10.2%) • Number (randomised/analysed): 100/88 (12 excluded after randomisation) ○ Treatment group (43); control group (45) • Sex (M/F): treatment group (20/23); control group (20/25) • Mean age ± SD (years): treatment group (44.2 ± 12.7); control group (40.9 ± 13.2) • Exclusion criteria: urethral catheter; ureteral stent; Proteus infection
Interventions	Treatment group • Antibiotic: choice of antibiotics was according to the antimicrobial susceptibility testing results ○ Duration of therapy: 10 days ○ Doses: not provided • In case of recurrence of asymptomatic bacteriuria during the follow-up period, treatment was repeated in the intervention arm Control group • No treatment
Outcomes	• Incidence of symptomatic UTI • Graft function as measured by SCr during the follow-up period • Incidence of relapse or persistent asymptomatic bacteriuria
Notes	• No specific strategy mentioned to obtain good quality urine samples • Primary outcome not defined • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	High risk	Quote: "According to the order of patients' transplant code, they were divided into two groups of case and control, in every other one manner" Comment: high-risk of selection bias is associated with quasi-RCTs
Allocation concealment (selection bias)	High risk	Quote: "According to the order of patients' transplant code, they were divided into two groups of case and control, in every other one manner" Comment: high-risk of selection bias is associated with quasi-RCTs
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "In case group, a 10-day oral antibiotic therapy was administered (...). The patients in control group were left untreated" Comment: as symptoms of UTIs are in part subjective, the absence of blinding may impact the number of symptomatic infections observed
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "In case group, a 10-day oral antibiotic therapy was administered (...). The patients in control group were left untreated" Comment: as symptoms of urinary tract infections are in part subjective, the absence of blinding may impact the number of symptomatic infections observed
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The patients with lost follow-up visits, acute rejection, and pyelonephritis leading to hospitalization during the study were excluded. (...) Twelve patients were excluded of the study, 11 because of lost follow-up visits and 1 because of acute pyelonephritis, and eventually, data from 88 patients were analyzed" Comment: Twelve enrolled patients (12%) were excluded from the analysis (11 subjects lost to follow-up and 1 patient due to occurrence of acute graft pyelonephritis). A high-risk of attrition bias was suspected
Selective reporting (reporting bias)	High risk	Comment: no published protocol. Authors did not divided outcomes into primary and secondary outcomes. Some expected outcomes such as incidences of antimicrobial resistance, pyelonephritis, graft rejec-

Moradi 2005 (*Continued*)

		tion and graft loss, all-cause mortality, incidence of hospitalisation for UTI and incidence of adverse reactions to antimicrobial agents were not reported
Other bias	High risk	Comment: Moradi 2005 did not provide a specific definition of the term "symptomatic UTI" and there were no details on the episodes of symptomatic UTI. Attempts to contact the corresponding author were unsuccessful

Origuen 2016

Methods	• Design: parallel RCT • Recruitment period: April 2011 to February 2014 • Duration of follow-up : the follow-up period was theoretically extended to the first 2 years after transplantation unless acute pyelonephritis (9 patients), graft loss (2 patients) or death (3 patients) occurred during the study period. Median follow-up time was 16.9 months (range 0.4 to 22), with 61/112 (54.5%) patients completing the follow-up until two years after transplantation
Participants	• Country: Spain • Setting: single centre • Inclusion criteria: men and women kidney transplant recipients ≥ 18 years with a diagnosis of asymptomatic bacteriuria according to IDSA guidelines; at least two months post-transplantation; both inpatients and outpatients were potentially eligible ○ Main causes of underlying disease: diabetes mellitus (23.2%), glomerulonephritis (21.4%), polycystic kidney disease (14.3%), hypertension (9.8%) • Number: treatment group (53); control group (59) patients • Mean age ± SD (years): treatment group (55.4 ± 14.5); control group (53.04 ± 15.8) • Sex (M/F): treatment group (28/25); control group (31/28) • Exclusion criteria: kidney-pancreas transplant recipients; double J ureteral stents or indwelling urethral catheter; pregnancy; graft loss within the first two months after transplantation; occurrence of at least one episode of asymptomatic bacteriuria between the end of the second month after transplantation and the study screening
Interventions	Treatment group • Antibiotics: choice of antibiotics: according to the antimicrobial susceptibility testing results ○ Duration of therapy: 3 to 7 days for the first episode of asymptomatic bacteriuria. The first relapse was theoretically treated for 14 days. In presence of two or more relapses, a urinary tract ultrasound examination was ordered to rule out obstruction, and a 6-week antibiotic course was prescribed. If a further relapse was detected, a long-term suppressive therapy with low doses of antibiotic was set up for 6 months ○ Doses: more than 10 different antimicrobial agents were used during this

Origuen 2016 (*Continued*)

	study, with choice and dosing selected according to parameters such as antimicrobial susceptibility testing results • In case of recurrence of asymptomatic bacteriuria during the follow-up period, treatment was repeated in the intervention arm Control group • No treatment
Outcomes	Primary outcome • Cumulative incidence of a first episode of acute pyelonephritis, as defined by the simultaneous presence of fever and bacteriuria and/or bloodstream infection along with at least one of the following symptoms: lumbar pain, graft pain, chills and/or irritative voiding symptoms Secondary outcomes • Incidence of lower UTI • Incidence of overall symptomatic UTI • Incidence of colonization or infection due to multi-drug resistant bacteria, with multi-drug resistance being defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories • Graft function as measured by eGFR at 12 and 24 months after transplant (MDRD equation) • Incidence of graft loss, including permanent return to dialysis or retransplant (does not include death with a functioning graft) • Incidence of acute graft rejection (biopsy-proven or not) • Incidence of adverse events • Incidence of persistent asymptomatic bacteriuria • Incidence of *Clostridium difficile,* defined as the passage of 3 or more unformed stools in 24 hours in the presence of a positive stool test for toxigenic *C. difficile* • Incidence of hospital admission for UTI • Incidence of all-cause mortality
Notes	• Specific strategies to obtain good quality urine samples: dedicated nurses instructed the patients in the proper collection of urinary samples to minimize the risk of contamination. In case of contamination of the culture, urine collection was repeated • Funding source: "This work was partially supported by the Fundacion Mutua Madrile˜na de Investigacion Medica (FMM Grant 2010/0015), by the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III (Fondo de Investigaciones Sanitarias [FIS] 12/02269 and Proyecto Integrado de Excelencia [PIE] 13/00045), and by the European Development Regional Fund (EDRF) "A way to achieve Europe"."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomised (1:1 ratio) using a predetermined computer-generated sequence and consecutively numbered sealed envelopes"

Origuen 2016 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "participants were randomised (1:1 ratio) using a predetermined computer-generated sequence and consecutively numbered sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label, parallel-group, randomised trial" Comment: as symptoms of UTIs are in part subjective, the absence of blinding may impact the number of symptomatic infections observed
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label, parallel-group, randomised trial" Comment: as symptoms of UTIs are in part subjective, the absence of blinding may impact the number of symptomatic infections observed
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "the 12- and 24-month follow-up periods were completed in 98 (86.6%) and 61 patients (54.4%), respectively" Comment: all the 112 participants were included into the intention-to-treat analysis. However, little more than half reached the end of the two year study period. Participants were withdrawn after they developed acute pyelonephritis, which could have biased results for the other outcomes
Selective reporting (reporting bias)	Low risk	Comment: all the expected outcomes were reported.
Other bias	Low risk	Quote: 'this work was partially supported by the Fundacio n Mutua Madrilen a de Investigacio n Me dica (FMM Grant 2010/0015), by the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III (Fondo de Investigaciones Sanitarias [FIS] 12/02269 and Proyecto Integrado de Excelencia [PIE] 13/00045), and by the European Development Regional Fund (EDRF) "A way to achieve Europe". J.O. holds a research-training contract "Rio Hortega" (CM13/00180) from the Spanish Ministry of Economy and Competitiveness (Instituto de Salud Carlos III). M.F.R. holds a clinical research contract "Juan Rode s" (JR14/

Origuen 2016 (*Continued*)

		00036) from the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III" Comment: a low-risk of sponsorship bias is expected due to the nature of the study

IDSA - Infectious Diseases Society of America; MDRD - Modification of Diet in Renal Disease; M/F - male/female; RCT - randomised controlled trial; SD - standard deviation; UTI - urinary tract infection

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Castelao 1993	Wrong population: evaluated the role of perioperative antibiotic prophylaxis
Cohen 1988	Wrong population: evaluated the role of perioperative antibiotic prophylaxis
Ferreira 1990	Wrong population: evaluated the role of perioperative antibiotic prophylaxis
Fox 1990	Wrong population: evaluated the effect of long-term prophylaxis with cotrimoxazole following kidney transplantation
Hall 1974	Wrong population: evaluated the risk of leucopenia associated with the use of cotrimoxazole in kidney transplant recipients having UTI
Hibberd 1992	Wrong population: compared two different regimen of long-term antibiotic prophylaxis following kidney transplantation
Khosroshahi 2006	Wrong population: compared various doses of prophylaxis with cotrimoxazole following kidney transplantation
Maddux 1989	Wrong population: evaluated the effect of antibiotics prophylaxis following kidney transplantation
Matteucci 1998	Wrong population: evaluated the effect of perioperative antibiotic prophylaxis
Melchor 1996	Wrong population: evaluated the effect of a 10-days antimicrobial prophylaxis following kidney transplantation
Moyses-Neto 1997	Wrong population: evaluated the effect of long-term prophylaxis with ciprofloxacin following kidney transplantation
NCT01820897	Wrong population: compares two regimen of long-term prophylaxis following kidney transplantation
Robles 1990	Wrong population: evaluated the role of perioperative antibiotic prophylaxis

(*Continued*)

Salehipour 2010	Wrong population: evaluated the effect of intravesical administration of antibiotics at the time of transplantation
Salmela 1990	Wrong population: evaluated the effect of intravesical administration of antibiotics just before transplantation
Tegzess 1986	Wrong population: evaluated different regimen of postoperative short-term antibiotics prophylaxis
Tolkoff 1982	Wrong population: evaluated the effect of long-term prophylaxis with cotrimoxazole following kidney transplantation
Townsend 1980	Wrong population: evaluated the role of perioperative antibiotic prophylaxis
Wilms 1986	Wrong population: evaluated the effect of antibiotic prophylaxis in kidney transplant recipients

UTI - urinary tract infection

Characteristics of ongoing studies *[ordered by study ID]*

BiRT Study 2013

Trial name or title	The Bacteriuria in Renal Transplantation (BiRT) study: a prospective, randomised, parallel-group, multicenter, open-label, superiority trial comparing antibiotics versus no treatment in the prevention of symptomatic urinary tract infection in kidney transplant recipients with asymptomatic bacteriuria
Methods	• Study design: parallel RCT • Duration of follow-up: 12 months • Power calculation: performed (sample size calculation: 198 patients) • Blinding: open-label
Participants	• Countries: Belgium, France • Setting: multicentre Inclusion criteria • Kidney transplant recipient with asymptomatic bacteriuria, defined as the isolation of a single bacterial species in a quantitative count ≥ 100.000 CFU/mL in a single collected urine specimen from a patient without biological or clinical signs or symptoms referable to UTI • Sex: both • Age : ≥ 18 years • Time from transplantation: from the end of the 2nd month post-transplantation • Other: in-patients and out-patients are included Exclusion criteria • Pregnant women or women who wish to become pregnant during the course of the study • Presence of indwelling urinary devices such as urethral catheter, ureteral catheter, nephrostomy and/or suprapubic catheter • Combined transplantation (liver-kidney, lung-kidney, heart-kidney) • Urinary tract surgery during the last two months • Surgical urological procedure planned in the next two weeks

BiRT Study 2013 (*Continued*)

	• Neutropenia ($\leq$ 500 neutrophils/mm^3) • Important intensification of immunosuppression (Solumedrol bolus and/or use of thymoglobulin) or any other treatment of an acute graft rejection in the last 2 months • Use of antibiotics at the time of the asymptomatic bacteriuria (except for prevention of *Pneumocystis jirovecii*) • ESKD requiring dialysis • Non-functioning native bladder (e.g. bladder dysfunction requiring intermittent self-catheterization, orthotopic ileal neobladder) • Recurrent acute graft pyelonephritis ($\geq$ 2 episodes in the last year) • Kidney transplant recipients who could not return for regular follow-up
Interventions	Treatment group • Antibiotics: choice of antibiotics started and selected according to the antibiogram results • Duration of therapy: 10 days • Doses: according to national recommendations • In case of recurrence of asymptomatic bacteriuria during the follow-up period, treatment repeated in the intervention arm Control arm • No antibiotics delivered in case of asymptomatic bacteriuria
Outcomes	Primary outcome • Cumulative incidence of a first episode of symptomatic UTI (time frame: 12 months) Secondary outcomes (to be evaluated during the 12 months of follow-up) • Incidence of a first episode of pyelonephritis • Incidence of urinary source bacteraemia • Proportion of patients with clearance of asymptomatic bacteriuria • Occurrence of new episodes of asymptomatic bacteriuria • Graft function (eGFR) and graft survival • Biopsy-proven graft rejection • Patient survival • Level of antimicrobial resistance. Investigators will compare resistance profiles as an outcome for both symptomatic urinary tract infection and asymptomatic bacteriuria. Investigators will evaluate both the rate of multidrug resistant (with multidrug-resistance being defined as non-susceptibility to at least one agent in three or more antimicrobial categories) and resistance to the antibiotic given for the treatment of asymptomatic bacteriuria (in the "antibiotics" arm) • Total number of days of antimicrobial therapy • Cost of antimicrobial treatment for asymptomatic bacteriuria and symptomatic UTI • Number of hospitalizations for asymptomatic bacteriuria and symptomatic UTI treatment • Incidence of *Clostridium difficile*-associated diarrhoea • Total number of symptomatic UTIs • Within-person reproducibility of urinanalysis results (at baseline) Specific strategies to obtain good quality urine samples • Diagnosis of asymptomatic bacteriuria based on results of culture of a urine specimen collected in a manner that minimizes contamination. Even in women, a second urine collection is not necessary for inclusion in the study, but is highly recommended • Samples with increased number of epithelial cells should encourage physicians to control the urine analysis • Analysis of urine samples performed within two hours following the collection in order to minimize ex-vivo bacterial multiplication and leukocytes lysis

BiRT Study 2013 (*Continued*)

	• Rules such as the need for clean catch midstream urine samples regularly recalled to the kidney transplant recipient
Starting date	April 2014
Contact information	Julien Coussement, MD (co-ordinating investigator) Dept. of Nephrology, Dialysis and Kidney Transplantation, Hôpital Erasme - Université Libre de Bruxelles Route de Lennik, 808, 1070 Brussels, Belgium. Phone: +32.2.555.30.49 / Fax: + 32.2.555.64.99 / E-mail: jcoussem@ulb.ac.be
Notes	Protocol published by The Lancet (reference: 14PRT/5447): http://www.thelancet.com/protocol-reviews/14PRT-5447

NCT01771432

Trial name or title	Antibiotic treatment versus no therapy in kidney transplant recipients with asymptomatic bacteriuria. A prospective randomised study (BAC01)
Methods	• Study design: parallel RCT • Duration of follow-up: 1st year after transplantation • Power calculation: yes (sample size calculation: 200 patients) • Blinding: open-label
Participants	• Country: Spain • Setting: multicentre Inclusion criteria • Patients who receive a transplant allograft during study period • Sex: both • Age: 18 to 85 years • Time from transplantation: unknown Exclusion criteria • No acceptation of study
Interventions	Treatment arm • Antibiotics Control arm • No therapy
Outcomes	Primary outcome • Incidence of pyelonephritis Secondary outcomes • Kidney function • Need for hospitalisation • Incidence of graft loss • Mortality • Infection by multiresistant microorganisms Specific strategies to obtain good quality urine samples: not specified

NCT01771432 (*Continued*)

Starting date	January 2013
Contact information	Núria Sabé Fernàndez Hospital Universitari de Bellvitge L'Hospitalet de Llobregat, Barcelona, Spain, 08907 Phone number: +34932607625 E-mail: nfsabe@bellvitgehsopital.cat
Notes	Estimated study completion date: December 2015

NCT02113774

Trial name or title	The impact of antimicrobial treatment for asymptomatic bacteriuria in renal transplant patients
Methods	• No details available (authors contacted)
Participants	• Country: Israel • Location: single centre Inclusion criteria • Kidney transplant recipients with a positive urine culture defined as $\geq 10^5$ CFU/mL of a known single pathogen • Sex : both • Age: $\geq$ 18 years • Time from transplantation: $\geq$1 month and $\leq$ 12 months after kidney transplantation Exclusion criteria • Any one of the following signs and symptoms: fever, abdominal pain, dysuria, frequency, urgency, flank pain, costovertebral-angel tenderness or tenderness over the transplanted kidney • Active infections in another site • Leucocytosis (WBC > 18,000/μL) or leucopenia (WBC < 3,000 /μL) • Elevation of SCr > 15% of its baseline level • Obstructive or other urological complications following transplantation as known foreign device (stent/double-J-Cath, any catheter) in the urinary tract system, known obstruction of the transplanted kidney, indwelling or intermittent catheterization • Pregnant or lactating women • Candidates to invasive urologic procedures • Inability to return for regular follow-up • Previous enrolment in this study • Patients unable to give informed consent
Interventions	Treatment group • Antimicrobial treatment according to in-vitro susceptibility Control group • No therapy
Outcomes	Primary outcome • Symptomatic UTI (at 30 days) Secondary outcomes • 25% reduction in eGFR (at 1 year)

NCT02113774 (*Continued*)

	• Graft loss (at 1 year) Specific strategies to obtain good quality urine samples: not specified
Starting date	April 2014
Contact information	Ruth Rahamimov Head of Transplant investigator service Rabin Medical centre, Israel
Notes	

CFU - colony forming units; ESKD - end-stage kidney disease; eGFR - estimated glomerular filtration rate; RCT - randomised controlled trial; SCr - serum creatinine; UTI - urinary tract infection; WBC - white blood cells

DATA AND ANALYSES

Comparison 1. Antibiotics versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic urinary tract infection	2	200	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.51, 1.45]
2 Antimicrobial resistance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Secondary dichotomous outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Graft loss	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Acute rejection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Hospitalisation for UTI	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Graft function (creatinine at end of study)	2	200	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.35, 0.18]

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: JC, AS, DA, EVN, AW
2. Study selection: JC, AS, EVN
3. Extract data from studies: JC, AS,
4. Enter data into RevMan: JC, AS
5. Carry out the analysis: JC, AS, EVN
6. Interpret the analysis: JC, AS, DA, EVN, AW
7. Draft the final review: JC, AS, DA, EVN, AW
8. Disagreement resolution: EVN
9. Update the review: JC

DECLARATIONS OF INTEREST

- Julien Coussement: is the coordinating investigator of a multicentre RCT comparing antibiotics versus no treatment in the prevention of symptomatic UTI in kidney transplant recipients with asymptomatic bacteriuria (BiRT Study 2013). This study was registered on Clinicaltrials.gov in May 2013 and started recruiting in April 2014. Results of this study are expected to become available from 2019. Julien Coussement received two grants from not-for-profit organisations for the purpose of initiating the study (David & Alice Van Buuren Research Grant 2014 & Prix 2014 du Fonds Carine Vyghen).

- Anne Scemla: is an investigator of a multicentre RCT comparing antibiotics versus no treatment in the prevention of symptomatic UTI in kidney transplant recipients with asymptomatic bacteriuria (BiRT Study 2013). This study was registered on Clinicaltrials.gov in May 2013 and started recruiting in April 2014. Results of this study are expected to become available from 2019.

- Daniel Abramowicz: is an investigator of a multicentre RCT comparing antibiotics versus no treatment in the prevention of symptomatic UTI in kidney transplant recipients with asymptomatic bacteriuria (BiRT Study 2013). This study was registered on Clinicaltrials.gov in May 2013 and started recruiting in April 2014. Results of this study are expected to become available from 2019.

- Evi V Nagler: is an investigator of a multicentre RCT comparing antibiotics versus no treatment in the prevention of symptomatic UTI in kidney transplant recipients with asymptomatic bacteriuria (BiRT Study 2013). This study was registered on Clinicaltrials.gov in May 2013 and started recruiting in April 2014. Results of this study are expected to become available from 2019.

- Angela C Webster: None known

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Following the 2005 IDSA guidelines (Nicolle 2005), we included an additional asymptomatic bacteriuria definition to be applied to catheterized patients. The following sentence was added: "a single catheterized urine specimen with one bacterial species isolated in a quantitative count $\geq$ 100 CFU/mL identifies bacteriuria in women or men".

We modified the criteria to evaluate the effect of antibiotics on the incidence of antimicrobial resistance between protocol and review. In hindsight, we considered the criteria we initially chose (incidence of bacteriuria resistant to primary antibiotic treatment) difficult to assess in studies with groups of untreated patients. We therefore decided to evaluate antimicrobial resistance using a widely accepted criterion that can easily be evaluated in both treated and untreated participants (isolation of a multidrug-resistant bacterium, with multidrug-resistance being defined as non-susceptibility to at least one agent in three or more antimicrobial categories).

The following definitions have been added in the section entitled "secondary outcomes":

Relapsing and persistent asymptomatic bacteriuria were defined as follows:

- Relapsing asymptomatic bacteriuria: recurrence of asymptomatic bacteriuria after clearance of the initial isolate

- Persistent asymptomatic bacteriuria: persistence of an organism similar to the initial isolate (same species with similar antimicrobial-susceptibility profile).