

## RESEARCH

# Antibiotic prophylaxis for urinary tract infections after removal of urinary catheter: meta-analysis

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## Abstract

**Objective** To determine whether antibiotic prophylaxis at the time of removal of a urinary catheter reduces the risk of subsequent symptomatic urinary tract infection.

**Design** Systematic review and meta-analysis of studies published before November 2012 identified through PubMed, Embase, Scopus, and the Cochrane Library; conference abstracts for 2006-12 were also reviewed.

**Inclusion criteria** Studies were included if they examined antibiotic prophylaxis administered to prevent symptomatic urinary tract infection after removal of a short term ( $\leq 14$  days) urinary catheter.

**Results** Seven controlled studies had symptomatic urinary tract infection after catheter removal as an endpoint; six were randomized controlled trials (five published; one in abstract form) and one was a non-randomized controlled intervention study. Five of these seven studies were in surgical patients. Studies were heterogeneous in the type and duration of antimicrobial prophylaxis and the period of observation. Overall, antibiotic prophylaxis was associated with benefit to the patient, with an absolute reduction in risk of urinary tract infection of 5.8% between intervention and control groups. The risk ratio was 0.45 (95% confidence interval 0.28 to 0.72). The number needed to treat to prevent one urinary tract infection was 17 (12 to 30).

**Conclusions** Patients admitted to hospital who undergo short term urinary catheterization might benefit from antimicrobial prophylaxis when the catheter is removed as they experience fewer subsequent urinary tract infections. Potential disadvantages of more widespread antimicrobial prophylaxis (side effects and cost of antibiotics, development of antimicrobial resistance) might be mitigated by the identification of which patients are most likely to benefit from this approach.

## Introduction

Urinary catheterization is common in patients in hospital, particularly for surgical patients in the perioperative period when physiological mechanisms of bladder emptying are suspended. Catheterization of the urinary tract, however, is associated with an increased risk of bacteriuria and symptomatic urinary tract infection, the risk being associated with the duration of catheterization.<sup>1</sup> National guidelines recommend removal of urinary catheters once they are no longer needed,<sup>2,4</sup> and surgical experts advocate discontinuation of catheterization as early as 24-48 hours postoperatively.<sup>5</sup> Bacteriuria in a patient with a catheter, however, can persist after the catheter is removed and can develop into a symptomatic urinary tract infection. Manipulation of the catheter itself during removal might also predispose to infection.<sup>6</sup> Current definitions<sup>1</sup> from the National Healthcare Safety Network (NHSN) for catheter associated urinary tract infection (CAUTI) reflect this by identifying infections up to 48 hours after catheter removal as catheter associated ([www.cdc.gov/nhsn/pdfs/pscmanual/7pscCAUTICurrent.pdf](http://www.cdc.gov/nhsn/pdfs/pscmanual/7pscCAUTICurrent.pdf)).<sup>3</sup>

Whether administration of prophylactic antibiotics when the catheter is removed will prevent subsequent symptomatic urinary tract infection is unclear. Randomized trials have yielded conflicting results,<sup>7,8</sup> and there has been no meta-analysis. Also, there is considerable heterogeneity in the management of antimicrobial prophylaxis around removal of a urinary catheter.<sup>9</sup> The 2009 Infectious Diseases Society of America (IDSA) guidelines for the diagnosis, management, and prevention of catheter associated urinary tract infection determined that there was insufficient evidence to recommend widespread antibiotic prophylaxis after catheterization.<sup>2</sup> In contrast, in their 2008 best

practice policy statement the American Urological Association (AUA) concluded that antibiotic prophylaxis should be considered for patients with bacteriuria at time of catheter removal, particularly for those with certain risk factors (such as advanced age, immunodeficiency, or anatomic abnormalities of the urinary tract).<sup>10</sup>

We performed a meta-analysis of controlled trials to clarify whether antibiotic prophylaxis at the time of urinary catheter removal confers a benefit in terms of preventing subsequent symptomatic urinary tract infections.

## Methods

### Search strategy and selection criteria

We followed the PRISMA guidelines for conducting and reporting meta-analyses.<sup>11</sup> We did two separate queries. First, we performed a systematic review of randomized and non-randomized controlled trials that compared antibiotic prophylaxis with placebo or a control group at the time of removal of a transurethral urinary catheter and tracked the occurrence of symptomatic urinary tract infections in the subsequent period (JM). For this purpose, we screened the medical literature in PubMed from 1947 up to November 2012 with the search terms urinary catheter, removal, prophylaxis, antibiotic prophylaxis randomized, and trial, and evaluated conference abstracts from 2006-2012 (from Infectious Diseases Society of America (IDSA) annual meeting, Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Society for Healthcare Epidemiology of America (SHEA) annual meeting, and the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)). In addition, we used Google to search for the same terms. Next, a medical librarian (SF) created a systematic search strategy that included a combination of standardized index terms and straight keywords. She ran that search in Embase, Scopus, the Cochrane Library (including CENTRAL), and clinicaltrials.gov, in addition to PubMed. We reviewed the reference lists of all potentially relevant studies to identify additional research data. We included non-English language and unpublished studies (fig 1).<sup>↓</sup>

Eligible studies were randomized and non-randomized controlled trials of short term catheterization in adults with symptomatic urinary tract infection as an endpoint. We defined short term catheterization as a maximum duration of 14 days. The endpoint of symptomatic urinary tract infection required the detection of measureable bacteriuria plus the presence of at least one symptom or sign compatible with urinary tract infection.<sup>2</sup> Not all studies, however, specified which clinical criteria were fulfilled for this endpoint. We did not include the endpoint bacteriuria because antibiotic treatment of asymptomatic bacteriuria is not indicated.<sup>12</sup> Because antibiotic prophylaxis was directed specifically at the prevention of symptomatic urinary tract infections, we did not assess additional outcomes such as survival. Subsequent symptomatic urinary tract infections caused by antibiotic resistant organisms would have been a meaningful secondary endpoint but none of the included studies assessed it.

One reviewer (JM) screened the titles and abstracts of eligible studies originating from the primary search. Two independent reviewers (JM, BWT) screened the titles and abstracts of eligible studies identified in the secondary search. Potentially relevant papers were obtained, and these reviewers assessed the full manuscript for possible inclusion. There were no restrictions with regard to the antibiotics used for prophylaxis or the length of follow-up after antibiotic prophylaxis in the reviewed studies.

### Data extraction and meta-analysis

We extracted information about the study design, inclusion criteria for patients, sample size, antimicrobial agents used for prophylaxis, and the duration of administration. We also noted the duration of catheterization until removal in intervention and control groups. Finally, we extracted the number of endpoints in intervention and control groups in relation to the patients assigned to each of the groups.

We assessed the internal validity of individual trials using a modification of the Cochrane Handbook quality assessment recommendations.<sup>13</sup> Two investigators (JM, CRC) independently rated each trial across four domains of bias: selection, performance, attrition, and detection. A priori, both investigators agreed to evaluate selection bias based on adequacy of randomization and allocation concealment for each study, while performance bias was judged on the probability for systematic differences in care after randomization. Investigators judged attrition bias based on any systematic difference in withdrawals between intervention and control groups. Detection bias was assessed on the timing and methods used to ascertain the primary outcome for each study. The reliability of quality assessment between raters was evaluated with Cohen's  $\kappa$ ,<sup>14</sup> with the statistical package SPSS version 20 (IBM Corporation, Armonk, NY). Discrepancies between raters were resolved by consensus.

All data were entered into the free online analysis tool "Meta-Analyst" ([http://tuftscaes.org/meta\\_analyst/](http://tuftscaes.org/meta_analyst/)).

Heterogeneity among the studies was assessed with  $\chi^2$  and  $I^2$  statistics (25%, 50%, and 75% representing low, moderate, and high heterogeneity).<sup>15</sup> We pooled the results of studies using random effects models, if appropriate, after consideration of heterogeneity among trials. We calculated individual and pooled statistics as relative risks and 95% confidence intervals. We conducted a sensitivity analysis of the pooled relative risk by sequentially excluding the non-randomized study and the unpublished study from the analysis. We also performed subgroup analyses of studies in surgical patients and mixed hospital populations. We evaluated potential publication bias with a funnel plot.<sup>16</sup>

## Results

The two literature searches identified 246 and 221 potentially relevant abstracts (fig 1<sup>↓</sup>). In the primary search, we identified 27 abstracts that led to full article review and two further studies by reviewing bibliographies or through conference abstracts. In the secondary search, two reviewers independently determined that 17 of 221 abstracts required review of the full manuscript. After review, we excluded studies in which the patients had suprapubic catheters,<sup>17 18</sup> the endpoint was not symptomatic bacteriuria,<sup>19-21</sup> or antibiotic prophylaxis was started shortly after catheter insertion rather than at the time of removal.<sup>22 23</sup> We also excluded studies that lacked a concurrent control group.<sup>24</sup> Seven studies met eligibility criteria.

This meta-analysis includes five published randomized controlled trials,<sup>7 8 25-27</sup> one unpublished randomized controlled trial,<sup>28</sup> and one non-randomized controlled study<sup>29</sup> (table 1<sup>↓</sup>). Three trials indicated that prophylaxis is associated with lower incidence of urinary tract infection,<sup>7 26 29</sup> whereas three published studies<sup>8 25 27</sup> and the single unpublished randomized study<sup>28</sup> did not report any benefit with prophylaxis. The quality of the included studies was variable: there was a low risk of detection bias and performance bias and a high risk of selection and attrition bias in most studies. Specifically, randomization and adequate allocation were inadequate in all studies except those

by Wazait and colleagues,<sup>27</sup> Pfefferkorn and colleagues,<sup>7</sup> and van Hees and colleagues.<sup>8</sup>

Attrition bias was a concern across all of the studies except those by Wazait and colleagues<sup>27</sup> and van Hees and colleagues.<sup>8</sup> The inter-rater  $\kappa$  to describe study quality was between 0.7 (attrition bias) and 1.0 (selection and performance bias). For the detection bias, we could not calculate  $\kappa$  because one rater's assessment was constant across studies (that is,  $\kappa=0$ ). Both raters resolved all discrepancies and achieved consensus (table 2).<sup>↓</sup>

Sample size calculations were missing for some studies,<sup>25-27</sup> and the calculations were based on the endpoint bacteriuria rather than symptomatic urinary tract infection for another study.<sup>8</sup> One study did not achieve the required sample size.<sup>7</sup> On the other hand, there were no missing data and no crossovers were reported.

The conference abstract of an unpublished study described a randomized controlled trial from the Netherlands.<sup>28</sup> In this study, 288 patients were randomized to either nitrofurantoin prophylaxis or placebo at time of catheter removal. Symptomatic urinary tract infections occurred in 18/151 (11.9%) of the intervention group and 12/137 (8.8%) of the control group; these rates were not significantly different. The one non-randomized prospective study evaluated antibiotic prophylaxis in 729 consecutive patients who underwent laparoscopic radical prostatectomy. In this study, patients were given antibiotic prophylaxis (a three day course of ciprofloxacin starting the day before catheter removal) if they were seen by surgeon A or no prophylaxis if the procedure was done by surgeon B.<sup>29</sup> Fewer patients in the intervention group experienced urinary tract infections (3.1% v 7.3%;  $P=0.02$ ). Additionally, the numbers of urinary tract infections in the various arms in the study reported by Harding and colleagues<sup>26</sup> were difficult to discern from the published text and were therefore confirmed via email with one of Harding's coauthors (L Nicolle, personal communication). Five out of seven included studies focused on surgical patients, including two studies in urology patients.

The meta-analysis indicated an overall reduction in symptomatic urinary tract infection when antibiotic prophylaxis was given, with a risk ratio of 0.45 (95% confidence interval 0.28 to 0.72) compared with controls<sup>7 8 25-29</sup> (fig 2<sup>↓</sup>). The absolute reduction of symptomatic urinary tract infection was 5.8% (31/665 (4.7%) in the antibiotic prophylaxis group v 90/855 (10.5%) in the control group). The number needed to treat to prevent one symptomatic urinary tract infection was 17 (95% confidence interval 12-30), with low heterogeneity ( $I^2=16\%$ ).

We repeated the meta-analysis without the single non-randomized study<sup>29</sup>; the risk ratio in the remaining six studies was 0.45 (95% confidence interval 0.23 to 0.86) and not different from the main analysis. The meta-analysis was also repeated without the single unpublished trial<sup>28</sup>; the pooled risk ratio was only slightly changed with 0.36 (0.22 to 0.59), again pointing to a benefit of antibiotic prophylaxis. Finally, we limited the analysis to studies conducted with surgical patients, and the risk ratio remained unchanged (0.45; 0.29 to 0.70). In contrast, when we pooled results from the two studies in mixed hospital populations<sup>26 27</sup> we found no significant advantage of the intervention (0.44; 0.02 to 9.40).

There was significant variation in the duration of monitoring after catheter removal, ranging from about four days in the study of Pfefferkorn and colleagues<sup>7</sup> to six weeks in the study by Pinochet and colleagues.<sup>29</sup> Also, various antimicrobial agents were used (trimethoprim/sulfamethoxazole, ciprofloxacin, nitrofurantoin, and a cephalosporin). The duration of prophylaxis ranged from single dose administration<sup>8 26</sup> to three day courses.<sup>29</sup>

The study by Harding and colleagues also had an arm in which patients were given a 10 day course of antibiotics<sup>26</sup>; this arm was not considered in our meta-analysis because 10 days was thought to represent pre-emptive treatment rather than prophylaxis.

The funnel plot (fig 3<sup>↓</sup>) suggests some publication bias, but funnel plots can be difficult to interpret if the number of included studies is small.<sup>16</sup> In addition, asymmetrical funnel plots are not sufficient proof of publication bias. Alternative explanations for asymmetry include heterogeneity between studies with the intervention fidelity or outcome assessment, as well as improved standard of care in the control groups as routine management evolves over time, which reduces the observed effect size. It is also possible that an asymmetric funnel plot is the result of chance alone.<sup>30</sup>

## Discussion

In our meta-analysis of pooled data from seven studies (six of which were randomized), there were significantly fewer symptomatic urinary tract infections in patients receiving prophylaxis during removal of a urinary catheter than in those not receiving prophylaxis. Our finding in favor of antibiotic prophylaxis, however, must be tempered by possible publication bias toward positive studies, the limitations of the included studies, and practical considerations about encouraging more widespread antibiotic use.

Indwelling urinary catheters pose several risks to patients, including urethral trauma, discomfort, and urinary tract infection.<sup>31</sup> In an era of increasingly constrained fiscal resources and evolving antibiotic resistance, evidence based antimicrobial prescribing is essential to promote antimicrobial stewardship.<sup>32</sup> Unfortunately, there is no consensus on whether clinicians should prescribe antibiotic prophylaxis to patients when an indwelling urinary catheter is removed.

## Current practice and variation in study designs

Administration of prophylactic antibiotics at the time of removal of a catheter might already be common practice, particularly among urologists. In a survey by Wazait and colleagues, conducted in 2004, antibiotic prophylaxis at the time of catheter removal was practiced by 60% of respondents from various medical specialties, and 40% of urologists indicated that they used antibiotic prophylaxis in all patients.<sup>9</sup> At the time of that survey, however, little objective evidence was available to guide management of bacteriuria after catheterization.<sup>26 27</sup> Variation in clinical practice is therefore not surprising given the inconclusive evidence at that time.<sup>33</sup> In addition, the survey by Wazait and colleagues showed that there was heterogeneity in the selection and duration of prophylactic antimicrobial agents.<sup>9</sup> This variation in practice was also evident in the trials included in our meta-analysis and precludes any formal recommendations about choice of antibiotics or duration of treatment.

Ciprofloxacin and trimethoprim/sulfamethoxazole were the most common drugs used, followed by nitrofurantoin (one study) and cefotaxime (in the oldest study). Dose varied from single dose to multiple day administration. Of note, current patterns of antimicrobial resistance in uropathogens clearly argue against the promotion of the use of both trimethoprim/sulfamethoxazole and ciprofloxacin.<sup>34-36</sup> Nitrofurantoin, although its activity is limited to the lower urinary tract, has broad activity against Gram positive and Gram negative pathogens and an acceptable toxicity profile and is not associated with important resistance issues.<sup>28</sup>

## Implications of promoting antibiotic prophylaxis and ideal target population

Antibiotic prophylaxis at the time of catheter removal could lead to a dramatic increase in consumption of antibiotics in hospital, based on the assumption that at least 20% of patients are catheterized at some point during their hospital stay.<sup>37</sup> Limitation of antibiotic prophylaxis to those patients who are bacteriuric would be logistically challenging because all catheterized patients would need to be screened, and the cost of these screening cultures would be substantial. Certain populations of patients, however, are most likely to benefit from antibiotic prophylaxis on catheter removal, and prophylaxis should be focused on these groups, as acknowledged in the AUA guidelines.<sup>10</sup> Future studies should attempt to identify specific populations at risk for the development of urinary tract infections after catheter removal that would be appropriate targets for antibiotic prophylaxis. Also, the results of our meta-analysis are largely driven by data on surgical patients and short term urinary catheters. Only two studies included non-surgical patients,<sup>26 27</sup> and their pooled findings indicated no significant difference between intervention and control group. Additional studies should examine medical patients, including those living in long term care facilities, who might be catheterized for longer. Lastly, the benefit of preventing urinary tract infections should be carefully weighed against the additional cost to the hospital of prophylactic antibiotics, the potential for adverse antibiotic effects, and the impact on resistance patterns of uropathogens. Stochastic modeling and cost effectiveness analyses might be ways to guide future decision making.

Limitations inherent to this meta-analysis include the potential for publication bias, although we also included unpublished abstracts in our search. Their quality grading was based on the subjective assessment of two authors. Furthermore, the included studies were distinctly different in design—with diverse populations of patients, choices of antibiotics, durations of prophylaxis, and a heterogeneous observation period after removal of the catheter—so that standardized recommendations are difficult to make. The largest included study was not randomized but instead compared patients of surgeon A (who gave prophylactic antibiotics) with patients of surgeon B (who did not give prophylactic antibiotics); these surgeons' practices and techniques could have differed in many other ways. Also, some of the studies did not use a placebo in the control arm, and patients' assessment and reporting of urinary symptoms could have been affected by their knowledge of treatment status. Lastly, only two of the included studies recorded information on adverse events associated with the antibiotics, such as drug toxicities, allergic reactions, or infections with *Clostridium difficile*.<sup>7 27</sup> None of the studies looked at the costs of antibiotic prophylaxis or at emerging antimicrobial resistance. Clinicians must assimilate these uncertainties when weighing advantages and disadvantages of implementing antibiotic prophylaxis after urethral catheterization.

## Conclusions

This meta-analysis of available data indicates an overall benefit of antibiotic prophylaxis at the time of removal of a urinary catheter to prevent subsequent urinary tract infections. The number needed to treat indicates that 17 patients would need to receive prophylaxis to prevent one symptomatic urinary tract infection. We know little, however, about the potential negative consequences of implementing antibiotic prophylaxis in this setting in a wider frame or indeed which types of patients would be most likely to benefit. Increasing antimicrobial resistance, healthcare costs for antibiotics, and the potential for side effects

of antibiotic administration are disadvantages that merit careful review. From a public health standpoint, we should be careful not to encourage antibiotic use when it might not be necessary. The healthcare provider of a catheterized patient, however, might consider antibiotic prophylaxis before catheter removal, after taking individual risk factors into account. Future studies should better characterize who is at risk of developing symptomatic urinary tract infection after catheter removal (whether bacteriuric or not) and then examine antibiotic prophylaxis in those at greatest risk.

We thank Afke Brandenburg, Leeuwarden, Netherlands, for providing additional details for their study, and Graham Colditz, Division of Public Health Sciences, Washington University in St Louis, for his review of the analyses.

Contributors: JM and BWT designed the study. JM and SF did the literature search. JM and BWT reviewed studies with regard to inclusion/exclusion criteria and identified the studies that were eventually included in this meta-analysis. JM and CRC assessed the quality of included studies. JM, CRC, and BWT analyzed the data. JM wrote the draft manuscript with input regarding the study methodology from SF and CRC. All authors reviewed the final manuscript critically and authorized the submission. JM is guarantor.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. BWT was funded during the time of manuscript preparation by a VA Career Development Award from rehabilitation research and development (B4623), by VA HSR&D IIR 09-104, and NIDDK R21 092293. BWT's work is also partially supported by the resources and facilities at the Houston VA Health Services Research and Development Center of Excellence (HFP90-020) at the Michael E DeBakey VA Medical Center. JM received support from the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) award through the NIH NCATS, a career development award (5K12HD001459-13). He is also the section leader for a subproject of the CDC Prevention Epicenters Program grant (U54 CK000162; PI Fraser). In addition, JM is funded by the Barnes-Jewish Hospital Patient Safety and Quality Fellowship Program and by a research grant from the Barnes-Jewish Hospital Foundation and Washington University's Institute for Clinical and Translational Science.

Competing interests: All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required. Because we did not have access to protected health information from patients included in the analyzed studies, review by the Human Research Protection Office at Washington University was not required.

Data sharing: No additional data are available.

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**What is already known on this topic**

Catheterization of the urinary tract is associated with an increased risk of bacteriuria and symptomatic urinary tract infection

Antibiotic administration at the time of removal of a urinary catheter might effectively reduce urinary tract infections, but guidelines for catheter associated infections note insufficient evidence to support this practice

**What this study adds.**

Antibiotic prophylaxis at the time of urinary catheter removal in general surgery, prostatectomy, and medical patients effectively reduced the incidence of symptomatic urinary tract infections with a number needed to treat of 17

The effect size of antibiotic prophylaxis in this meta-analysis was stable to sensitivity analyses with exclusion of non-randomized trials and two studies in non-surgical patients

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Accepted: 13 May 2013

Cite this as: *BMJ* 2013;346:f3147

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## Tables

**Table 1 | Summary of studies on effect of antibiotic prophylaxis for urinary tract infections after removal of urinary catheter included in this meta-analysis**

Author	Year published	Design	Patients analyzed	Median duration of catheterization (days)		Antibiotic used	No of cases*		Observation period
				Antibiotics	Control		Antibiotics	Control	
Van Hees <sup>8</sup>	2011	Randomized, placebo	91 general surgery	5/6	4.5	Ciprofloxacin (n=31) or TMP/SMX (n=24) x1 dose before removal	1/55	1/36	2 weeks
Pinochet <sup>29</sup>	2010	Prospective, comparative (patients of surgeon A vs. surgeon B)	713 radical prostatectomy	11	7	Ciprofloxacin (3 day course starting day before removal)	8/261	33/452	6 weeks
Pfefferkorn <sup>7</sup>	2009	Randomized, no placebo	205 abdominal surgery	7	6.5	TMP/SMX (3 doses, first before removal) or ciprofloxacin	5/103	22/102	4 ±2 days after catheter removal
Brandenburg <sup>28</sup>	2006	Randomized, placebo	288 general surgical	3	33	Nitrofurantoin (2 doses, first before removal)	12/137	18/151	4 weeks
Wazait <sup>27</sup>	2004	Randomized, placebo	48 on medical and surgical wards, excluding genitourinary surgery	3.8	3.6	Ciprofloxacin (4 doses, two daily, first before removal)	2/25	1/23	2 weeks
Harding <sup>26</sup>	1991	Randomized, no placebo	79 women on medical and surgical wards with bacteriuria	2.	2	TMP/SMX (single dose)	0/37	7/42	4 weeks (prophylaxis) v 2 weeks (no prophylaxis)
Grabe <sup>25</sup>	1984	Randomized, no placebo	96 transurethral prostatectomy	1.9	1.8	Cefotaxime (3 doses, two daily, first before removal)	3/47	8/49	1 week

TMP/SMX=trimethoprim/sulfamethoxazole.

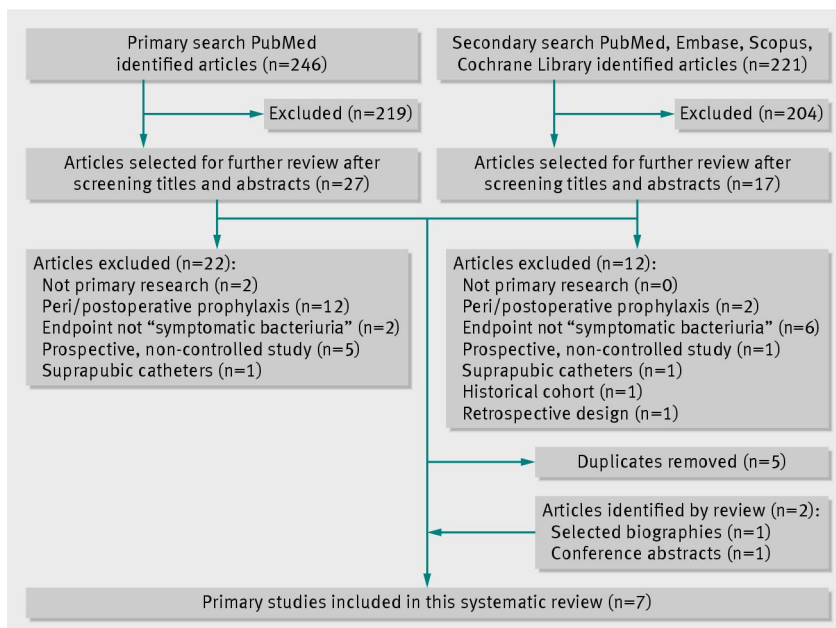
\*Total was 31/665 (4.7%) in antibiotic group and 90/855 (10.5%) in control group.

**Table 2| Assessment of quality in studies on effect of antibiotic prophylaxis for urinary tract infections after removal of urinary catheter included in this meta-analysis**

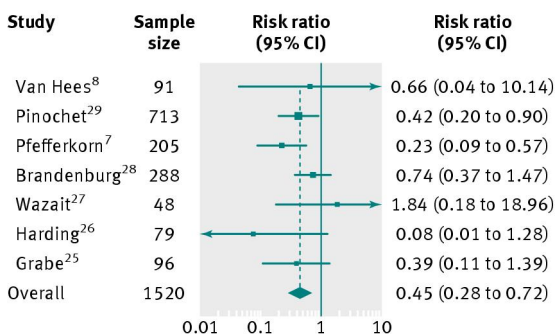
Domain:	Selection bias	Performance bias	Attrition bias	Detection bias
Van Hees <sup>6</sup>	0	0	0	0
Pinochet <sup>29</sup>	1	1	1	1/0
Pfefferkorn <sup>7</sup>	0	0	0/1	0
Brandenburg <sup>28</sup>	1	1	1	0
Wazait <sup>27</sup>	0	0	0	0
Harding <sup>26</sup>	1	0	1	0
Grabe <sup>25</sup>	1	0	1	0
Rating agreement (κ)	1.0	1.0	0.7	NA

NA=not applicable; 0=low risk; 1=high risk or uncertain.

## Figures

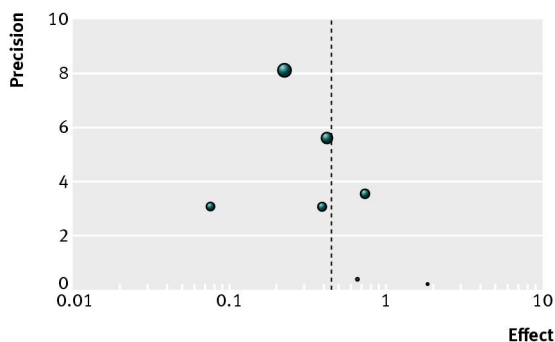


**Fig 1** Selection of studies for meta-analysis of trials investigating antibiotic prophylaxis for urinary tract infections after removal of urinary catheter



Cochrane's Q test:  $\chi^2=7.13$ ,  $P=0.31$ ,  $I^2=0.16$

**Fig 2:** Forest plot of seven included studies with 1520 participants on effect of antibiotic prophylaxis on urinary tract infections after removal of urinary catheter



**Fig 3** Funnel plot of seven included studies with 1520 participants on effect of antibiotic prophylaxis on urinary tract infections after removal of urinary catheter