Original Article

Catheter-Associated Urinary Tract Infections in Adult Patients

Preventive Strategies and Treatment Options

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Summary

Background: Urinary tract infections are among the more common types of nosocomial infection in Germany and are associated with catheters in more than 60% of cases. With increasing rates of antibiotic resistance worldwide, it is essential to distinguish catheter-associated asymptomatic bacteriuria from catheter-associated urinary tract infection (CA-UTI).

Methods: This review is based on publications from January 2000 to March 2019 that were retrieved by a selective search in Medline. Randomized clinical trials and systematic reviews in which the occurrence of CA-UTI in adult patients was a primary or secondary endpoint were included in the analysis. Two authors of this review, working independently, selected the publications and extracted the data.

Results: 508 studies were identified and 69 publications were selected for analysis by the prospectively defined criteria. The studies that were included dealt with the following topics: need for catheterization, duration of catheterization, type of catheter, infection prophylaxis, education programs, and multiple interventions. The duration of catheterization is a determinative risk factor for CA-UTI. The indications for catheterization should be carefully considered in each case, and the catheter should be left in place for the shortest possible time. The available data on antibiotic prophylaxis do not permit any definitive conclusion, but they do show a small benefit from antibiotic-impregnated catheters and from systemic antibiotic prophylaxis.

Conclusion: Various measures, including careful consideration of the indication for catheterization, leaving catheters in place for the shortest possible time, and the training of nursing personnel, can effectively lower the incidence of CA-UTI. The available evidence is markedly heterogeneous in some respects, and thus no recommendations can be given on certain questions relevant to CA-UTI.

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Urinary tract infections account for 21.6% of all nosocomial infections in Germany and are thus among the more frequent types of nosocomial infection, along with lower respiratory infections (24%), postoperative wound infections (22.4%), Clostridium difficile infections (10%), and primary sepsis (5.1%) (1, 2).

In more than 60% of cases (407 of 670 patients), nosocomial urinary tract infections are associated with catheters (2, 3). 15–25% of all hospitalized patients are catheterized at some time during their hospital stay (4); among patients in intensive care units, the corresponding percentage has been reported as 18% to 81.7% (5–7). The incidence of bacteriuria in medical facilities rises by 3–8% per day for each day after catheter insertion; nearly all patients have bacteriuria after 30 days of catheterization (8, 9). Most episodes of catheter-associated bacteriuria are asymptomatic (catheter-associated asymptomatic bacteriuria, CA-ABU), and fewer than 5% of cases lead to bacteremia requiring treatment (10). Overall, catheter-associated bacteremia accounts for 15% of nosocomial bloodstream infections (11) and is associated with 10% mortality (12, 13).

With antibiotic resistance on the rise and presenting major challenges, including increased costs, to health-care systems worldwide (14), it has become essential to distinguish CA-ABU, which needs no treatment, from CA-UTI, which must be treated (15).

The goal of this article is to provide an overview of urinary catheter management and UTI prevention.

Method

A rapid evidence analysis (16) was performed with a literature search in Medline for the period January 2000 to March 2019. Symptomatic CA-UTI in adults was a primary or secondary endpoint of all of the included studies. Only randomized trials and systematic reviews were included in the present analysis. Further information on the methods of this analysis can be found in the supplementary material available over the Internet *(eBox)*.

Results

Findings of the literature search

The literature search yielded 508 hits *(eFigure),* of which 69 studies were included in the analysis

The clinical perspective

- An important distinction is drawn between catheter-associated asymptomatic bacteriuria (CA-ABU), which does not need to be treated, and catheter-associated urinary tract infection (CA-UTI), which needs treatment with antimicrobials.
- In choosing the appropriate antibiotic, the physician must considered the local resistance situation, both to optimize the efficacy of treatment and to avoid the further selecting out of resistant organisms.
- So-called antibiotic stewardship must be borne in mind whenever antimicrobial drugs are given. This term refers to the rational, responsible use of such drugs, comprising an appropriate choice of drug as well as appropriate dosing, mode of administration, and adaptation of the duration of treatment. The goal is to treat patients optimally while preventing the development of resistance.
- The duration of catheterization (i.e., the length of time that a catheter is in place) is a determinative risk factor for CA-UTI. It follows that the indication for catheterization must always be critically considered, and that the catheter should be left in place for the shortest possible time.
- Various measures (critical consideration of the indication for, and duration of, catheterization; education of nursing staff, etc.) should be bundled, in order to keep the risk of CA-UTI as low as possible for every patient.

(eTable). The included studies were thematically clustered: need for catheterization (n = 2), duration of catheterization (n = 11 studies), type of catheter (n = 17), prophylaxis (n = 25), education programs (n = 9), and studies with multiple interventions (n = 5). A total of 28 systematic reviews (including nine Cochrane reviews [6–15]) and 41 randomized, controlled trials (RCTs) were identified.

Need for catheterization

The authors of a systematic review (SR) concluded that the routine insertion of indwelling catheters in women undergoing cesarean section was associated with more risk than benefit (relative risk [RR] of urinary tract infection in non-catheterized vs. catheterized patients in two RCTs, 0.08, with 95% confidence interval [0.01; 0.64]; RR in a single non-randomized study, 0.10 [0.02, 0.57]) (17).

Duration of catheterization

The time during which a catheter was left in place, after insertion at varying time points associated with gynecological interventions, was studied in nine RCTs (18–26). The catheters were removed either immediately after surgery or within 24 hours (18, 19, 25, 27). Bray et al. and Hakvoort et al. chose removal after 48 to 72 hours as the condition for the comparison group (20, 24). Weemhoff et al. compared catheterization times of two vs. five days (26). The authors of all of these RCTs concluded that the catheter should be left in place for as short a time as possible to minimize the frequency of urinary tract infection. The rate of CA-UTI was significantly lowered by this strategy in some, but not all studies (18, 20, 23–26), but no adverse side effects were encountered.

A single systematic review was identified that dealt with the duration of catheterization. This review included data from patients who were catheterized for ambulatory or inpatient surgery, as well as patients in nursing institutions (28). There were a total of 741 included patients from eight separate RCTs. In four of them, no significant differences in CA-UTI rates were found in patients who had undergone either transurethral resection of the prostate (TURP) or gynecological procedures (RR: 0.55; [0.30; 1.03]). In one RCT that compared catheterization for 1 vs. 5 days, a significant difference in the CA-UTI rate was, indeed, demonstrable: the rate was twice as high in the latter group (RR: 0.48; [0.27; 0–85]).

Two Cochrane reviews dealing with transurethral and suprapubic catheterization were included as well (29, 30). Cooper et al. reported that the CA-UTI rate was 65% lower when catheters were regularly changed (monthly and/or when medically indicated, vs. only when medically indicated) (RR: 0.35; [0.13; 0.95]) (29). Phipps et al. studied the following durations of catheterization: one vs. two days (48% fewer CA-UTIs with the shorter interval) (one study: RR: 0.52; [0.05; 5.40]), one vs. three days (three studies, not pooled, constituting one-third of the primary studies with a significant finding [RR: 0.11; (0.03; 0.43)]), one day vs. five days (two studies, not pooled), and one vs. 14 days (one study). Although most of these studies did not show a statistically significant benefit for the shorter interval, the point estimators nonetheless uniformly indicated that the shorter duration was advantageous (30).

Peri- and postoperative catheterization

A single RCT investigated perioperative transurethral catheterization in patients undergoing knee replacement surgery (31). Two different protocols were compared: preoperative catheterization (n = 306) vs. catheterization as needed for postoperative urinary retention (n = 346). The CA-UTI rate was 1.6% (5/306) in the former group and 1.7% (6/346) in the latter.

Type of catheter

Temporary transurethral vs. suprapubic catheterization

Three RCTs (32–34) and three SRs (35–37) on this topic were identified, the latter including one Cochrane review (37). Only two publications included urological interventions (33, 34). These studies did not reveal any statistically significant differences in CA-UTI rates. The systematic review by Hunter et al. included both experimental studies and clinical observational studies (36). The authors did not conduct any meta-analysis and did not favor either of the two methods of catheterization over the other on the basis of their findings. In contrast, the meta-analysis by Healy et al., which included twelve RCTs, did show a significantly

lower CA-UTI rate with suprapubic catheterization (OR: 0.31; [0.18; 0.51]) (36). The meta-analysis that was part of the Cochrane review by Kidd et al., in which five RTCs with a total of 575 patients were included, did not reveal any difference in CA-UTI rates between the two methods of catheterization (RR: 1.01; [0.61; 1.69]) (37).

Intermittent (self-)catheterization vs. temporary indwelling catheters

Two RCTs (38, 39) and one SR were identified (e1) in which intermittent (self-)catheterization was compared with the use of temporary indwelling catheters. Hakvoort et al. reported a significantly ($p = 0.03$) lower CA-UTI rate with intermittent catheterization compared to an indwelling catheter left in place for three days (38). Hälleberg Nyman et al. included 182 patients who had undergone hip surgery; they concluded that both approaches are clinically acceptable (39). The absolute risk difference in the group that underwent intermittent catheterization was only 2.4%, a statistically insignificant effect (8 out of 85 patients with CA-UTI in the intermittently catheterized group, vs. 10 out of 85 patients in the group with indwelling catheters). Nor was any statistically significant difference found in the meta-analysis by Zhang et al. (9 RCTs; 1771 patients; RR: 1.23; [0.85; 1.76]) (e1).

Clamping vs. free urinary drainage

Intermittent catheter clamping can be used as a method of training the bladder (the bladder fills while the catheter is clamped and empties during the period of free drainage). One RCT (e2) and two SRs (e3, e4) were identified that dealt with this question. The RCT did not reveal any statistically significant difference between the two groups (210 women who had undergone hysterectomy; CA-UTI in 22.9% vs. 20.3%) (e2). In a systematic review, Fernandez et al. referred to an RCT in which three different modes of catheter management were compared (e3): intermittent clamping for 72 hours (group 1) vs. free drainage and removal after 24 hours (group 2) vs. free drainage and removal after 72 hours (group 3). 106 women who had undergone gynecological surgery were included. No significant differences were found in the rates of CA-UTI with free drainage for 24 hours vs. clamping (RR: 1.12 [0.24; 5.18]) or with free drainage for 72 hours vs. clamping (RR: 0.55; [0.15; 2.01]). Likewise, Wang et al., in a meta-analysis, did not find any statistically significant difference between clamping and free drainage (four RCTs; OR: 0.76; [0.33; 1.73]) (e4). They concluded that the limited available evidence provided no reason to alter the current clinical practice of free drainage.

Irrigation vs. no irrigation

A Cochrane review was devoted to the question whether some catheter irrigation schemes might be better than others with respect to efficacy, acceptability to patients, complication rates, and quality of life (e5). One of the RCTs cited compared irrigation with normal saline to no irrigation at all; in this trial, however, none of the patients in either group developed a CA-UTI.

Stabilization dressings with a catheter attachment or valve

An RCT dating back to 2006 investigated the effect of the StatLock system (e6), a stabilization dressing with a catheter attachment, serving the purpose of securing the catheter and thereby lessening the risk of inadvertent dislocation.

In the intervention group (60 of the 118 patients in the trial), which received a StatLock, the rate of CA-UTI was 45% lower, but this effect did not reach statistical significance (RR: 0.55; [0.25; 1.22]). One SR addressed the question whether a system with a valve was more beneficial than a simple bag to receive the urine (e7). This SR identified two RCTs on the subject, but results relating to the endpoint CA-UTI were only reported in a single RCT dating back to 1997. 30 of the 50 patients in the intervention group with the valve developed CA-UTI, compared to 34 of 50 in the control group. This 8% absolute difference in infection rates was statistically insignificant ($p = 0.286$).

Prophylaxis

Antibiotic-based prophylaxis strategies

Eleven studies compared the effect of antibiotic catheter impregnation or systemic antibiotic administration with that of no antibiotic prophylaxis at all: five of these were RCTs (e8–e12) and six were SRs (e11, e13–e17), among them four Cochrane reviews (e14–e17). In men who had undergone radical prostatectomy, the use of minocycline combined with rifampicin-impregnated catheters lowered the frequency of CA-UTI (1 in 56, vs. 6 in 68 patients in the control group (single trial, RR: 0.20; [0.03; 1.63]) (e14). A statistically significant difference was likewise found for the use of nitrofural-impregnated catheters compared to standard catheters (single trial; 4297 patients; RR: 0.84; [0.71; 0.99]) (e15), as well as for the systemic intravenous administration of trimethoprim/sulfamethoxazole (single trial; 90 patients; RR: 0.20; [0.06; 0.66]) (e16). The systematic prophylactic administration of antibiotics was also found to be superior to antibiotic administration only when clinically indicated, with respect to the frequency of CA-UTI (single trial; 90 patients; RR: 020; [0.06; 0.66]) (e17).

In their SR, Marschall et al. similarly reported a clinical benefit in the group of patients that received systemic antibiotic prophylaxis (cefotaxime, trimethoprim/sulfamethoxazole, ciprofloxacin, or Nitrofurantoin), with a modest absolute risk reduction of 5.8% (six RCTs, one observational study; RR: 0.45; [0.28; 0.72]). They calculated a number needed to treat (NNT) of 17 (95% confidence interval, 12 to 30) to prevent a single CA-UTI. On the other hand, no benefit was found in the SR by Van Hees et al., which included patients who had undergone surgery and received a single prophylactic antibiotic dose (trimethoprim/sulfamethoxazole [n = 46] or ciprofloxacin [n = 43] vs. placebo [n = 51]) (e18).

TABLE

The state of the evidence

Question	Best current answer
Indication for catheterization	Routine catheterization often has more risks than benefits. The need for catheterization should always be critically considered.
Duration of catheterization	CA-UTI is more common when catheters are left in place for longer times. The duration of catheterization should, therefore, be kept as short as possible.
Peri- and postoperative catheterization	No randomized trials in urology were carried out on this topic in the period of the publications reviewed here, so no statement for clinical practice can be made.
Transurethral vs. suprapubic catheterization	Transurethral catheters probably have no advantage over suprapubic ones.
Clamping vs. free urinary drainage	The current evidence does not justify any recommendation.
Irrigation vs. no irrigation	The current evidence does not justify any recommendation.
Antibiotic prophylaxis	Antibiotic prophylaxis lessens the frequency of CA-UTI.
Antiseptic-impregnated catheters	The current evidence does not justify any recommendation.
Antiseptic- vs. antibiotic-impregnated catheters	The evidence is limited. Antibiotic-impregnated catheters may be advantageous.
Cleansing/disinfection of the urethral orifice	No significant differences have been demonstrated among the various methods of cleansing and/or disinfecting the external urethral orifice.
Phytotherapy as prophylaxis	The evidence regarding cranberry products is mixed.

Antiseptic-impregnated vs. standard catheters

13 studies compared the effect of antiseptic catheter surfaces vs. catheters that were not antiseptically treated (e12, e19). In one Cochrane review, a statistically significant advantage of silver-coated catheters was reported (seven RCTs; RR: 0.60; [0.50; 0.73]) (e14). Two other Cochrane reviews from 2012 and 2014 did not reveal any advantage of silver-coated catheters (one RCT; 20 patients; RR: 10; [0.83; 1.2]) (e20); nor did a trial involving 4241 patients (RR: 0.99; [0.85; 1.16] [e15]). Jahn et al. concluded that the currently available data are insufficient as a basis for any recommendation for clinical practice (e20).

Antiseptic-impregnated vs. antibiotic-impregnated catheters

A Cochrane review of 2014 compared catheters with an antiseptic-impregnated surface to catheters with an antibiotic-impregnated surface (e15). The findings suggested an advantage of antiseptic-impregnated catheters compared to nitrofural-impregnated catheters (one study; 4250 patients; RR: 0.84; [071; 1.00]).

Cleansing and/or disinfection of the external urethral orifice

The network meta-analysis of 2018 included 36 studies with a total of 6490 patients and analyzed seven different methods of cleansing and/or disinfecting the external urethral orifice (tap water vs. soapy water vs. normal saline vs. mechanical cleaning alone vs. iodine vs. chlorhexidine vs. antibacterial solution) (e21). According to the authors, current data do not show the superiority of any of these methods over the others with respect to the frequency of CA-UTI (e15). Similarly heterogeneous findings were reported in another SR that included 28 RCTs and nine SRs (e22).

Phytotherapy for prophylaxis

It was investigated in two RCTs (e23, e24) whether the preventive administration of cranberry capsules might prevent the occurrence of CA-UTI. In the study by Gunnarson et al., women with hip fractures were divided into two groups: group 1 received 2 capsules containing 550 mg of cranberry powder three times daily until the fifth postoperative day, while group 2 received a placebo. No statistically significant difference was found in the rate of positive urine cultures ($p = 0.975$): cultures were positive in 19 of 50 patients in the intervention group (38%) and 23 of 61 (38%) in the placebo group (e23). In a study from the USA, the intervention group was given two cranberry capsules twice daily for six weeks after a gynecological procedure, while the control group was given a placebo preparation. The CA-UTI rate was markedly lower in the intervention group: 15 of 80 patients (19%) vs. 30 of 80 patients (38%) with positive urine culture; OR: 0.38; [0.19; 0.79]) (e24).

Education programs

Nine studies were found that dealt with educational approaches, among them five RCTs (17, e25–e28) and four systematic reviews (e29–e32). Education programs in the hospital were systematically assessed by Meddings et al., who pooled the results in a meta-analysis. It was found that the frequency of CA-UTI can be reduced by 52% by a reminder system or a defined catheter removal timepoint, and this effect is highly statistically significant (seven trials; RR: 0.48;

Key messages

- There is no evidence of any difference between transurethral and suprapubic catheterization with respect to the development of catheter-associated urinary tract infection.
- Nor are there any relevant differences among the various types of catheter material (latex vs. silicone vs. polyvinyl chloride vs. polyurethane) with respect to the endpoint "catheter-associated urinary tract infection."
- The putative benefit of antiseptically coated catheters, compared to uncoated standard catheters, is unclear. Antibiotically impregnated catheters seem to be associated with fewer catheter-associated urinary tract infections than antiseptically coated ones.
- None of the various methods of cleansing and/or disinfecting the external urethral orifice for transurethral catheterization is better than the others with respect to the development of catheter-associated urinary tract infection.
- The current state of the evidence on phytotherapy for the prevention of catheter-associated urinary tract infection does not justify the issuance of any recommendation for clinical practice.

[0.28; 0.68]; p = 0.001) (e31). A systematic review including 29 studies likewise showed that protocols for nurses can lower the rate of CA-UTI. In a further SR, the efficacy of the implementation of prevention protocols in nursing institutions was described (e30). The authors concluded that little attention has been paid to CA-UTI prevention until now and that the available evidence is too heterogeneous to derive a coherent synthesis of the results.

Studies involving multiple interventions

Studies involving multiple interventions have shown that transurethral catheters left in for a short period of time (24 hours) are superior to suprapubic catheters left in for a longer period of time (96 hours) (p = 0.034) (e33).

Discussion

Even though our literature search revealed a large number of existing studies on the prevention and management of CA-UTI, the results with respect to duration of catheterization, catheter type, and prophylaxis are highly heterogeneous, and the state of the evidence is still limited. Moreover, the definition of the endpoint and the distinction between CA-UTI and CA-ABU is highly heterogeneous in the primary studies. Some of them use the term CA-UTI to describe catheter-associated asymptomatic bacteriuria or catheter-associated bacteriuria. Many of the relevant studies date back to the 1990s or to the first decade of the present century. The applicability of their findings—in particular, those relating to antibiotic prophylaxis—to the current clinical situation is uncertain, as antibiotic prescribing practices and resistance patterns may well have changed in the meantime.

A study from the USA showed that 41% of treating physicians did not know that the patient under their care was catheterized, and that there was no medical indication for catheterization in 31% of the catheterized (e34). Further studies yielded similar figures (25–63%) with respect to catheterizations that were not medically indicated and/or not ordered by a physician (e35).

Umscheid postulated in 2011 that 65–70% of catheter-associated bloodstream infections and CA-UTI could have been prevented with the (then) current evidence-based strategies (e36). He calculated that the number of preventable infections of these types in the USA lies in the range of 95 483 to 387 550 per year (e36). The costs of preventable CA-UTIs was estimated to be in the range of 115 million to 1.82 billion dollars per year (e36).

Overview

Even though many studies have been published on the questions that are asked in this review, the state of the evidence is highly heterogeneous, and the comparability of the studies is very limited. It is, therefore, difficult to synthesize their results coherently.

Nonetheless, a small number of concise conclusions are stated in detail in the *Table*, so that physicians will have a few useful recommendations for practice that are based on the scientific literature and thus represent a successful transfer of knowledge from research to everyday clinical routine.

Conflict of interest statement

PD Dr. Kranz has served as a paid consultant for Farco-Pharma.

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The remaining authors state that they have no conflict of interest.

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► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref0620

eFigures, eBoxes, eTables:
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Supplementary material to:

Catheter-Associated Urinary Tract Infections in Adult Patients

Preventive Strategies and Treatment Options

by Jennifer Kranz*, Stefanie Schmidt*, Florian Wagenlehner, and Laila Schneidewind

Dtsch Arztebl Int 2020; 117: 83–8. DOI: 10.3238/arztebl.2020.0083

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eBOX

Search strategy

A literature search was carried out in March 2019 in the Medline biomedical database (via Ovid). The search terms—"urinary tract infections," "complicated urinary tract infections," "cystitis," "pyelonephritis," "percutaneous nephrostomy," "catheters," "pcnl"—were entered as MesH terms and as free text. The search strategy is shown below.

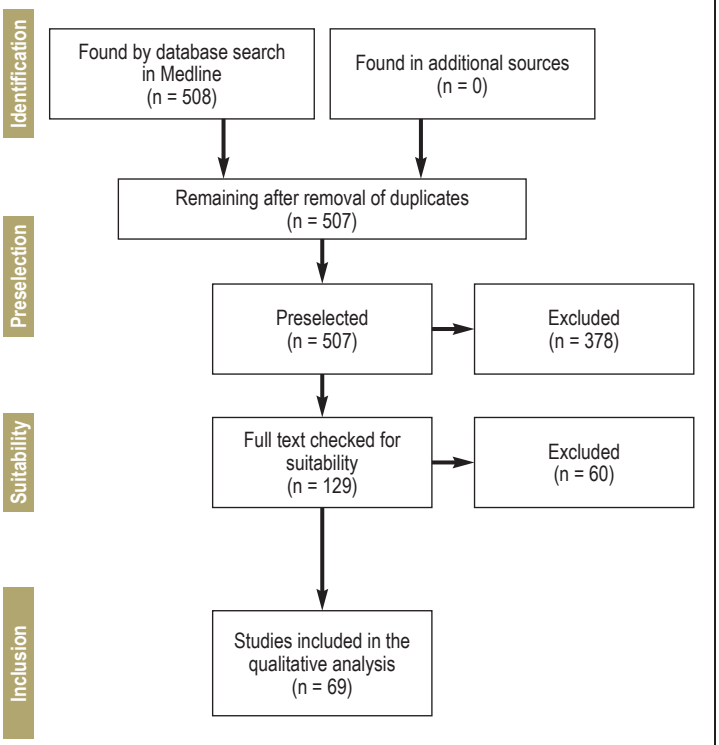
We included only randomized, controlled trials (RCTs) and systematic reviews (SRs). Studies dealing with any type of intervention in catheterized adults in either the inpatient or outpatient setting were included as long as symtpomatic catheter-associated urinary tract infection was a primary or secondary endpoint. Only full-text publications in English or German from the year 2000 or later were included. Studies on catheter-associated bacteriuria were not included.

Two authors of the present review (JK and SS) independently screened the retrieved publications and checked them for suitability for inclusion according to the above criteria. The following study data were extracted by two of the authors (SS, LS): study information and objective, patient population, description of intervention, endpoints, and authors' conclusions.

Medline Ovid: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

1 exp urinary tract infections/
2 exp cystitis/
3 exp pyelonephritis/
4 exp Percutaneous Nephrostomy/
5 cystitis.tw.
6 complicated urinary tract infection*.tw.
7 urinary tract infection*.tw.
8 uti.tw.
9 cauti.tw.
10 pyelonephriti*.tw.
11 exp catheters, indwelling/
12 exp urinary catheters/
13 urinary catheter*.tw.
14 indwelling catheter*.tw.
15 permanent catheter*.tw.
16 suprapubic catheter*.tw.
17 transurethral catheter*.tw.
18 Percutaneous Nephrostomy.tw.
19 (pcn or pcnl).tw.
20 or/1–10
21 or/11–17
22 18 or 19
23 21 or 22
24 20 and 23
25 Randomized Controlled Trials as Topic/
26 randomized controlled trial/
27 Random Allocation/
28 Double Blind Method/
29 Single Blind Method/
30 clinical trial/
31 clinical trial, phase i.pt.
32 clinical trial, phase ii.pt.
33 clinical trial, phase iii.pt.
34 clinical trial, phase iv.pt.
35 controlled clinical trial.pt.
36 randomized controlled trial.pt.
37 multicenter study.pt.
38 clinical trial.pt.
39 exp Clinical Trials as topic/
40 or/25–39
41 (clinical adj trial$).tw.
42 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
43 PLACEBOS/
44 placebo$.tw.
45 randomly allocated.tw.
46 (allocated adj2 random$).tw.
47 or/41–46
48 40 or 47
49 case report.tw.
50 letter/
51 historical article/
52 or/49–51
53 48 not 52
54 Meta-Analysis as Topic/
55 meta analy$.tw.
56 metaanaly$.tw.
57 Meta-Analysis/
58 (systematic adj (review$1 or overview$1)).tw.
59 exp Review Literature as Topic/
60 or/54–59
61 cochrane.ab.
62 embase.ab.
63 (psychlit or psyclit).ab.
64 (psychinfo or psycinfo).ab.
65 (cinahl or cinhal).ab.
66 science citation index.ab.
67 bids.ab.
68 cancerlit.ab.
69 or/61–68
70 reference list$.ab.
71 bibliograph$.ab.
72 hand-search$.ab.
73 relevant journals.ab.
74 manual search$.ab.
75 or/70–74
76 selection criteria.ab.
77 data extraction.ab.
78 76 or 77
79 Review/
80 78 and 79
81 Comment/
82 Letter/
83 Editorial/
84 animal/
85 human/
86 84 not (84 and 85)
87 or/81–83,86
88 60 or 69 or 75 or 80
89 88 not 87
90 24 and 53
91 24 and 89
92 90 or 91
93 limit 92 to (english or german)
94 limit 93 to yr="2000 -Current"
95 limit 94 to humans

eFIGURE



PRISMA flow diagram for the sequential phases of the systematic review (e37). For further information, see www.prisma-statement.org.