

Relationship of catheter-associated urinary tract infection to mortality and length of stay in critically ill patients: A systematic review and meta-analysis of observational studies

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Objective: To determine whether catheter-associated urinary tract infections are associated with increased morbidity and mortality in critically ill patients.

Data Sources: MEDLINE, HealthStar, EMBASE, and CINAHL databases from inception to June 2010 and bibliographies of included studies without language restriction.

Study Selection: Studies reporting mortality or morbidity in adult intensive care unit patients with and without catheter-associated urinary tract infections.

Data Extraction: Two authors independently selected studies and extracted data on study methodology, quality, and patient outcomes using a standardized form. Meta-analyses were performed using random-effects models.

Data Synthesis: Of 720 citations, 11 studies enrolling 2,745 patients with and 60,719 patients without catheter-associated urinary tract infections met inclusion criteria. Catheter-associated urinary tract infection was associated with a significant increase in mortality (odds ratio [OR], 1.99; 95% confidence interval [CI], 1.72–2.31; $p < .00001$; $I^2 = 54%$; eight studies; 62,063 patients) and length of stay in the intensive care unit (weighted mean difference of + 12 days; 95% CI, 9–15; $p < .00001$; $I^2 = 96%$; seven studies; 13,011 patients) and hospital (mean difference + 21 days; 95% CI, 11–32; $p < .0001$; $I^2 = 98%$; five studies; 10,183 patients). Restricting the analysis only

to the two studies that adjusted for other outcome predictors, catheter-associated urinary tract infections were not associated with an increase in mortality (OR, 0.97; 95% CI, 0.82–1.16; $p = .77$; $I^2 = 0%$; two studies; 5,626 patients). Although both studies individually demonstrated significantly increased intensive care unit length of stay after adjustment, pooled data showed that catheter-associated urinary tract infections were associated with a significant increase in intensive care unit length of stay using only a fixed effects model (mean difference + 2.6 days; 95% CI, 2.3–3.0; $p < .00001$) and not a random effects model (mean difference + 8 days; 95% CI, –13 to +28 days; $p = .46$) due to the high degree of heterogeneity for this outcome between the two studies ($I^2 = 99.6%$) which results in a larger CI.

Conclusions: Catheter-associated urinary tract infection is associated with significantly increased mortality and length of stay in unmatched studies. Increased mortality and possibly increased length of stay appear to be consequences of confounding by unmeasured variables. These findings highlight the importance of evaluating risks and benefits of commonly used treatments such as antibiotics to manage catheter-associated urinary tract infection. (Crit Care Med 2011; 39:1167–1173)

KEY WORDS: catheter; urinary tract infections; mortality; critically ill

Catheter-associated urinary tract infection (CAUTI) is one of the most common nosocomial infections in intensive care units (ICUs) (1). Nosocomial CAUTI is associated with large antimicrobial use resulting in the urinary tract being a reservoir of antimicrobial-resistant pathogens that may cause other more serious infections (2). Recent practice guidelines

(3) emphasized the challenges associated with the management of CAUTI in the ICU: the need for urinary catheters, the lack of reliable diagnostic tests to differentiate between colonization and infection, the paucity of controlled studies to guide treatment, the low rates of progression from CAUTI to bacteremia or fungemia, and the general perception that CAUTI is of low risk to patients (4, 5).

Despite this perception of minimal risk, CAUTI is frequently treated with antimicrobials even in asymptomatic patients (6, 7). This potentially inappropriate use of antimicrobials may contribute to the problematic issue of rising antimicrobial resistance and healthcare costs. The discordance between the perceived low risk of CAUTI and frequent prescription of antimicrobials may reflect conflicting published reports. Older studies have found CAUTI to be associated with an increased risk of mortality, whereas recent studies that control for potential confounders have not (8–10).

Recent systematic reviews have evaluated the association between two other causes of ICU-related infections, ventilator-associated pneumonia (11, 12) and catheter-related bloodstream infections (13), and mortality. However, no system-

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Dr. Marshall consulted for Eisner, Pfizer, Eli Lilly, and Spectral. Dr. Friedrich is supported by a Clinician

Scientist Award from the Canadian Institutes of Health Research. The remaining authors have not disclosed any potential conflicts of interest.

All work performed at St Michael's Hospital.

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DOI: 10.1097/CCM.0b013e31820a8581

atic review has been conducted for CAUTI, although CAUTI may become the most common infection in ICU patients with the widespread implementation of patient safety prevention bundles designed to reduce the rates of these other infections (14, 15). Indeed, the US Medicare program has stopped hospital payments for treating CAUTI, deeming it a preventable infection (16). The aim of this study is to evaluate the attributable mortality and morbidity of CAUTI in critically ill patients through a systematic review and meta-analysis of available observational studies.

MATERIALS AND METHODS

Data Sources. We searched MEDLINE, HealthStar, EMBASE, and CINAHL electronically from inception to June 2010 using the following key words: urinary catheterization, urinary tract infections, indwelling catheters, sepsis, bacterial infections, cross infections, iatrogenic infections, urosepsis, critical care, critical illness, intensive care unit, morbidity, and mortality. Terms were “exploded” and combined using Boolean operators where appropriate. The search strategy (Appendix 1) was designed with the assistance of a librarian. No language restrictions were applied.

Study Selection. Citations were retrieved and independently reviewed by two investigators (C.C., O.M.S.). Full papers were retrieved and evaluated for citations in which the title or abstract suggested to either reviewer that the study may report mortality or morbidity in critically ill adult patients with and without CAUTI. From this subset, studies that examined CAUTI in adult patients during their ICU stay where most patients would be expected to have urinary catheters in place and that reported either mortality or length of stay (LOS) in patients with and without CAUTI were included. Disagreements regarding inclusion were reconciled by consensus or by a third investigator (J.O.F.).

Data Extraction. A standardized data abstraction form was designed before the literature search. Two unblinded reviewers (C.C., J.O.F.) independently abstracted the following data from included studies: publication related (year and country), ICU characteristics (type, number), study design (prospective/retrospective, matching criteria if used), CAUTI data (definition, number of cases), and outcomes (mortality, ICU, and hospital LOS). These characteristics were used to assess study quality. Selected authors were also contacted to clarify data when it was unclear from the publication.

Data Analysis. Our primary outcome was all-cause mortality in patients with CAUTI compared with patients without CAUTI determined at hospital discharge; 90, 60, 30, or 28 days after study enrollment; or ICU discharge (in descending order of preference). The main

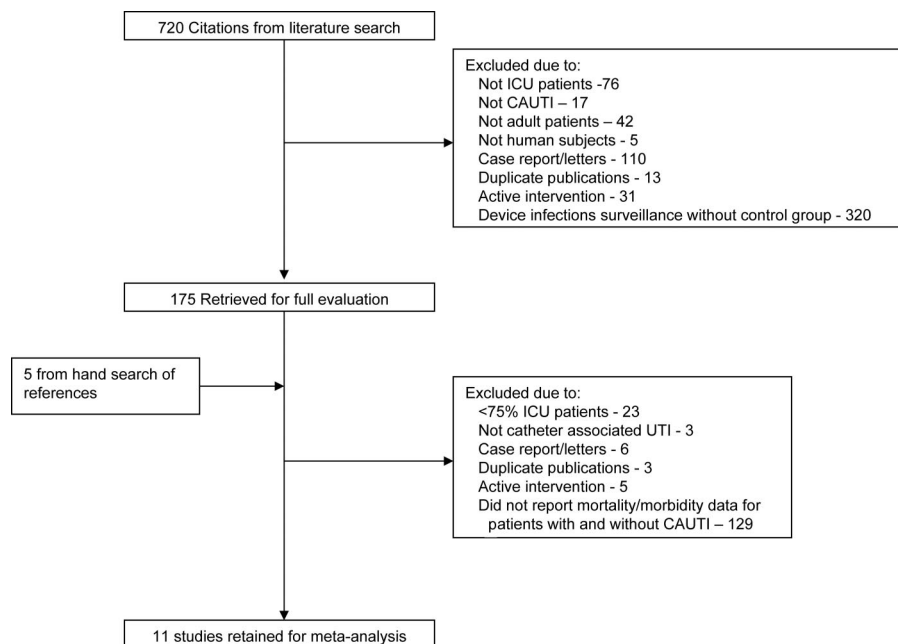


Figure 1. Flow chart of study selection. ICU, intensive care unit; CAUTI, catheter-associated urinary tract infection.

secondary outcomes were ICU and hospital LOS in patients with CAUTI compared with patients without CAUTI. All analyses were performed using Review Manager (RevMan version 4.2.8; Cochrane Collaboration, Oxford, UK). We used a random-effects model that incorporated between-trial heterogeneity and gives wider confidence intervals (CIs) when heterogeneity is present (17). We assessed statistical heterogeneity among trials using I^2 , defined as the percentage of total variability across studies attributable to heterogeneity rather than chance, and used published guidelines for low ($I^2 = 25\text{--}49\%$), moderate ($I^2 = 50\text{--}74\%$), and high ($I^2 > 75\%$) heterogeneity (18). Odds ratios (ORs) were used to pool mortality data and weighted mean differences (MD) to pool LOS data. Medians and ranges were converted to means and variances using published guidelines where required (19). Differences between pooled OR were evaluated using z tests. We considered (two-sided) $p < .05$ as significant and reported individual trial and summary results with 95% CIs. To assess for publication bias, we visually examined a funnel plot comparing effect measure for the primary outcome of mortality with study precision for evidence of asymmetry.

RESULTS

Study Selection. The initial search strategy found 720 citations, of which 175 were retrieved for full review and eight met inclusion criteria (9, 10, 20–25) (Fig. 1). The majority of studies were excluded as a result of non-CAUTI content (eg, vascular catheter-related infec-

tions) and for not reporting outcomes by those with and without CAUTI. Review of references of the selected studies resulted in five additional studies by one research group (26–30) of which three studies reported data that were not duplicated (26–28). One study (20) provided group-specific LOS data but not group-specific mortality rates, and one study (21) provided only mortality data using a control group of noninfected patients (ie, no CAUTI and no other diagnosed infection). Both authors were unable to provide further information when contacted. One citation (31) provided LOS data for those with and without CAUTI, however, in only a subgroup of patients who either survived the ICU stay or were discharged with a urinary catheter still in place. Given the potential bias on LOS data by only reporting on a subgroup, this study was only included in our sensitivity but not our primary analysis.

Description of Included Studies. The characteristics of the studies included in the meta-analysis are described in Table 1. Most studies were prospective (20, 21, 23, 25–28) and multicentered (9, 10, 21, 22, 25–28). Studies included both medical and surgical patients except for two single-center studies that included only trauma patients (20, 24). All but one of the multicenter and one of the four single-center trials specified that all consecutive patients admitted for at least 24

Table 1. Characteristics of selected studies for meta-analysis

Study (Country)	Type/No. of ICUs	Percent of Patients/Percent Patient-Days With Catheters	Study Design Including Patient Enrollment Years	Definition of CAUTI	Incidence of CAUTI	Microbiology of CAUTI ^a
Clec'h (9) (France)	MS 12	100%/NR	Retrospective matched nested case-control; CAUTI only 1997–2005	≥10 ³ CFU/mL of 1 or 2 organisms	12.9/1000 catheter days	GP (16%) GN (60%) F (24%)
Laupland (10) (Canada)	MS, CV 4	NR	Retrospective linked databases; CAUTI only 2000–2002	≥10 ⁵ CFU/mL of 1 or 2 organisms from day 3 of ICU stay or later	9.6/1000 ICU days	GP (22%) GN (49%) F (29%)
Bochicchio (20) (USA)	T 1	98%/NR	Prospective CAUTI only 2000–2002	≥10 ⁵ CFU/mL of 1 or 2 organisms or ≥10 ³ WBC/mm ³ in urinalysis along with symptoms	18/1000 catheter days	NR
Rosenthal (21) (Argentina)	MS 3	NR	Prospective DAI length of stay >7 days 1998–2000	≥10 ⁵ CFU/mL of 1 or 2 organisms with symptoms	23/1000 catheter days	NR
Laupland (22) (Canada)	MS 3	NR	Retrospective linked databases; CAUTI only 1999–2000	≥10 ⁵ CFU/mL of 1 or 2 organisms from Day 3 of ICU stay or later	11.3/1000 ICU days	GP (32%) GN (36%) F (32%)
Appelgren (23) (Sweden)	MS 1	“Majority”/NR	Prospective DAI 1989–1993	≥10 ⁵ CFU/mL of 1 or 2 organisms with symptoms in 2 consecutive cultures after 2 days in the ICU	7/1000 ICU days	NR
Rosser (24) (USA)	T 1	100%/NR	Retrospective urosepsis only 1994–1995	≥10 ⁵ CFU/mL of 1 or 2 organisms or pyuria/bacteriuria/leukocyte esterase positive urinalysis with ≥2 SIRS criteria after ICU stay of 4 days	15.8% (urosepsis)	GP (22%) GN (67%) F (NR) ^c
van der Kooi (25) (the Netherlands)	MS, T 23	86%/82%	Prospective DAI 1997–2000	≥10 ⁵ CFU/mL of 1 or 2 organisms with symptoms in 2 consecutive cultures after 2 days in the ICU	9/1000 catheter days	NR
Alvarez-Lerma (26) (Spain)	MS, C, and T 74	NR/79–85%	Prospective DAI 2003–2005	≥10 ⁵ CFU/mL of 1 or 2 organisms with symptoms after 24 hrs in the ICU	6.0/1000 catheter days	GP (13%) GN (45%) F (34%)
Alvarez-Lerma (27) (Spain)	MS, C, and T 85	NR/78%	Prospective DAI 2002	≥10 ⁵ CFU/mL of 1 or 2 organisms with symptoms after 24 hrs in the ICU	4.8/1000 catheter days	GP (20%) GN (55%) F (20%)
Alvarez-Lerma (28) (Spain)	MS, C, and T 67	NR/75% ^b	Prospective DAI 1997–2001	≥10 ⁵ CFU/mL of 1 or 2 organisms with symptoms after 24 hrs in the ICU	6.2/1000 catheter days	GP (32%) GN (36%) F (32%)

ICU, intensive care unit; CAUTI, catheter-associated urinary tract infection; MS, medical surgical; CV, cardiovascular; T, trauma; C, coronary; NR, not reported; DAI, device-associated infection (CAUTI, ventilator-associated pneumonia, catheter-related bloodstream infection); CFU, colony-forming units; WBC, white blood cell count; SIRS, sepsis inflammatory response syndrome; GP, Gram-positive; GN, Gram-negative; F, fungus.

^aMay not add up to 100% as not all organisms causing CAUTI were reported and some CAUTI were polymicrobial; ^baverage for 2000 and 2001 only (29, 30); ^cboth urine and blood cultures positive.

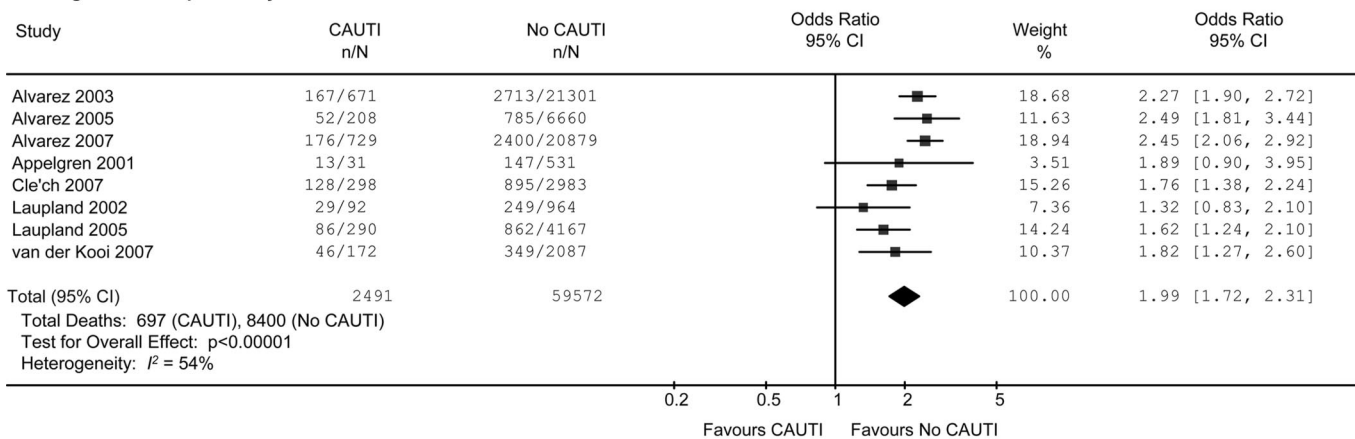
(26–28) or 48 (10, 22, 23, 25) hrs or who had a urinary catheter present while in the ICU (9) were included. Two single-center (20, 24) and the smallest multicenter study (21) did not specifically state that all consecutive patients admitted to the ICU meeting inclusion criteria were included. Two of these three studies also required specific LOS inclusion criteria in addition to being admitted to ICU such as survival past 5 days in the ICU (24) or hospital

stay >7 days (21). All the studies used the Centers for Disease Control and Prevention definition for CAUTI (32) with modifications except for one study that used a lower bacterial count of 10³/mL (9). All studies collected data on all initial and subsequent episodes of CAUTI for each patient.

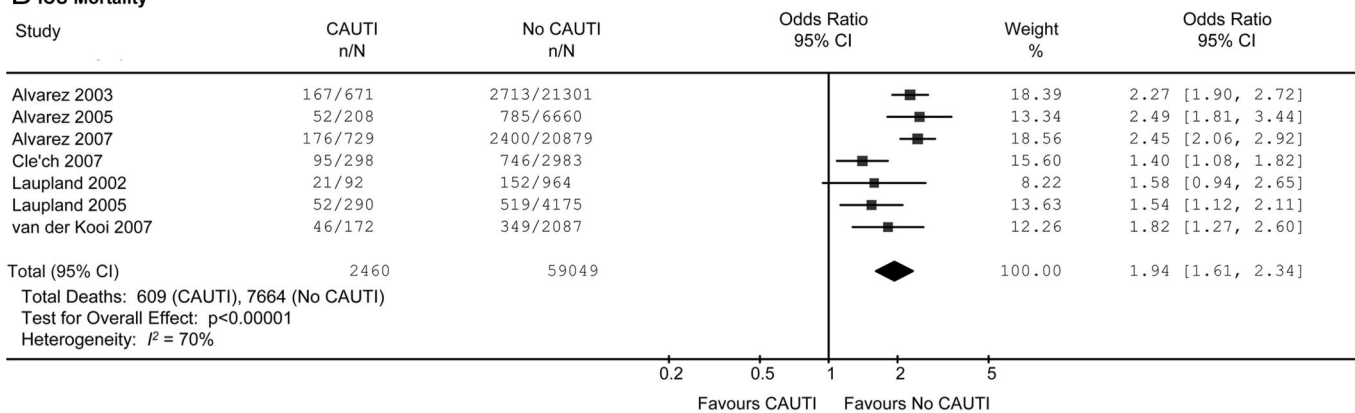
Morbidity and Mortality. The 11 included studies reported data on 2,745 patients with CAUTI and 60,719 patients without CAUTI. Pooled data from eight

studies (n = 2491 with and n = 59,572 without CAUTI) that reported mortality suggested that CAUTI was associated with increased crude mortality (OR, 1.99; 95% CI, 1.72–2.31; p < .00001; I² = 54%) (Fig. 2). A high degree of heterogeneity was observed, although all studies reported a higher numeric value for mortality in the CAUTI group. Visual inspection of the funnel plot (Appendix 2) did not suggest publication bias. Similar re-

A Longest Follow Up Mortality



B ICU Mortality



C Hospital Mortality

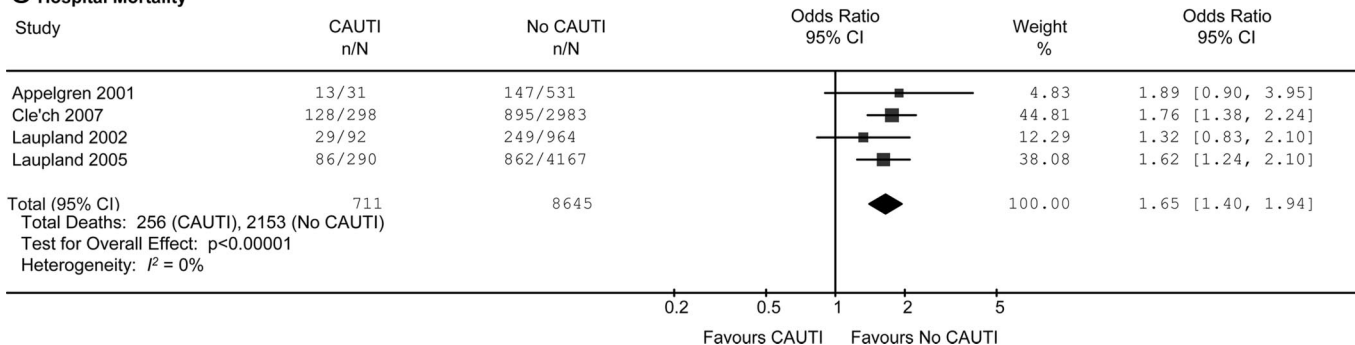


Figure 2. Attributable mortality associated with catheter-associated urinary tract infection (CAUTI). Effect of CAUTI on longest follow up mortality (A), intensive care unit (ICU) mortality (B), and hospital mortality (C). The pooled odds ratio with 95% confidence interval (CI) was calculated using a random-effects model. Weight refers to the contribution of each study to the overall pooled estimate.

sults were obtained when we restricted the analysis to studies reporting ICU mortality (OR, 1.94; 95% CI, 1.61–2.34; $p < .00001$; $I^2 = 70\%$; seven studies, $n = 2460$ with and $n = 59,049$ without CAUTI) or hospital mortality (OR, 1.65; 95% CI, 1.40–1.94; $p < .00001$; $I^2 = 0\%$; four studies, $n = 711$ with and $n = 8645$ without CAUTI). Using a control group of patients with no infection (ie, no CAUTI as well as no other diagnosed infections), CAUTI was associated with an even higher increase in mortality (OR, 2.62;

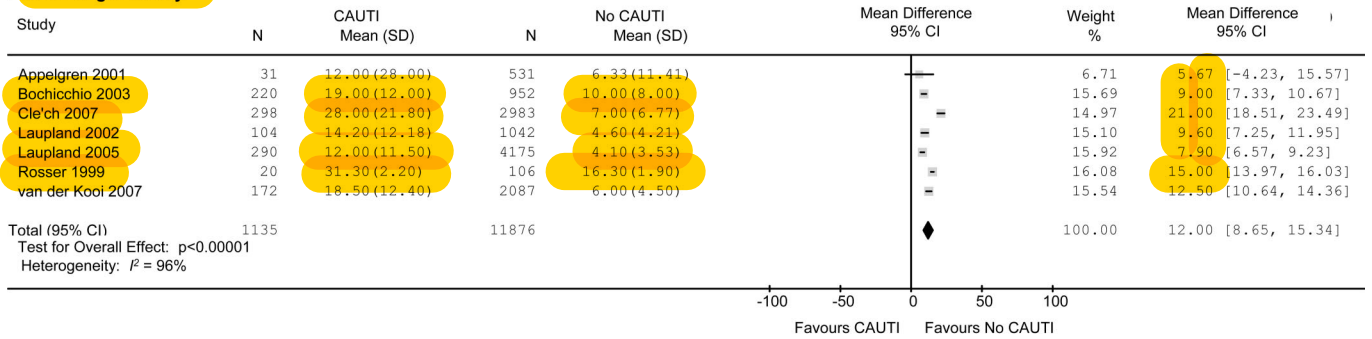
95% CI, 2.20–3.12; $p < .00001$; $I^2 = 0\%$; three studies, $n = 716$ with CAUTI and $n = 20,204$ with no infection).

Only one study reported mortality outcomes by type of microorganism causing CAUTI. This study specifically compared unadjusted ICU mortality rates in patients with CAUTI caused by *Enterococcus* species vs. all other pathogens and found no significant differences (28.7% vs. 24.2%, $p = .32$) (28).

With regard to morbidity outcomes, CAUTI was associated with an increased

ICU (MD of + 12 days; 95% CI, 9–15; $p < .00001$; $I^2 = 96\%$; seven studies, $n = 1135$ with and $n = 11,876$ without CAUTI) and hospital (MD of + 21 days; 95% CI, 11–32; $p < .0001$; $I^2 = 98\%$; five studies, $n = 932$ with and $n = 9251$ without CAUTI) LOS (Fig. 3). Again, a high degree of heterogeneity was observed, although all studies reported a higher value for both measures of LOS in the CAUTI group. Sensitivity analysis including the results of the potentially biased study (31) did not change the results

A ICU Length of Stay



B Hospital Length of Stay

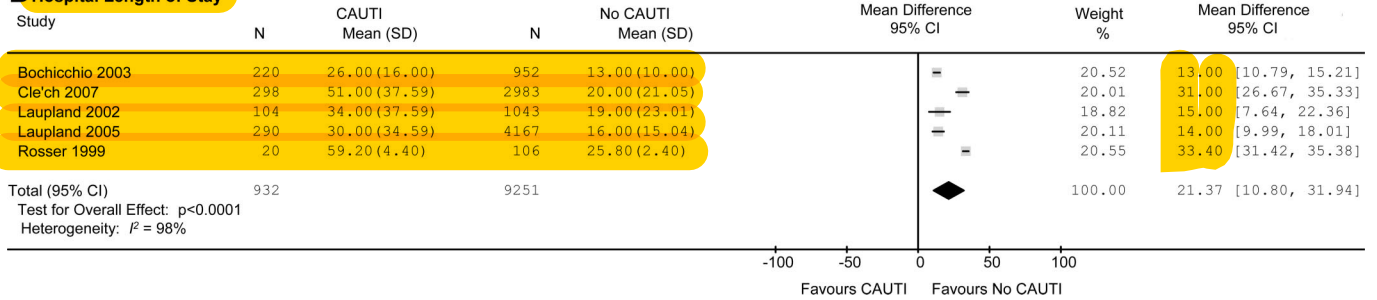


Figure 3. Attributable length of stay associated with catheter-associated urinary tract infection (CAUTI). Effect of CAUTI on intensive care unit (ICU) (A) and hospital (B) length of stay. The weighted mean difference was calculated using a random-effects model. Weight refers to the contribution of each study to the overall pooled estimate. We converted medians to means (19) where required (9, 10, 22, 23, 25) and estimated sds from the range (23) or interquartile range (IQR) (9, 10, 22, 25) using published guidelines (19). Sensitivity analysis including Taalat et al (31), which reported ICU length of stay (LOS) on 161 patients with CAUTI (29.7 ± 20.6 days) and 178 patients without CAUTI (17.3 ± 14.6 days), did not alter the overall results (mean difference of + 12 days; 95% CI, 9–15; $p < .00001$; $I^2 = 95\%$; eight studies, $n = 1296$ with and $n = 12,054$ without CAUTI).

for ICU LOS (MD of + 12 days; 95% CI, 9–15; $p < .00001$; $I^2 = 95\%$; eight studies, $n = 1296$ with and $n = 12,054$ without CAUTI).

Two studies provided outcomes after adjusting for predictors of mortality using either a matched case–control design (9) or multivariable logistic regression (10). Neither study found a significant association between CAUTI and mortality after adjustment. Combining data from these two studies gives a pooled adjusted OR for hospital mortality of 0.97 (95% CI, 0.82–1.16; $p = .77$; $I^2 = 0\%$; two studies, $n = 563$ with and $n = 5063$ without CAUTI). Even after adjustment, the same two studies reported significantly increased LOS in the ICU: median increase of 13 days ($p < .0001$) (9) and mean increase of 2.4 days ($p < .001$) (10). Pooling the data from these two trials results in a nonsignificant increase in LOS as a result of the large amount of heterogeneity (MD of + 8 days; 95% CI, of –13 to + 28; $p = .46$; $I^2 = 99.6\%$; two studies, $n = 378$ with and $n = 1949$ without CAUTI). Using a fixed effects model, which does not include between-study heterogeneity and thus results in narrower CIs, results in a smaller but statistically significant

increase in ICU LOS (MD + 2.6 days; 95% CI, 2.3–3.0; $p < .00001$).

DISCUSSION

We found that CAUTI in ICU patients is associated with increased mortality and LOS in unadjusted analysis. However, after adjustment for other prognostic factors, CAUTI is no longer associated with increased mortality but may be associated with increased ICU LOS. In contrast, a systematic review of observational studies of catheter-related bloodstream infection suggests that catheter-related bloodstream infection is associated with increased mortality even after matching for severity of illness (13), whereas two systematic reviews of observational studies of ventilator-associated pneumonia provided more equivocal results regarding whether ventilator-associated pneumonia was associated with increased mortality (11, 12). It is unclear whether there is a causal association between increased ICU LOS and CAUTI, and if there is, whether CAUTI results in increased LOS or whether patients with longer ICU stays have an increased risk of developing CAUTI. Three studies reported when CAUTI occurred and these times were rel-

atively long after catheter insertion (8–11 days [9, 25]) or after ICU admission (16 days [23]), which supports the latter relationship.

All studies in this systematic review used the presence of bacteriuria as the primary criterion for diagnosing CAUTI because it is difficult to reliably identify or attribute traditional urinary tract infection symptoms (hesitancy, frequency) in catheterized critically ill patients with an impaired level of consciousness (4). Therefore, one potential explanation for the lack of association between adjusted mortality and CAUTI is that bacteriuria may simply reflect colonization of the catheter and not true infection. Measures that identify, or predict, which patients with bacteriuria have, or will develop, definitive or systemic infections, which can be serious in vulnerable ICU patients, are lacking (5). The inability to differentiate colonization from infection is important and is reflected in our national survey of ICU physicians that demonstrates a high frequency of antimicrobial prescription for CAUTI even in the absence of symptoms (6).

Given the apparent lack of association between CAUTI and mortality, and the

contribution of antimicrobial use to the development of resistance, efforts should be undertaken to investigate which, if any, patients benefit from antimicrobial therapy. To the best of our knowledge, there is only one single-center underpowered randomized controlled trial evaluating the use of antimicrobials for asymptomatic bacteriuria in the ICU. In this study of 60 patients, treatments with antimicrobials and catheter change did not improve mortality or LOS when compared with no intervention (33). Therefore, to achieve similar successes as seen with ventilator-associated pneumonia and catheter-related bloodstream infection patient safety prevention bundles, more rigorous evidence than is currently available about the effects of treatment of CAUTI on outcomes is needed.

The strengths of our study include the use of rigorous systematic review and meta-analytic methods, including a reproducible and comprehensive literature search strategy without language restriction, clearly defined inclusion criteria, duplicate citation review, duplicate data abstraction, and a predefined statistical analysis plan. These are all elements outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement on the reporting of meta-analyses (34). Furthermore, the included observational studies were of relatively high methodologic quality. In particular, most were prospective multicentered studies from a variety of international ICUs, which increases the generalizability of the findings. Furthermore, all but the smallest multicenter study and one of the three single-center studies specified that data from all consecutively admitted ICU patients who met inclusion criteria were included.

Our study also has limitations. These include the large unexplained heterogeneity and the small number of studies that matched and/or adjusted for confounders. Given the differences in practice in the diverse study sites, patient populations, the definition and microbiological etiology of CAUTI, some heterogeneity would be expected. Unfortunately, we could not clearly identify any study characteristics that accounted for the heterogeneity in this relatively small group of studies. In addition, ICU LOS is affected by numerous factors, and the studies included in our meta-analysis do not report the time to CAUTI and do not allow for a more rigorous analysis of ICU LOS after CAUTI or whether the CAUTI

episodes were treated with antimicrobials. Finally, although there was heterogeneity, it was primarily in the magnitude rather than the direction of each effect because essentially all of the studies individually demonstrated statistically significant increases in each unadjusted outcome.

CONCLUSIONS

Our systematic review and meta-analysis of observational studies identified that **CAUTI is associated with increased crude mortality rates and LOS**. Restricting the analysis to studies that adjusted for other factors associated with outcome, CAUTI was no longer associated with increased mortality but was possibly still related to a small increase in ICU LOS. These findings support further investigations into the optimal management of CAUTI to minimize potentially inappropriate antimicrobial use.

ACKNOWLEDGMENTS

We acknowledge Dr. Francisco Alvarez-Lerma for clarifying and providing additional data for his studies. We also acknowledge the assistance of David Lightfoot with executing the literature searches, Marina Simms for retrieving foreign language articles, and Joyce Fenuta for financial support with article retrieval costs.

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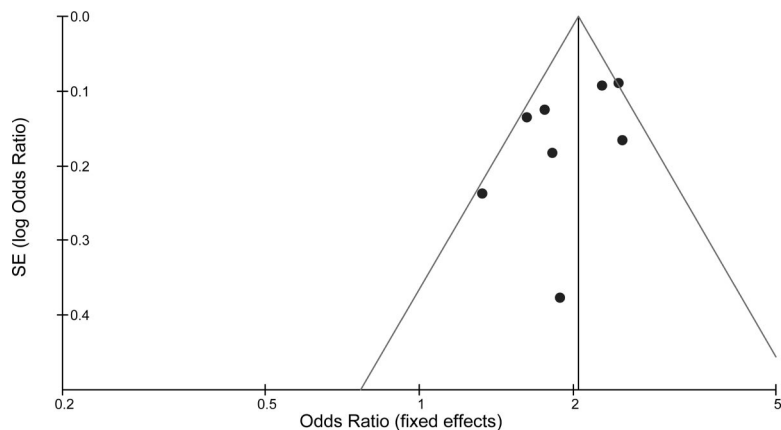
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Appendix 1. Detailed MEDLINE search strategy^a

No.	Searches
1	exp urinary catheterization/
2	exp catheters, indwelling/
3	exp urinary tract infections/
4	exp catheterization/and (exp urinary tract/or exp urogenital system/or urin\$.mp.) [mp = title, original title, abstract, name of substance word, subject heading word]
5	or/1–4
6	exp bacterial infections/or bacteremia.mp.
7	exp cross infection/
8	exp iatrogenic disease/or (iatrogen\$ or noscomial\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word])
9	exp sepsis/
10	urosepsis.mp.
11	exp critical care/or (critical adj1 care).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
12	exp critical illness/or (critical adj2 Ill\$.mp. [mp = title, original title, abstract, name of substance word, subject heading word])
13	intensive care.mp. or exp Intensive Care/
14	icu.mp.
15	or/6–10
16	or/11–14
17	16 and 15 and 5
18	incidence.mp. or exp Incidence/
19	morbidity.mp. or exp Morbidity/
20	mortality.mp. or exp Mortality/
21	retrospective study.mp. or exp Retrospective Studies/
22	population surveillance.mp. or exp Population Surveillance/
23	mo.fs.
24	ae.fs.
25	sn.fs.
26	ep.fs.
27	exp Epidemiology/
28	17 and (or/18–27)
29	limit 28 to (“adolescent (13 to 18 yrs)” or “young adult (19 to 24 yrs)” or “adult (19 to 44 yrs)” or “young adult and adult (19–24 and 19–44)” or “middle age (45 to 64 yrs)” or “middle aged (45 plus years)” or “all aged (65 and over)” or “aged (80 and over)”)
30	limit 28 to “all child (0 to 18 yrs)”
31	28 not 30
32	29 or 31

^aSimilar search strategy was used for EMBASE, HealthStar, and CINAHL databases.



Appendix 2. Funnel plot for pooled analysis of mortality.