

## ORIGINAL ARTICLE

## Does Catheter-Associated Urinary Tract Infection Increase Mortality in Critically Ill Patients?

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**OBJECTIVE.** To produce an accurate estimate of the association between catheter-associated urinary tract infection (UTI) and intensive care unit (ICU) and hospital mortality, controlling for major confounding factors.

**DESIGN.** Nested case-control study in a multicenter cohort (the OutcomeRea database).

**SETTING.** Twelve French medical or surgical ICUs.

**METHODS.** All patients admitted between January 1997 and August 2005 who required the insertion of an indwelling urinary catheter. Patients who developed catheter-associated UTI (ie, case patients) were matched to control patients on the basis of the following criteria: sex, age ( $\pm 10$  years), SAPS (Simplified Acute Physiology Score) II score ( $\pm 10$  points), duration of urinary tract catheterization, and presence or absence of diabetes mellitus. The association of catheter-associated UTI with ICU and hospital mortality was assessed by use of conditional logistic regression.

**RESULTS.** Of the 3,281 patients who had an indwelling urinary catheter, 298 (9%) developed at least 1 episode of catheter-associated UTI. The incidence density of catheter-associated UTI was 12.9 infections per 1,000 catheterization-days. Crude ICU mortality rates were higher among patients with catheter-associated UTI, compared with those without catheter-associated UTI (32% vs 25%,  $P = .02$ ); the same was true for crude hospital mortality rates (43% vs 30%,  $P < .01$ ). After matching and adjustment, catheter-associated UTI was no longer associated with increased mortality (ICU mortality: odds ratio [OR], 0.846 [95% confidence interval {CI}, 0.659-1.086];  $P = .19$  and hospital mortality: OR, 0.949 [95% CI, 0.763-1.181];  $P = .64$ ).

**CONCLUSION.** After carefully controlling for confounding factors, catheter-associated UTI was not found to be associated with excess mortality among our population of critically ill patients in either the ICU or the hospital.

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Urinary tract infection (UTI) is the most common infection acquired by hospitalized adult patients, accounting for 30%-40% of all nosocomial infections.<sup>1,2</sup> In the hospital, the intensive care unit (ICU) has the highest prevalence of UTI (8%-21% of nosocomial infections); more than 95% of ICU cases are associated with the presence of an indwelling urinary catheter.<sup>3,4</sup>

Although catheter-associated urinary tract infection (UTI) is a very common infection, its link with mortality remains controversial. In a large cohort study conducted in 1982, Platt et al.<sup>5</sup> reported a significantly higher risk of hospital mortality in patients with catheter-associated UTI. Two more-recent

studies found similar results.<sup>6,7</sup> Three other studies, however, reported the opposite result, that catheter-associated UTI did not increase the risk of hospital mortality.<sup>8-10</sup> The discrepant results of these studies could be ascribed to patients' baseline heterogeneity and subsequent in-hospital events, which may have confounded the link between catheter-associated UTI and mortality.

Knowing the real impact of catheter-associated UTI on patients' outcome is undoubtedly necessary for clinicians who must decide whether specific treatments are required. Particularly, this knowledge would help resolve some important issues that frequently arise in the ICU, such as whether it is

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necessary to change the urinary catheter or administer antibiotics. Thus, we performed this study to yield a more accurate estimation of the association between catheter-associated UTI and mortality in the ICU and in the hospital as a whole, matching patients for the probability of ICU-acquired UTI and further controlling for major confounding factors.

## METHODS

### Study Design and Data Source

We conducted a nested case-control study in a multicenter cohort (the OutcomeRea database) from January 1997 to August 2005. The database, which receives information from 12 French ICUs, is designed to record daily severity scores and the occurrence of iatrogenic events. Data on a random sample of patients older than 16 years with ICU stays longer than 24 hours was entered into the database each year. Briefly, each participating ICU could choose between 2 sampling methods: consecutive admitted patients in randomized beds or consecutive admitted patients in a randomized month.

In accordance with French law, the OutcomeRea database was declared to and approved by the Commission Nationale de l'Informatique et des Libertés. Because routine collection of clinical and paraclinical data did not modify patients' management in any way, and statistical analyses were processed anonymously, informed consent was waived for participation in the study.

### Method of Data Collection

The senior physicians of the participating ICUs were closely involved in establishing the daily data collected for the database. For each patient, the investigators entered the data into a computer case-report form using the data-capture software VigiRea (OutcomeRea) and imported all records to the OutcomeRea database. All codes and definitions were written prior to data collection.

### Quality of the Database

The data-capture software immediately conducted an automatic check of most of the variables entered by the investigators. Multiple automatic checking of internal consistency generated queries that were sent to the ICUs before the new data were incorporated into the database. At each participating ICU, the quality control procedure involved having a senior physician from another participating ICU check a 2% random sample of study data.  $\kappa$  coefficients ranged from 0.5 to 0.9 for qualitative variables, and interrater correlation coefficients ranged from 0.67 to 1 for clinical variables, disease severity scores, and organ dysfunction scores.

The lowest  $\kappa$  coefficient was obtained for the McCabe class. The lowest interrater correlation was obtained for lactate level on day 3. Otherwise, the  $\kappa$  coefficient was always higher than 0.62 for qualitative variables; the interrater coefficient ranged

between 0.72 and 0.99 for quantitative variables (it was 0.78–0.91 for disease severity and organ dysfunction scores, and was 0.99 for duration of mechanical ventilation, ICU stay, and hospital stay).

### Study Population and Definitions

All patients in the database were eligible. Patients who had UTI before insertion of the urinary catheter and patients without a urinary catheter were excluded.

Patients were cautiously screened for catheter-associated UTI. Urine specimens were systematically collected for culture, either once per week, or at the time a new episode of sepsis occurred. Catheter-associated UTI was deemed present if a urine culture yielded at least  $10^3$  colony-forming units (cfu)/mL of 1 or 2 microorganisms.<sup>11,12</sup> A bacteremic or fungemic catheter-associated UTI was considered present if there was a catheter-associated UTI accompanied by blood cultures positive for the same microorganism within a 48-hour period.

Case patients were those who developed catheter-associated UTI. For inpatients who developed several episodes of catheter-associated UTI, only the first episode was included in the analysis. Control patients were selected from among the remaining patients. Case patients were matched to control patients on the basis of predicted mortality and known risk factors for ICU-acquired UTI,<sup>13–17</sup> by use of an algorithm available from OutcomeRea.<sup>18</sup> More precisely, the matching criteria were as follows: sex, age ( $\pm 10$  years), SAPS (Simplified Acute Physiology Score) II ( $\pm 10$  points), presence or absence of diabetes mellitus, and duration of urinary tract catheterization. In addition, we imposed the condition that the time to the onset of catheter-associated UTI from the insertion of the urinary catheter in case patients be equal to or less than the duration of urinary tract catheterization in their respective control patients.

### Data Collection

The following data were collected: age; sex; McCabe class (class 1, no fatal underlying disease; class 2, underlying disease fatal within 5 years; class 3, underlying disease fatal within 1 year)<sup>19</sup>; comorbidities (assessed according to the Acute Physiology and Chronic Health Evaluation II definitions)<sup>20</sup>; severity of illness at ICU admission and daily during the ICU stay, assessed using the SAPS II score<sup>21</sup>; the sequential organ failure assessment score<sup>22</sup> and the logistic organ dysfunction (LOD) score<sup>23</sup>; admission category (ie, medical, scheduled surgery, or unscheduled surgery); admission diagnosis; whether the patient was transferred from a ward (defined as a stay in an acute care bed or ward for 24 hours or longer immediately before ICU admission); length of ICU stay and of hospital stay; and vital status at ICU and hospital discharge. Data on invasive procedures (ie, placement of an arterial or central venous catheter, and endotracheal intubation), treatments for organ failure (ie, receipt of catecholamine infusion

TABLE 1. Demographic and Clinical Characteristics of Intensive Care Unit (ICU) Patients With and Patients Without Catheter-Associated Urinary Tract Infection (UTI)

Variable	Patients with catheter-associated UTI (n = 298)	Patients without catheter-associated UTI (n = 2,983)	P <sup>a</sup>
Age, median (IQR), years	69 (57-77)	66 (51-76)	.001
Male sex	160 (54)	1,831 (61)	.10
SAPS II score, median (IQR)	46 (36-57)	42 (30-57)	.014
LOD score, median (IQR)	5 (3-7)	4 (2-7)	.12
Admission category			
Medical	186 (62)	1,862 (62)	.12
Scheduled surgery	38 (12)	484 (16)	
Unscheduled surgery	74 (25)	637 (21)	
Chronic coexisting condition			
Cardiac disease	51 (17)	467 (16)	.51
Respiratory disease	62 (21)	496 (17)	.07
Renal disease	6 (2)	100 (3)	.22
Liver disease	17 (6)	170 (6)	.99
Immunodeficiency	39 (13)	371 (12)	.75
Uncomplicated diabetes mellitus	50 (17)	463 (16)	.57
Complicated diabetes mellitus	17 (6)	126 (4)	.23
Therapy received ≤48 h after ICU admission			
Catecholamine infusion	164 (55)	1,369 (46)	.01
Mechanical ventilation	137 (46)	923 (31)	<.01
Antibiotics	224 (74)	2,203 (73)	.91
Broad-spectrum antibiotics	163 (54)	1,665 (56)	.71

NOTE. Data are expressed as no. (%) of patients, unless otherwise indicated. IQR, interquartile range; SAPS II, Simplified Acute Physiology Score version II; LOD, logistic organ dysfunction.

<sup>a</sup> Wilcoxon test for continuous data, and  $\chi^2$  test for categorical data.

and/or mechanical ventilation), and use of antibiotics were also recorded.

### Statistical Analyses

Comparisons between patients in the whole cohort were based on  $\chi^2$  tests for categorical data and on the Wilcoxon test for continuous data. Assuming an ICU mortality of 30% among patients without catheter-associated UTI and assuming that catheter-associated UTI would occur in more than 250 patients, we calculated that 3 control patients per case patient would be necessary to unmask a difference in the mortality-associated odds ratio of 1.5 with an  $\alpha$  risk of 5% and a power of 80%.

Comparisons between matched patients were initially based on bivariate conditional logistic regression. Multivariate conditional logistic regression was then used to examine the association between catheter-associated UTI and ICU and hospital mortality, adjusting for potential confounding variables (ie, variables that had a *P* value of .10 or less in bivariate analysis). The Wald  $\chi^2$  test was used to determine the significance of each variable. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each parameter estimate.

A *P* value less than .05 was considered significant. Analyses were computed with the SAS 9.1 software package (SAS Institute).

## RESULTS

### Study Population

Of the 4,811 patients in the OutcomeRea database, 64 (1.3%) had UTI on ICU admission and were thus excluded. Of the remaining 4,747 patients, 3,281 (69.1%) had an indwelling urinary catheter, and 298 (9%) had catheter-associated UTI. The overall incidence density of catheter-associated UTI was 12.9 infections per 1,000 catheterization-days. Bacteremic or fungemic catheter-associated UTI occurred in 4 case patients, for an overall incidence density of 0.17 infections per 1,000 catheterization-days. The median time to onset of catheter-associated UTI was 11 days (interquartile range [IQR], 6-19 days) from the time the urinary catheter was inserted.

On the day that catheter-associated UTI occurred, 64 (21.5%) of the patients required catecholamine infusion, and 198 (66.4%) of the patients were receiving antibiotics for extra-urinary sepsis. The demographic and clinical characteristics of study patients are shown in Table 1.

Several factors present at admission or within 48 hours after ICU admission were associated with an increased risk of developing catheter-associated UTI. Patients with catheter-associated UTI, compared with those without catheter-associated UTI, were older, had higher SAPS II scores, and were more likely to have received catecholamine infusion or mechanical ventilation during the first 48 hours of their ICU stay (Table 1).

### Microbiologic Findings

A total of 232 patients (77.8%) had 1 episode of catheter-associated UTI, 44 patients (14.8%) had 2 episodes, and 22 patients (7.4%) had 3 or more episodes. Most episodes (93.6%) were monomicrobial. The microorganisms recovered from urine cultures are listed in Table 2. The microorganisms identified both in urine and blood cultures were *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Escherichia coli*, and *Candida albicans*.

### Matching

Among the 298 patients with catheter-associated UTI, 273 (91.6%) were matched successfully to 896 control patients for all matching criteria. Unmatched patients were younger and had a longer duration of urinary catheterization than matched patients, but had similar SAPS II and LOD scores at ICU admission.

Case patients were less likely than control patients to have received antibiotics within 72 hours before onset of catheter-associated UTI (or the corresponding day, for control patients). General characteristics and in-ICU events that were potentially associated with mortality in case and control patients are shown in Table 3.

### Outcomes

Overall, the ICU mortality rate was 32% among patients with catheter-associated UTI and 25% among patients without catheter-associated UTI ( $P = .02$ ). The hospital mortality rate was 43% among patients with catheter-associated UTI and 30% among patients without catheter-associated UTI vs ( $P < .01$ ). The length of ICU stay was significantly longer for in patients with catheter-associated UTI, compared with those without catheter-associated UTI (median, 28 days [IQR, 16-45 days] vs 7 days [IQR, 4-13 days];  $P < .001$ ); the same was true for the duration of hospital stay (median, 51 days [IQR, 30-80 days] vs 20 days [IQR, 10-38 days];  $P < .001$ ).

After matching for risk factors for catheter-associated UTI, unadjusted analysis revealed that catheter-associated UTI was not associated with lower rates of ICU or hospital survival (Table 4). The duration of ICU stay remained significantly increased for patients with catheter-associated UTI, compared with those without (median, 26 days [IQR, 16-43 days] vs 13 days [IQR, 8-23 days];  $P < .0001$ ); the same was true for the length of hospital stay (median, 49 days [IQR, 29-78 days] vs 29 days [IQR, 18-54 days];  $P < .0001$ ). After further ad-

TABLE 2. Microbial Etiology of Catheter-Associated Urinary Tract Infection in Intensive Care Unit Patients

Microorganism	No. (%) of isolates
<i>Escherichia coli</i>	88 (29.5)
<i>Candida</i> spp	85 (28.5)
<i>Pseudomonas aeruginosa</i>	54 (18)
<i>Enterococcus</i> spp	42 (14)
<i>Klebsiella</i> spp	25 (8.4)
<i>Proteus</i> spp	22 (7.4)
<i>Enterobacter</i> spp	20 (6.7)
<i>Streptococcus</i> spp	9 (3)
<i>Citrobacter</i> spp	8 (2.7)
<i>Staphylococcus aureus</i>	7 (2.4)

NOTE. The number of isolates (360) exceeds the number of patients with catheter-associated UTI (298) because some patients had polymicrobial infection.

justment for confounding factors (ie, septic shock, multiple organ failure, and coma as reason for ICU admission; receipt of mechanical ventilation during the first 48 hours of ICU stay; extra-urinary sepsis; and antibiotic use), there was still no difference in rates of ICU or hospital survival (Table 4).

### DISCUSSION

Development of a nosocomial UTI is a common complication among ICU patients who require urinary catheterization. Several studies have evaluated the risk of death associated with nosocomial UTI, but only a few of them specifically focused on ICU patients.<sup>6,7,9</sup> To our knowledge, this study is one of the largest to have evaluated the impact of catheter-associated UTI on ICU and hospital mortality. Crude mortality was higher among patients with catheter-associated UTI, compared with those without, but there was no excess mortality after careful matching and adjustment for confounding factors.

In a widely cited prospective cohort study, Platt et al.<sup>5</sup> found a significantly increased risk of hospital mortality among patients with catheter-associated UTI. Nevertheless, they did not focus on ICU patients, and it was not clear whether mortality was indeed attributable to catheter-associated UTI. More recently, Rosenthal et al.<sup>6</sup> also reported an increased risk of mortality associated with ICU-acquired UTI, but they did not adjust for potentially important confounding factors, including severity of illness. Another study showed similar results.<sup>7</sup> After controlling for confounding factors, Laupland et al.<sup>9</sup> concluded that ICU-acquired UTI was not a significant attributable cause of mortality. However, the confounding factors that were adjusted for in that study were not well defined, and patients in the study may have been heterogeneous with regard to the probability of developing ICU-acquired UTI.

In our study, we dealt with heterogeneity more extensively by matching patients on the basis of predicted mortality and known risk factors for catheter-associated UTI.<sup>13-17</sup> Moreover, we clearly defined and adjusted for confounding factors.

TABLE 3. General Characteristics and Intensive Care Unit (ICU) Events Potentially Associated With Mortality in Case Patients With Catheter-Associated Urinary Tract Infection and Control Patients

Variable	Case group ( <i>n</i> = 273)	Control group ( <i>n</i> = 896)	<i>P</i> <sup>a</sup>
Patient characteristics at ICU admission			
SAPS II score, median (IQR)	45 (36-57)	44 (34-57)	.58
LOD score, median (IQR)	3 (1-6)	3 (1-6)	.85
McCabe class			
1	127 (47)	452 (50)	.61
2	130 (47)	366 (41)	
3	16 (6)	78 (9)	
Admission category			
Medical	167 (61)	527 (59)	.74
Scheduled surgery	35 (13)	152 (17)	
Unscheduled surgery	71 (26)	217 (24)	
Transfer from ward	170 (63)	558 (64)	.79
Chronic coexisting condition			
Cardiac disease	50 (18)	150 (17)	.62
Respiratory disease	60 (22)	174 (19)	.21
Renal disease	6 (2)	29 (3)	.32
Liver disease	16 (6)	44 (5)	.28
Immunodeficiency	34 (12)	98 (11)	.99
Uncomplicated diabetes mellitus	50 (18)	171 (19)	.16
Complicated diabetes mellitus	14 (5)	29 (3)	.28
Reason for ICU admission			
Septic shock	38 (14)	156 (17)	.04
Cardiogenic shock	9 (3)	28 (3)	.67
Hemorrhagic shock	10 (4)	32 (4)	.99
Acute respiratory failure	80 (29)	262 (29)	.95
Acute exacerbation of COPD	15 (6)	40 (5)	.40
Acute renal failure	13 (5)	42 (5)	.95
Coma	54 (20)	131 (15)	.04
Trauma	4 (1)	11 (1)	.97
Multiple organ failure	20 (7)	39 (4)	.05
Other	30 (11)	155 (18)	.07
Therapy received ≤48 h after ICU admission			
Catecholamine infusion	153 (56)	482 (54)	.84
Mechanical ventilation	12 (44)	314 (35)	.02
Antibiotics	197 (72)	688 (77)	.03
Broad-spectrum antibiotics	143 (52)	575 (64)	<.01
Events >48 h after ICU admission			
Extra-urinary sepsis	203 (74)	474 (53)	<.001
Antibiotics <sup>b</sup>	198 (73)	701 (78)	.02
Shock or failure of any organ	267 (98)	872 (97)	.80

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; SAPS II, Simplified Acute Physiology Score version II; LOD, logistic organ dysfunction; COPD, chronic obstructive pulmonary disease.

<sup>a</sup> Conditional logistic regression.

<sup>b</sup> Antibiotic therapy received within 72 hours before the day of catheter-associated UTI onset (or before the corresponding day in control patients).

Thus, we were able to identify more precisely the independent effect of catheter-associated UTI on mortality. The conclusion that catheter-associated UTI did not worsen patients' outcome has potentially important implications for the management of patients with indwelling urinary catheters. First,

frequent and regular performance of urine cultures for patients with an indwelling urinary catheter may be unnecessary and, consequently, unduly costly. Second, regular changing of the urinary catheter in cases of catheter-associated UTI may not be recommended, all the more so as it could be

TABLE 4. Association Between Mortality and Catheter-Associated Urinary Tract Infection in Intensive Care Unit (ICU) Patients

Variable	OR (95% CI)	P <sup>a</sup>
Unadjusted analysis		
ICU death	1.020 (0.796-1.306)	.88
Hospital death	1.185 (0.954-1.481)	.12
Adjusted analysis		
ICU death	0.846 (0.659-1.086)	.19
Hospital death	0.949 (0.763-1.181)	.64

NOTE. For details of adjustment, see Methods.

<sup>a</sup> Conditional logistic regression.

associated with septicemia. Finally, catheter-associated UTI could be considered colonization rather than infection, and antibiotics should not be given in the absence of associated bacteremia or fungemia (which is a rather rare occurrence), pyelonephritis, or prostatitis. Receiving antibiotics seems to decrease the risk of catheter-associated UTI, but, conversely, not receiving antibiotics does not seem to have a negative impact on the risk of catheter-associated UTI.

Some limitations of this study merit consideration. First, the observational design of our study precludes making any definite recommendation. Further prospective interventional studies are needed to confirm our findings. Specifically, these studies should assess the impact of changing urinary catheters and administering antibiotic therapy among patients with catheter-associated UTI. Second, there might be some masked confounding factors, because this was not a controlled study. However, by matching for known risk factors for ICU-acquired UTI and controlling for usual risk factors for mortality, we dealt with confounding more extensively than any previous report, to our knowledge.

Third, not all patients with catheter-associated UTI could be matched. Yet the proportion of unmatched patients was very low, in spite of the large number of matching criteria, and those patients had the same probability of death, as defined by severity scores on ICU admission. This fact is thus very unlikely to have changed the results.

Fourth, we did not define catheter-associated UTI according to the Centers for Disease Control and Prevention criteria for nosocomial infections.<sup>24</sup> However, these criteria are difficult to apply to the ICU: functional signs are impossible to identify in sedated patients with an indwelling urinary catheter, fever is either absent or nonspecific, and bacterial growth may be impaired by ongoing antibiotic therapy for extra-urinary sepsis. Thus, most episodes of catheter-associated UTI are asymptomatic. That is why we had to collect urine specimens for cultures weekly or when a new episode of sepsis occurred. That the overall incidence densities of catheter-associated UTI and of bacteremic or fungemic catheter-associated UTI were consistent with previous reports shows the diagnosis of catheter-associated UTI was neither overestimated nor underestimated in our study.<sup>9,25-27</sup>

Fifth, one may argue that the implementation of specific

treatment (ie, changing urinary catheters and administering antibiotic therapy) might reduce ICU and hospital lengths of stay for patients with catheter-associated UTI. It must be emphasized, however, that the benefits of such a treatment are hypothetical. Additionally, the greater lengths of stay observed in this study were probably related to more-severe underlying conditions and greater disease severity, rather than to catheter-associated UTI itself.

Sixth, the fact that most patients with catheter-associated UTI were receiving antibiotic therapy may also have confounded the results by protecting patients against septic shock and death. Nevertheless, those factors were adjusted for, and patients with catheter-associated UTI received fewer antibiotics than their matched control patients.

Finally, it must be kept in mind that the prognosis of catheter-associated UTI may depend on the microorganisms involved. Particularly, the risk of death may be increased in case of candiduria.<sup>28</sup> Infection with other pathogens, such as *P. aeruginosa* or *E. coli*, may also carry a higher risk of death. This issue remains to be clarified.

In conclusion, catheter-associated UTI does not seem to be associated with increased mortality among ICU patients, after careful matching and controlling for confounding factors. Further prospective interventional studies are required to confirm our results.

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