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Length of stay and mortality associated with healthcare-associated urinary tract infections: a multi-state model

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SUMMARY

Background: The emergence of antimicrobial resistance is of particular concern with respect to urinary tract infections, since the majority of causative agents are Gram-negative bacteria. Healthcare-associated urinary tract infections (HAUTIs) are frequently associated with instrumentation of the urinary tract, specifically with indwelling catheters.

Aim: To evaluate the current incidence, mortality, and length of hospital stay associated with HAUTIs.

Methods: A non-concurrent cohort study design was used, conducted between January 1st, 2010 and June 30th, 2014. All patients admitted to one of the eight participating Australian hospitals and who were hospitalized for more than two days were included. The primary outcome measures were the incidence, mortality, and excess length of stay associated with HAUTIs.

Findings: From 162,503 patient admissions, 1.73% [95% confidence interval (CI): 1.67–1.80] of admitted patients acquired a HAUTI. Using a multi-state model, the expected extra length of stay due to HAUTI was four days (95% CI: 3.1–5.0 days). Using a Cox regression model, infection significantly reduced the rate of discharge (hazard ratio: 0.78; 95% CI: 0.73–0.83). Women were less likely to die (0.71; 0.66–0.75), whereas older patients were more likely to die (1.40; 1.38–1.43). Death was rarer in a tertiary referral hospital compared to other hospitals, after adjusting for age and sex (0.74; 0.69–0.78).

Conclusion: This study is the first to explore the burden of HAUTIs in hospitals using appropriate statistical methods in a developed country. Our study indicates that the incidence of HAUTI, in addition to its associated extra length of stay in hospital, presents a burden to the hospital system. With increasing incidence of UTI due to antimicrobial-

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resistant organisms, surveillance and interventions to reduce the incidence of HAUTI are required.

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Introduction

Healthcare-associated infections (HCAIs) including healthcare-associated urinary tract infections (HAUTIs) are frequently occurring and largely preventable infections affecting the provision of healthcare globally. The point prevalence of HAUTIs is ~1.4%, with HAUTIs responsible for 17% of all HCAIs.[1,2] The provision of evidence-based treatment is essential in ensuring that healthcare professionals minimize the incidence and attributed mortality of these opportunistic infections. HAUTIs are frequently associated with instrumentation of the urinary tract, specifically with indwelling catheters.[3–5] This represents an opportunity for relatively inexpensive prevention strategies, such as minimizing catheter use, appropriate insertion, careful maintenance and removal of catheters at the earliest opportunity, coupled with approaches that are more systematic.[5–10]

The emergence of antimicrobial resistance is of particular concern with respect to urinary tract infections (UTIs), since the majority of causative agents are Gram-negative bacteria.[11] This adds further value to endeavours that aim to understand the burden of UTIs and interventions to reduce their incidence.

Our study aimed to evaluate the current incidence, mortality, and length of stay associated with HAUTIs in a large health district during a four-and-a-half-year period. We sought to determine the proportion of patients that develop a laboratory-diagnosed HAUTI, the extra length of hospital stay in patients with HAUTI, and increased risk of inpatient mortality associated with HAUTI.

Methods

Study design

A non-concurrent cohort study design was used.

Setting

The setting was a large health district in New South Wales, Australia. The health district provides services to around 850,000 people (3.6% of Australia's population) and covers a geographical area of >130,000 km^2. Eight hospitals within this health district were included: one tertiary referral hospital, two rural referral hospitals, and five district hospitals. The combined total number of overnight beds at these hospitals was 1250.

Participants

All patients admitted to one of the eight participating hospitals between January 1st, 2010 and June 30th, 2014 and who were hospitalized more than two days were included. The sample timeframe was chosen by convenience consideration and also to reflect the most recent data available.

Definitions

HAUTI was considered present when patients had a positive urine culture more than two days after admission, according to the following criteria: positive for at least one species of Enterobacteriaceae, $>10^5$/mL of urine, and no more than two species of micro-organisms. This approach is consistent with existing definitions and studies.[12–15] All patients with a positive urine culture not meeting this definition were excluded. When a patient had more than one HAUTI during an admission, the first HAUTI was included, all others excluded.

A healthcare-associated bacteraemia secondary to HAUTI was defined as a positive blood culture occurring in a patient hospitalized >48 h, where the source was the urinary tract, as indicated by clinical findings and/or a positive urine culture with the same isolate. This definition is considered further in the Discussion.

Multi-resistance was defined as an organism resistant to three or more of amoxicillin + clavulanate, ceftriaxone, gentamicin, trimethoprim, or norfloxacin, using methods described by the Clinical and Laboratory Standards Institute or by the calibrated dichotomous sensitivity test method.

Data sources

Data were collected from two sources: the clinical coding department and the microbiology department. The data sets were merged using the unique district patient hospital number. Data collected from the clinical coding department included patient demographic data, admission and discharge dates, date of death (inpatient mortality, if applicable) and International Classification of Diseases (ICD-10AM) codes for each patient admission. Microbiology data included cultured organism(s), white cell count, and date of specimen collected.

Ethical considerations

Ethics approval for this project was provided by the Human Research Ethics for the Health District and the Human Research Ethics Committees at Avondale College of Higher Education.

Statistical analysis

A descriptive data analysis was performed using IBM SPSS Version 20.0 (IBM, New York, NY, USA). Charlson comorbidity index (CCI) was calculated using an algorithm developed by Sundararajan *et al.*[16] The CCI data were calculated to supply basic comparisons between groups only. This variable was not included in subsequent models, as the timing of comorbidities within an admission period could not be determined due to coding being completed on discharge. For example, we could not determine whether a comorbidity occurred before or after an infection. The comparisons of characteristics between those who acquired HAUTI and those who did not were compared using a chi-squared test or the Mann–Whitney *U*-test for data

that did not follow a normal distribution. Unadjusted odds ratios were calculated using Mantel—Haenszel methods.

Differences in length of stay between those with an infection and those without were calculated using a multi-state model using the 'etm' package in R.[17] Infection is a time-dependent variable, and it is essential to use statistical methods that account for this; otherwise, effects can be severely biased.[6,18,19] Our multi-state model uses four states: susceptible, infected, discharged alive, and dead (Figure 1). Patients become susceptible after admission and they may be discharged, die, or they first become infected. If the time to infection is not modelled, this leads to a time-dependent bias that will overestimate the extra length of stay due to infection.[20] The variance (and confidence intervals) in the extra length of stay was estimated using 1000 bootstrap resamples.

To examine the risk of infection and death, we used the log link in order to obtain the prevalence ratios for death, rather than odds ratios (ORs) (logistic regression) which are prone to time-dependent bias.[21] We subsequently used a survival analysis using a Cox regression model with the day of admission as the time variable to avoid a time-dependent bias.[22] Results are presented as hazard ratios and 95% confidence intervals (CIs). Infection was modelled as a possible predictor of death or discharge; we also examined the interaction between infection and hospital to determine whether post-infection risks differ by hospital. To understand how risk accumulates with time, cumulative incidence functions were calculated.

Results

Overview

There were 162,503 eligible patient admissions from eight participating hospitals. The principal referral hospital for the health district accounted for 94,476 patient admissions (58%). During this time, 2821 or 1.73% (95% CI: 1.67—1.80) of admitted patients acquired a HAUTI. There was no statistically significant difference in the annual incidence of patients acquiring a HAUTI during the study period. Table I summarizes the characteristics of the cohort, comparing those with a HAUTI to those without. Females were significantly more likely to have acquired an infection compared to males (unadjusted OR: 2.5; 95% CI: 2.3—2.7). Those who had an infection were also more likely to die in the hospital than those without an infection (unadjusted OR: 2.3; 95% CI: 1.9—2.7). There were significantly more patients who acquired a HAUTI at the tertiary referral hospital than at a district hospital in the same health service, at 1.9% vs 1.5% ($P < 0.001$). Seventy-eight percent of patients with a HAUTI had a urine white cell count >50 cells/10^6/L. Antimicrobial susceptibility data were analysed in patients who had a HAUTI caused by one organism. These data are presented in Table II.

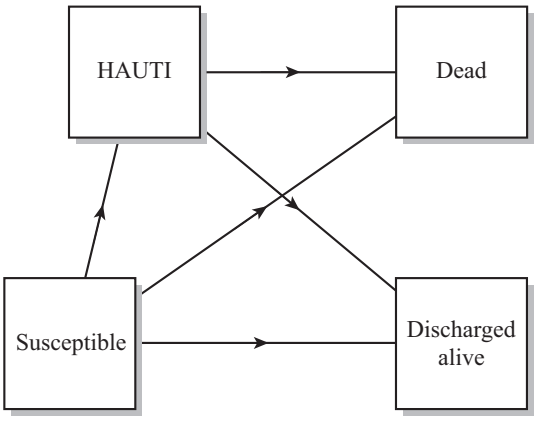


Figure 1. Multi-state model used to determine length of stay.

Seven patients (0.22%) who had a HAUTI were subsequently diagnosed with a healthcare-associated bacteraemia secondary to the HAUTI. In three instances, the causative organism for the healthcare-associated bacteraemia was *Escherichia coli*. All seven patients were discharged alive.

Length of stay

Using a multi-state model, the expected extra length of stay due to HAUTI was four days (95% CI: 3.1—5.0) based on a standard error of 0.48 days. The difference in the extra length of stay remained relatively constant by day of infection (Figure 2). The weight panel shows the frequency of infections over time. The extra length of stay calculated for the tertiary referral hospital in this study was 3.5 days [95% CI: 2.4—4.6; standard error (SE): 0.55]. For all other hospitals combined, the extra length of stay due to HAUTI was 5.0 days (95% CI: 3.4—6.6; SE: 0.8).

Inpatient mortality

Table III presents the data using a Cox regression model adjusting for age, sex, and admission to a tertiary hospital. Women were more likely to acquire an infection and more likely to be discharged. The elderly were less likely to be discharged. There was a significantly reduced risk of discharge at the tertiary referral hospital, which means generally longer hospital stays. Infection also significantly reduced the rate of discharge, which we saw previously with the increased length of stay using a multi-state model.

An infection acquired in the tertiary referral hospital significantly increased the relative hazard of discharge. Therefore, compared with acquiring an infection in another hospital, the extra length of stay is reduced in the tertiary referral hospital. This result was also shown in the extra length of stay estimates using a multi-state model (3.5 days in a tertiary hospital versus 5 days in others). Women were less likely to die, whereas older patients were more likely to die. Death was rarer in the tertiary referral hospital compared to other hospitals, after adjusting for age and sex, whereas acquiring an infection reduced the risk of death.

Cumulative incidence functions are shown in Figure 3. Most infections occurred within the first 50 days of admission (left panel). The cumulative probability of discharge for an infected patient was consistently below that for a non-infected patient (central panel). The cumulative probability of death was greater for an infected patient after around day 20 (right panel). This increased risk was likely to be an indirect effect resulting from the extra length of hospital stay.

Discussion

In all, 1.7% of patients who were hospitalized for more than two days acquired a HAUTI. The elderly and females were at a

Table I
Characteristics of patients with and without a healthcare-associated urinary tract infection (HAUTI)

Characteristic	HAUTI ($N = 2821$)	No HAUTI ($N = 159,682$)	Total ($N = 162,503$)	*P*-value
Sex				
Female	2095 (2.4%)	85,786 (97.6%)	87,881	<0.001
Male	726 (1.0%)	73,896 (99.0%)	74,622	
Age (years)				
Mean (SD)	73 (18.4)	51 (28.5)	52 (28.5)	
Median	78	58	58	<0.001
Length of stay[a]				
Mean (SD)	33.3 (41.4)	8.7 (12.2)	9.1 (13.7)	
Median	21	5	5	<0.001
Charlson comorbidity index				
Mean (SD)	0.84 (1.4)	0.55 (1.1)	0.55 (1.2)	<0.001
Median	0	0	0	
Discharge outcome				
Discharge alive	2660 (94.3%)	155,542 (97.4%)	158,202 (97.4%)	
Inpatient mortality	161 (5.7%)	4140 (2.6%)	4301 (2.6%)	<0.001
Hospital				
Tertiary referral hospital ($N = 1$)	1819 (1.9%)	92,657 (98.1%)	94,476	<0.001
District hospitals ($N = 7$)	1002 (1.5%)	67,025 (98.5%)	68,027	
Infection details				
Mean days to infection	13.7 (18.1)	–		
Median days to infection	8	–		
Causative organisms	3126			
Escherichia sp.	1735 (55.5%)			
Klebsiella sp.	401 (12.8%)			
Proteus sp.	341 (10.9%)			
Citrobacter sp.	271 (8.7%)			
Enterobacter sp.	219 (7.0%)			
Morganella sp.	80 (2.6%)			
Serratia sp.	57 (1.8%)			
Providencia sp.	10 (0.3%)			
Pantoea sp.	6 (0.2%)			
Salmonella sp.	3 (0.1%)			
Raoutella sp.	2 (0.1%)			
Hafnia sp.	1 (<0.1%)			

[a] Provided for background information only. This analysis suffers from length bias.

greater risk of acquiring a HAUTI. We estimate that for each HAUTI, the average extra length of stay in hospital is four days. The incidence of HAUTIs, in addition to the extra length of stay, suggests that HAUTIs place a significant burden on health services. The use of appropriate statistical methods to estimate length of stay due to HAUTIs has been rarely reported in the literature and this study is the first to publish results using a multi-state model from patients in a developed country. As such, our study provides reliable and valuable information for clinicians, infection control professionals, health administrators and policy-makers regarding why HAUTI prevention measures need to be further strengthened.

The incidence of 1.7% of patients acquiring a HAUTI is consistent with other literature, but lower than a multicentred French study that reported an incidence of 4.8%.[1,3,23,24] In the USA, a recent multi-site point prevalence study involving 183 hospitals identified the point prevalence of all HCAIs as 4.0%, with 14.4% of these having a HAUTI.[25] An alarming finding from that study was that 23.6% of all patients on the survey day had a urinary catheter in place.[25] As HAUTIs are frequently associated with urinary catheters, this favours indwelling catheter interventions, such as the prevention of catheter insertion in the first instance and early catheter removal.[26] This point is of greater consequence, as the majority of HAUTIs occur after catheter insertion, which is often unnecessary, as well as due to clinicians being unaware of their existence.[27–30] In our study, we were unable to obtain data on catheter use and the proportion of HAUTIs that were catheter-related. However, we have reported contemporary estimates of the incidence of HAUTIs in Australian settings in previous work.[1]

Studies have documented the extra length of stay due to HAUTIs.[31,32] However, the statistical analysis undertaken did not account for time-dependent bias, and therefore the results are likely to overestimate the impact.[20,33,34] The only study we identified that estimated the extra length of stay due to HAUTIs that accounts for time-dependent bias was conducted on data from 10 developing countries.[35] On average, a UTI infection led to 1.59 extra days (95% CI: 0.58–2.59) in the intensive care unit. The extra length of stay was longest in Turkey (mean: 5.88 days).[35] Our study, conducted in a developed country, identified a much higher length of stay due to HAUTIs. If the extra

Table II
Antimicrobial susceptibility for urine isolates in patients with a healthcare-associated urinary tract infection (HAUTI)

Organism group	No. of strains	% total	Percent susceptible								Multi-resistant[a]
			Ampicillin	Cefazolin/cephalexin	Nitrofurantoin	Amoxicillin + clavulanate	Ceftriaxone	Gentamicin	Trimethoprim	Norfloxacin	
CLSI											
All isolates	1191	100	35%	54%	73%	68%	96%	94%	78%	97%	5%
Escherichia coli	751	63%	44%	63%	97%	75%	98%	96%	79%	96%	3%
Klebsiella sp.	147	12%	0	57%	51%	86%	95%	93%	86%	98%	6%
Proteus mirabilis	114	10	75%	59%	2%	87%	99%	99%	65%	99%	1%
Enterobacter sp.	66	6%	2%	2%	27%	3%	73%	73%	62%	95%	30
Citrobacter sp.	48	4%	0	21%	88%	23%	83%	81%	85%	100	15%
Morganella sp.	29	2%	0	0	3%	0	97%	97%	62%	100	3%
Serratia sp.	30	3%	0	0	0	0	100	100	93%	100	0
Other sp.[b]	6	1%	0	33%	50	50	100	100	83%	100	0
CDS											
All isolates	676	100	53%	87%	80	88%	N/T	97%	89%	97%	2%
Escherichia coli	441	37%	66%	97%	98%	97%		98%	88%	98%	1%
Klebsiella sp.	77	6%	8%	88%	59%	92%		95%	89%	96%	4%
Proteus mirabilis	65	5%	83%	97%	12%	99%		100	94%	100	0
Enterobacter sp.	52	4%	12%	31%	36%	29%		92%	92%	96%	6%
Citrobacter sp.	24	2%	8%	48%	73%	46%		88%	88%	85%	13%
Morganella sp.	8	1%	13%	0	20	0		100	100	100	0
Serratia sp.	5	0	0	60	80	60		100	80	100	0
Providentia sp.	4	0	0	0	0	0		100	100	100	0

N/T, not tested.
CLSI, Clinical and Laboratory Standards Institute, http://clsi.org/.
Calibrated Dichotomous Sensitivity (CDS) Test Method, Sydney, Australia: an Australian antimicrobial testing standard, http://web.med.unsw.edu.au/cdstest/GTF_CDS_site/WebPages/HomeLevel/CDSoverview.htm.
Antimicrobial susceptibility data were analysed in patients who had a HAUTI caused by one organism. During the study period, four hospitals used a laboratory using CLSI and four hospitals used CDS. No changes in methods were undertaken during the study period.
[a] Resistant to three or more of amoxicillin + clavulanate, ceftriaxone, gentamicin, trimethoprim, or norfloxacin.
[b] *Raoutella* and *Providentia* species.

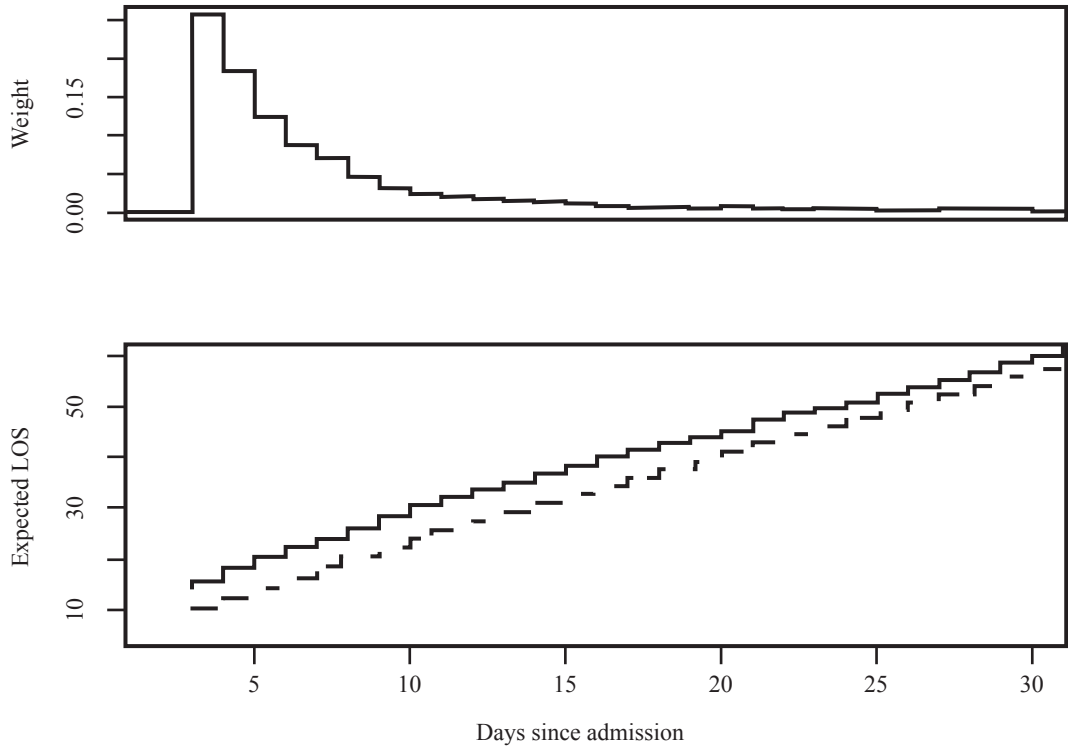


Figure 2. Extra length of stay in patients with (solid line) and without (dashed line) a healthcare-associated urinary tract infection. LOS, length of stay.

length of stay due to HAUTIs in developed countries were closer to the rate identified in our study, the burden HAUTIs place on healthcare systems internationally would be considerable. Further, there are additional costs, such as diagnostic and medical costs, associated with catheter-associated UTIs, one widespread type of HAUTI.[36]

Our data suggest that 1.73% of patients admitted to hospital acquire a HAUTI. Assuming there are 5.5 million admissions to public hospitals each year in Australia, ~95,150 patients admitted would acquire a HAUTI each year in Australia (assuming that our data were nationally representative).[37] This equates to ~380,600 extra public hospital bed-days used each year in Australia, purely because of patients acquiring a HAUTI in hospital. A 10% reduction in the incidence of HAUTI could free up ~38,600 bed-days.

Table III
Risk of HAUTI, discharge, and death using a Cox regression model

Outcome	Predictor	HR	95% CI	*P*-value
HAUTI	Sex (female)	2.74	2.57–3.04	<0.001
HAUTI	Age (10-year increase)	1.31	1.28–1.33	<0.001
HAUTI	Tertiary hospital	1.26	1.16–1.37	<0.001
Discharge	Sex (female)	1.12	1.11–1.13	<0.001
Discharge	Age (10-year increase)	0.91	0.91–0.92	<0.001
Discharge	Tertiary hospital	0.80	0.79–0.80	<0.001
Discharge	HAUTI (yes vs no)	0.78	0.73–0.83	<0.001
Discharge	Tertiary hospital and HAUTI	1.23	1.14–1.32	<0.001
Dead	Sex (female)	0.71	0.67–0.75	<0.001
Dead	Age (10-year increase)	1.40	1.38–1.43	<0.001
Dead	Tertiary hospital	0.74	0.69–0.78	<0.001
Dead	HAUTI (yes vs no)	0.77	0.60–0.98	0.034
Dead	Tertiary hospital and HAUTI	1.08	0.78–1.48	0.650

HAUTI, healthcare-associated urinary tract infection; HR, hazard ratio; CI, confidence interval.

We identified that the risk of acquiring a HAUTI was higher in a tertiary referral hospital compared to district hospitals. Perhaps this reflects more complex and older patients being admitted to this type of hospital. However, deaths were rarer in the tertiary referral hospital compared to other hospitals after adjusting for age and sex. Conversely, acquiring an infection reduced the risk of death, perhaps reflecting the ability of a tertiary referral hospital to successfully treat and manage those with a HAUTI. We identified differences in mortality between those with a HAUTI and those without, consistent with other studies.[32,35,38] However, after adjusting for other factors, we were unable to identify any difference in mortality between hospitals, a finding consistent with Rosenthal *et al.*[35]

There are limitations to our study. Our use of a laboratory-diagnosed definition of a HAUTI would contribute to an ascertainment bias. This may result in an underestimation of the incidence of HAUTIs, as uncomplicated UTIs may be diagnosed and treated by clinicians without sending a laboratory sample for culture. Furthermore, positive cultures with Gram-positive or fungal pathogens or with low counts of Enterobacteriaceae were excluded. Conversely, complicated or recurring UTIs are potentially more likely to have a urine sample sent for analysis. Also, for various reasons, urine cultures that exhibit bacteriuria may be submitted from minimally symptomatic patients who

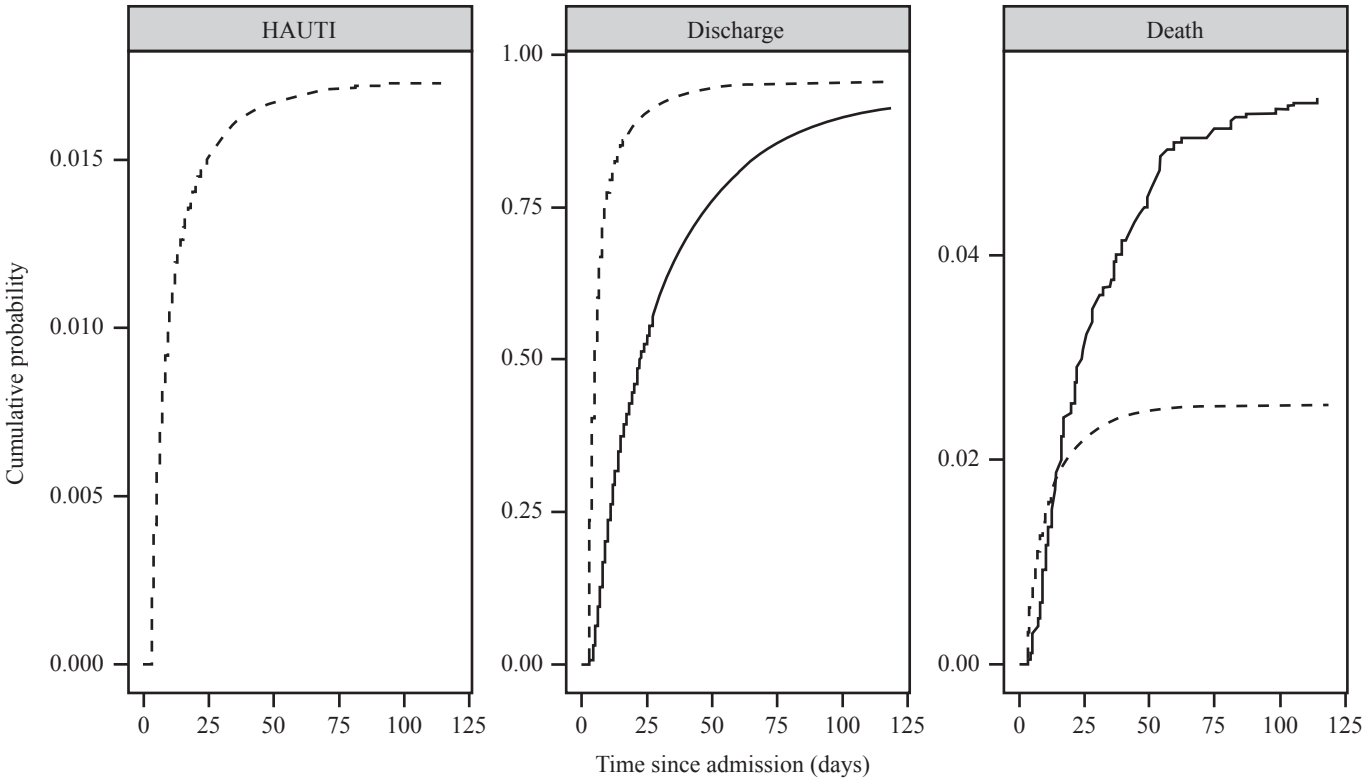


Figure 3. Cumulative incidence functions for healthcare-associated urinary tract infection (HAUTI), discharge, and death (unadjusted). Solid lines: HAUTI; dashed lines: no HAUTI.

do not in fact have a UTI, i.e. asymptomatic bacteriuria. To address this concern, we reviewed the medical notes of a random sample of 318 HAUTI patients. The sample number of 318 was based on a 5% margin of error, with a 50% distribution of patients who had an electronic medical record. The vast majority of these patients (83%; 95% CI: 74—94%) had signs or symptoms of UTI (based on definitions from the National Healthcare Safety Network, Centers for Disease Control and Prevention, Atlanta, GA, USA) or a medical diagnosis of UTI explicitly documented in their notes.[12] Of the remainder (54 patients), 50% ($N = 27$) had catheter, making diagnosis more challenging. None the less, 13 of the 27 patients had documented evidence of a change in urine appearance coinciding with the specimen collection date. We therefore believe the definition applied in our study was robust and suitable for the outcome measures observed. The definition we used is consistent with one approach described in the literature.[39,40] We were also unable to ascertain the proportion of HAUTIs that were catheter-associated or catheter utilization rates. Such an analysis was beyond the available resources due to the sample size of the study and, as catheter-associated UTIs were not an outcome measure, such data are not relevant.

Our study indicates that the incidence of HAUTI, alongside its associated extra length of stay in hospital, presents a burden to the Australian hospital system. These findings, coupled with increasing antimicrobial resistance and point prevalence studies undertaken in several Australia hospitals, suggest that it is time to consider systematic interventions to reduce the incidence and the potential for a form of national HAUTI surveillance.[1]

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Conflict of interest statement
None declared.

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