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Risk factors for catheter-associated urinary tract infections

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<td>Complete List of Authors:</td>
<td>Letica, Allison; Massachusetts General Hospital, Department of Surgery Salmasian, Hojjat; Brigham and Women's Hospital, Department of Quality and Safety; Harvard Medical School, Division of General Internal Medicine Vawdrey, David; NewYork-Presbyterian Hospital, Value Institute; Columbia University Medical Center, Department of Biomedical Informatics Youngerman, Brett; Columbia University Medical Center, Department of Neurological Surgery Green, Robert; NewYork-Presbyterian Hospital, Deartment of Quality; Columbia University, Department of Medicine Furuya, E. Yoko; Columbia University College of Physicians and Surgeons, Division of Infectious Disease, Department of Medicine Calfee, David; NewYork-Presbyterian Hospital; Columbia University College of Physicians and Surgeons, Division of Infectious Disease, Department of Medicine Perotte, Rimma; NewYork-Presbyterian Hospital, Value Institute; Columbia University Medical Center, Department of Biomedical Informatics</td>
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Risk factors for catheter-associated urinary tract infections

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Word Count: 2,652

Abstract

Motivation: Catheter-associated urinary tract infections (CAUTI) are a common and serious healthcare-associated infection. Despite many efforts to reduce the occurrence of CAUTI, there remains a gap in the literature about CAUTI risk factors, especially pertaining to the effect of catheter dwell-time on CAUTI development.
Objective: To determine the risk factors associated with CAUTI and to assess whether time from catheter insertion to CAUTI event varied according to demographic differences such as age, sex, patient type (surgical vs. medical), and comorbidities.

Design: Retrospective cohort study of all patients who were catheterized across a period of 4 years from 2012-2016, including those who did and did not develop CAUTI events. Both pediatric and adult patients were included. The study population was 49,298 patients who collectively had 62,692 catheterizations. Indwelling urinary catheterization is the exposure variable. The variable is interval, as all participants were exposed but for different lengths of time.

Setting: Urban academic health system of over 2,500 beds. The system encompasses two large academic medical centers, two community hospitals, and a pediatric hospital.

Results: The primary outcome was catheter dwell-time’s effect on the time-to-CAUTI after controlling for patient demographic variables. Secondary outcomes included other factors associated with CAUTI infections and the differences between pediatric and adult populations. 884 patients (1.41%) developed a CAUTI. The overall mean duration of catheterization was 11.06 days (SD = 10.2) for those who developed a CAUTI and 6.19 (SD=5.8) for those who did not. CAUTI rates were found to increase non-linearly for each day of catheterization to 4.19% on day 14 and 11.7% on day 30.

Conclusions: For all patients, regardless of age, sex, or comorbidities, the duration of catheterization is a significant risk factor for developing a CAUTI.

Article Summary

Strengths and limitations of this Study

- The analysis focused on a very large population of patients: four years of data across 62,000 catheterizations and over 40,000 patients.
• The methodology not only controls for age, gender, and patient type but patient comorbidities as well.
• The study assesses CAUTI risk factors in both the pediatric and adult populations.
• The definition used for CAUTI was changed by the CDC in January 2015 and therefore the CAUTI population in our study is not homogeneous.
• The capabilities of the EHR limited our ability to collect some granular data that may have supplemented the analysis.

Introduction

Catheter-associated urinary tract infections (CAUTI) continue to be among the most common healthcare-associated infections in the United States. In 2011, there were an estimated 93,000 cases of CAUTI in U.S. acute care hospitals.[1] CAUTIs can lead to more serious complications such as sepsis and endocarditis, and it is estimated that over 13,000 deaths each year are associated with healthcare-associated UTIs.[2]

For an infection to be classified as a CAUTI under guidelines published by the U.S. Centers for Disease Control and Prevention (CDC), a patient must have: (a) had an indwelling urinary catheter for more than two days by the date of event (with “day one” being the day of catheter insertion); (b) one sign or symptom including fever, suprapubic tenderness, CVA tenderness, urinary frequency or urgency or dysuria; and (c) urine culture with more than $10^5$ CFU/ml of one bacterial species (non-bacterial pathogens have been excluded since 2015). As it is estimated that 69% of CAUTI events are avoidable,[3] the U.S. Department of Health and Human Services spearheaded national efforts in 2009 to reduce CAUTI rate.[4] The efforts undertaken to reduce CAUTI rates include avoiding unnecessary catheterization, reducing duration of catheterization (e.g., by using reminder systems to encourage catheter removal when the catheter is no longer indicated), emphasizing antiseptic technique for insertion, and using hydrophilic-coated catheters.[5-6]

Despite advances in prevention guidelines, there remains a lack of knowledge concerning risk factors for CAUTI. A seminal study from Garibaldi and colleagues in 1974 examined 405 patients with indwelling urinary catheters,
concluding that female sex, age greater than 50 years, higher severity of illness, non-surgical illness, and no systemic antibiotics were independent risk factors for the development of CAUTI (defined then as bacteriuria of more than $10^2$ CFU/ml).[7] Importantly, Garibaldi also reported that catheter dwell-time (i.e., number of days spent catheterized) was a significant risk factor for CAUTI, with a 7.4% risk of infection in the 24 hours following insertion, and a steady 8.1% risk increase each subsequent day for the first seven days.[7] Further studies in the 1980s reproduced these risk factors, adding catheter care violations and non-sealed catheter junctions as risk factors as well.[8]

Overall, there have been very few studies that focus on understanding CAUTI risk factors, including dwell-time of the catheter.[9-10] To the best of our knowledge, no study since 1974 has attempted to provide an estimate of the daily risk of maintaining a urinary catheter, a principle that could have significant implications in refining CAUTI prevention guidelines. Further, additional risk factors in subpopulations such as pediatric patients need to be better identified. We conducted a retrospective review of data from electronic health records to help illuminate CAUTI risk factors.[11]

The objective of this study was to identify the risk factors for CAUTI in adult and pediatric populations, analyzing data from a large EHR dataset of routine nursing documentation.

**Methods**

**Setting**

The study was conducted at an urban academic health system comprising of two large academic medical centers, two community hospitals, and a pediatric hospital. Together the hospitals had over 2,500 beds. The Institutional Review Board reviewed the study and granted approval.

**Review of Electronic Health Record Nursing Documentation**

We reviewed all infections associated with catheters that occurred between January 1, 2012 and March 30, 2016. For all patients hospitalized at the study sites during this time period, we identified “catheter days”, i.e., the number
of calendar days during which the patient had an indwelling urinary catheter (IUC) as recorded in nursing
documentation in the EHR. CAUTI events were matched to respective IUC data based on patients’ medical record
number and admission date. Data were excluded if duration of IUC was less than two days to match the CDC
criteria for defining CAUTI.[12] If multiple CAUTI events occurred during one IUC period, only the earliest
CAUTI was included in our analysis (i.e., our analysis examined event-free survival for each IUC period). All ages
and all types of infections (bacterial and fungal) were included in the study.

Statistical Analysis
We performed analyses to identify: the factors associated with CAUTI; and to determine if the time from IUC
insertion to a CAUTI event varied according to demographic differences. The EHR data were analyzed to assess the
effect of the catheter duration on CAUTI development. For categorical data, analyses were carried out using chi-
squared tests of independence to identify differences in patients and for continuous data, t-tests were used to test for
significance.

Survival analyses were completed on the EHR nursing documentation data, with primary outcomes being event-free
survival—i.e., number of days between IUC insertion and either CAUTI occurrence or IUC removal with no CAUTI
event. Sex and age factors were examined. A comorbidity score was computed for each patient, using the Charlson
Comorbidity Index (CCI)[13] using an automated method described in [14]. The CCI assigns weights to 17 different
comorbidities and was originally designed to predict 10-year survival in patients (i.e. the higher a patient’s CCI, the
more likely they are to die).

Survival analysis was carried out with the 17 comorbidities that Charlson extracts, controlling for sex, age, and
patient type (medical vs. surgical). In addition, to assess the risk factors for CAUTI in the pediatric population and
how they differ from the adult population, the population was broken into pediatric (0-17 years of age) and adult (18
or more years of age) patients. The significance of each variable's effect on time-to-infection was assessed using the
Cox proportional hazards model. Kaplan-Meier curves demonstrating the cumulative risk of CAUTI over 30 days
were created for each of the factors found to be significant. All statistical analyses were carried out using the R
programming language.[15]
Results

From January 2012 to March 2016, there were 49,298 patients with 62,692 IUCs in place for greater than two days. From this total population of patients with IUCs, there were 884 CAUTI events (1.41%). Overall mean duration of IUC from first insertion was 11.06 days (SD = 10.2) for patients who developed a CAUTI and 6.19 (SD=5.8) for those who did not.

Catheterizations and CAUTI Rates

The study of over 60,000 catheterization events for the 2012-2016 time period found a CAUTI rate of 1.64 per 1000 catheter-days. The CAUTI rates for the pediatric population (0-17 years of age) and adult population (18 or more years of age) were 2.1 and 1.6 per 1000 catheter-days, respectively, a non-statistically significant difference.

There were significant differences identified in terms of sex, adult vs. pediatric patients, and mean duration of catheterization between the patients that developed a CAUTI and those that did not (Table 1). Females were 1.8 times more likely to develop CAUTI than males and pediatric patients were found to be more likely to develop CAUTIs.

Time-to-event analysis

Mean duration of catheterization for all IUCs was 6.26 days (SD = 5.89), and the duration was longer in those who had a CAUTI event compared to those who did not (Table 1). Of the 884 CAUTIs that occurred in the 4-year time period, the highest proportion of infections occurred on day 4 of IUC (13.4%). Cumulatively, 76.4% of all CAUTIs occurred by day 14 and 94.1% occurred by day 30 of IUC period, respectively (Figure 1). The cumulative CAUTI rate increased non-linearly to 4.19% and 11.70% by IUC days 14 and 30, respectively, while the total number of patients with indwelling catheters decreased steadily for each duration (Figure 2a and Figure 2b).

Analyzing disease-free survival demonstrated that pediatric patients were at a higher risk of developing a CAUTI, the pediatric population had 1.45x the risk of CAUTI (p=0.013) (Figure 3). Additionally, our study confirmed
previous reports that female sex was a significant risk factor for CAUTI in the overall population (p<.001), males had 0.55x the hazard of developing a CAUTI (Figure 4a). This effect remained for the pediatric population as well, however the effect was smaller, with males having 0.32x the hazard of being infected with a CAUTI (p=0.004) (Figure 4b).

The Charlson Comorbidity Index score for all catheterized patients ranged from 0-22, with a median of 4 and a mean of 4.6. CCI score was found to not be a significant factor, even when patients were stratified between scores of 0-2 and 3+. Multivariate analysis of the CCI variables controlling for age and sex demonstrated that congestive heart failure (CHF) was associated with a lower incidence of CAUTI by 0.72x (p<0.001), whereas cerebral vascular accident (CVA) and paraplegia (PAR) increased the risk by 1.93x (p<0.001) and 1.26x (p=0.009), respectively. The addition of comorbidities did not substantially change the hazard for males (0.56x), however an age of >65 years was found to be a non-significant risk factor after adjusting for comorbidities. Non-significant CCI variables in the multivariate analysis were as follows: acute myocardial infarction, peripheral vascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, severe liver disease, diabetes complications, renal disease, cancer, metastatic cancer. Overall, adding CCIs as covariates slightly improved the model fit, but the other predictors remained significant.

Discussion

CAUTIs pose a significant burden on patients, both in terms of morbidity and mortality. Apart from the clear harm posed to patients, governmental pressure has helped hospitals across the country focus even more effort on CAUTI reduction. CAUTI rates are incorporated into both government quality ratings through the Centers for Medicaid and Medicare quality star ratings, as well as financial penalties through the HACRP (Hospital Acquired Condition Reduction Penalty) program.

However, while some CAUTI-reduction efforts have shown positive results,[3,16] CAUTI rates in the U.S. still increased by 6.0% from 2009 to 2013.[3] CAUTIs remain one of the most common nosocomial infections, however, there is little evidence on what specific factors lead to these infections. If we are able to identify factors that are
associated with the development of CAUTIs, we will then be able to modulate our preventive strategy accordingly, specifically modifying the standard of care for hospital practice as well as implementing targeted electronic alerts, such as alerting at a higher frequency for pediatric patients.

Prompt removal of indwelling urinary catheters at the earliest possibility has been a cornerstone of CAUTI reduction programs in the published literature, and the toolkit developed by the Agency for Healthcare Research and Quality to reduce CAUTIs also emphasizes on prompt removal of IUCs.[17] Nevertheless, evidence on the additive hazard of IUC duration in development of CAUTI had not been updated for more than three decades. Our study is the first to revisit this association for a very large cohort of patients and provide novel evidence about the various risk factors for CAUTI in hospitalized patients.

**Root Cause Analyses for CAUTI events**

In addition to the EHR-derived IUC data, we were able to obtain the records from a collection of root cause analyses (RCA) performed for patients who contracted a CAUTI. RCAs are routinely performed at healthcare institutions and have been previously found to help in understanding the underlying causes for infection.[18]

Our study had RCA data available for 10% of the total CAUTIs in the study population. Analysis of the RCA data identified that the most common indications for catheterization were recording inputs and outputs, critical illness, peri-operative status, and diuresis. The most common contributing factors for CAUTI that were identified by the clinical teams and infection preventionists were comorbidities, lapses in catheter care protocols, active infection, fecal incontinence, and duration of indwelling urinary catheter. The duration of indwelling urinary catheter was identified as a contributing factor for 16.5% of the CAUTI cases, however, for almost 25% of the cases reviewed in the RCAs, the clinical teams and infection preventionists stated that the catheters could have been removed earlier.

**Contributions to the CAUTI risk factor literature**

Our study upholds previous findings and provides new insights as well. As has been previously reported, longer duration of catheterization and female sex are both risk factors for the development of CAUTI[7,19-22].

Interestingly, using the same adult age brackets (18-50 years old and over 50 years old) as the Garibaldi et al. 1974 study, we found that younger adults had a 1.33x greater hazard for developing a CAUTI (p < 0.001), which is the...
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opposite of the results in the original study. When we adjust for life expectancy differences and look at patients ages 18-64 vs. patients ages 65+, the risk of CAUTI remained higher in younger patients than in older patients. However, when adding comorbidities to the analysis, age was no longer found to be a significant factor, implying that age in itself may not be a risk factor.

As the data for CAUTIs in pediatric patients is limited, the current study supplements available medical literature. Goudie et al [23] studied healthcare-associated infections in the pediatric population and found that the risk of CAUTIs in girls was more than three times higher than that in boys. Our study demonstrated a very similar significant difference between the sexes. In addition, our study showed that pediatric patients had a higher risk of being infected than their adult counterparts, suggesting that even more caution should be undertaken in children with catheters.

While there is little literature to compare to our findings regarding the Charlson Comorbidity Index, there were both expected and unexpected findings with this data. Both stroke and paraplegia being risk factors for CAUTI were expected, as neurologic units have been shown to have higher rates of CAUTI as compared to other units. [24] As was demonstrated by Titsworth et al.,[25] introducing UTI bundles and practicing a higher-level vigilance in neurological intensive care units can decrease the rate of infection in this subset of patients. Although the CCI was created to predict mortality and not infection susceptibility, it was unexpected that the overall comorbidity score did not affect risk of CAUTI as we expect increased comorbidity burden to increase risk of infection. The most surprising result was congestive heart failure (CHF) was associated with a lower risk of CAUTI in our population. One possible explanation for this result is that many patients with CHF have a very specific indication for catheterization, namely diuresis, and are monitored vigilantly for euvolemic fluid status which prompts timely removal of the catheter. The current analysis does not distinguish between patients with a longstanding diagnosis of CHF and patients that are in the hospital for a CHF exacerbation, so this data cannot be extrapolated to infer that patients with CHF exacerbation have a lower risk of CAUTI, but this is an area that is important for future analysis.

While previous studies have reported on various metrics of CAUTI risk relative to IUC duration, our study demonstrates a nonlinear increase in the cumulative risk hazard as duration increases, suggesting that each extra day...
of catheterization incrementally increases the risk of CAUTI. As the RCA data revealed that almost one quarter of patients could have had their catheters removed earlier and the EHR-derived data identified that the highest proportion of CAUTIs were contracted on day 4, these results can help encourage automated alerts for the removal of IUCs and inform their timing.

Our study also has a number of limitations. First, the definition used for CAUTI was changed by the CDC in January 2015 and therefore the CAUTI population in our study is not homogeneous; for instance, non-bacterial forms of UTI could be counted as CAUTI in the data from 2012 to 2014, but not in the data from 2015 and 2016.[26] If we assume that the daily additional risk of CAUTI differs in fungal versus bacterial UTI, then this heterogeneity in the data may have confounded our results. Second, the capabilities of the EHR limited our ability to collect some granular data that may have supplemented the analysis.

Conclusions

Our findings indicate that indwelling urinary catheter dwell-time is a significant risk factor for patients who develop CAUTIs, even when controlling for sex, age, and patient comorbidities. Our study finds that approximately 12% of patients who have a catheter inserted for 30 days will develop a CAUTI. The findings of this study can help guide efforts for future CAUTI reduction programs.

Contributorship

Concept and design: Letica, Salmasian, Vawdrey, Perotte.

Acquisition, analysis, or interpretation of data: Letica, Salmasian, Perotte, Youngerman.

Drafting of the manuscript: Letica, Salmasian, Vawdrey, Green, Furuya, Calfee, Perotte, Youngerman.

Critical revision of the manuscript for important intellectual content: Letica, Salmasian, Vawdrey, Youngerman, Green, Furuya, Calfee, Perotte.

Statistical analysis: Letica, Perotte, Salmasian.

Supervision: Perotte, Vawdrey, Salmasian.
Data Sharing

No additional data available.

Funding and Competing Interests Statement

There is no funding to report for this research. No competing interests declared for any author.

References


Table 1: Descriptive Data for the Full Population of Catheterized Patients. The table compares descriptive statistics for patients who developed CAUTIs and those who did not.

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<td>120 (13.6%)</td>
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<td>258 (29.2%)</td>
<td>16701 (27.2%)</td>
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<tr>
<td>65+</td>
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<td>Sex</td>
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<tr>
<td>Female</td>
<td>537 (60.8%)</td>
<td>30069 (49.1%)</td>
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<td>Duration of catheterization</td>
<td>Mean (days)</td>
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<td>6.19 (SD 5.8)</td>
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*Student’s t-test, Chi-squared analysis.

Figure 1: Cumulative percentage of 884 catheter-associated urinary tract infections (CAUTI) developed by day of indwelling urinary catheter (IUC). The scale starts at day 3 as only patients who had catheters inserted for at least two days were included in the analysis.

Figure 2: (a) Cumulative Total CAUTI Rate at Each Day of IUC up to 30 days. Error bars are 95% CI for single proportions without continuity correction. Power trend lines were fit with equation and the coefficient of determination (R^2) demonstrated.

(b) Total Number of Patients with IUCs inserted vs. Cumulative CAUTI Rate up to 30 days.

Figure 3: Infection-free survival stratified by age group. Kaplan-Meier survival curve comparing adult (18+ years old) versus pediatric (0-17 years old) groups for up to 30 days.

Figure 4: Infection-free survival stratified by gender, for each age group. Kaplan-Meier survival curves for (a) all patients and (b) pediatric patients up to 30 days.
Cumulative percentage of 884 catheter-associated urinary tract infections (CAUTI) developed by day of indwelling urinary catheter (IUC). The scale starts at day 3 as only patients who had catheters inserted for at least two days were included in the analysis.
Cumulative Total CAUTI Rate at Each Day of IUC up to 30 days. Error bars are 95% CI for single proportions without continuity correction. Power trend lines were fit with equation and the coefficient of determination (R²) demonstrated.
Total Number of Patients with IUCs inserted vs. Cumulative CAUTI Rate up to 30 days.
Infection-free survival stratified by age group. Kaplan-Meier survival curve comparing adult (18+ years old) versus pediatric (0-17 years old) groups for up to 30 days.

287x172mm (300 x 300 DPI)
Infection-free survival stratified by gender, for each age group. Kaplan-Meier survival curves for all patients.
Infection-free survival stratified by gender, for each age group. Kaplan-Meier survival curves for pediatric patients up to 30 days.

287x172mm (300 x 300 DPI)
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**Secondary Subject Heading:** Epidemiology

**Keywords:** Infection control < INFECTIONOUS DISEASES, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Catheter-Related Infections, Patient Safety

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Identifying the risk factors for catheter-associated urinary tract infections: a large cross-sectional study of six hospitals

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Keywords: Catheter-Related Infections; Patient Safety; Infection Control; Quality Indicators, Health Care

Word Count: 3,040
Abstract

Motivation: Catheter-associated urinary tract infections (CAUTI) are a common and serious healthcare-associated infection. Despite many efforts to reduce the occurrence of CAUTI, there remains a gap in the literature about CAUTI risk factors, especially pertaining to the effect of catheter dwell-time on CAUTI development and patient comorbidities.

Objective: To examine how the risk for CAUTI changes over time. Additionally, to assess whether time from catheter insertion to CAUTI event varied according to risk factors such as age, sex, patient type (surgical vs. medical), and comorbidities.

Design: Retrospective cohort study of all patients who were catheterized from 2012-2016, including those who did and did not develop CAUTIs. Both pediatric and adult patients were included. Indwelling urinary catheterization is the exposure variable. The variable is interval, as all participants were exposed but for different lengths of time.

Setting: Urban academic health system of over 2,500 beds. The system encompasses two large academic medical centers, two community hospitals, and a pediatric hospital.

Results: The study population was 47,926 patients who had 61,047 catheterizations, of which 861 (1.41%) resulted in a CAUTI. CAUTI rates were found to increase non-linearly for each additional day of catheterization; CAUTI-free survival was 97.3% [CI: 97.1-97.6] at 10 days, 88.2% [CI: 86.9-89.5] at 30 days, and 71.8% [CI: 66.3-77.8] at 60 days. This translated to an instantaneous hazard ratio of .49%-1.65% in the 10-60 day time range. Paraplegia, cerebrovascular disease and female sex were found to statistically increase the chances of a CAUTI.

Conclusions: Using a very large data set, we demonstrated the incremental risk of CAUTI associated with each additional day of catheterization, as well as the risk factors that increase the hazard for CAUTI. Special attention should be given to patients carrying these risk factors, e.g. females or those with mobility issues.
Article Summary

Strengths and limitations of this study

- The analysis focused on a very large population of patients: four years of data across 61,000 catheterizations and over 47,000 patients.
- The methodology not only controls for age, sex, and patient type but patient comorbidities as well.
- The definition used for CAUTI was changed by the CDC in January 2015 and therefore the CAUTI population in our study is not homogeneous.
- The capabilities of the electronic health record limited our ability to collect some granular data that may have supplemented the analysis.

Introduction

Catheter-associated urinary tract infections (CAUTI) continue to be among the most common healthcare-associated infections in the United States. In 2011, there were an estimated 93,000 cases of CAUTI in U.S. acute care hospitals.[1] CAUTIs can lead to more serious complications such as sepsis and endocarditis, and it is estimated that over 13,000 deaths each year are associated with healthcare-associated UTIs.[2]

For an infection to be classified as a CAUTI under guidelines published by the U.S. Centers for Disease Control and Prevention (CDC), a patient must have: (a) had an indwelling urinary catheter for more than two days by the date of event (with “day one” being the day of catheter insertion); (b) one sign or symptom including fever, suprapubic tenderness, costovertebral angle tenderness, urinary frequency or urgency or dysuria; and (c) urine culture with more than 10^5 CFU/ml of one bacterial species (non-bacterial pathogens have been excluded since 2015). As it is estimated that 69% of CAUTI events are avoidable,[3] the U.S. Department of Health and Human Services spearheaded national efforts in 2009 to reduce CAUTI rate.[4] The efforts undertaken to reduce CAUTI rates include avoiding unnecessary catheterization, reducing duration of catheterization (e.g., by using reminder systems to encourage catheter removal when the catheter is no longer indicated), emphasizing antiseptic technique for insertion, and using hydrophilic-coated catheters.[5-6]

Despite advances in prevention guidelines, there remains a lack of knowledge concerning risk factors for CAUTI. A seminal study from Garibaldi and colleagues in 1974 examined 405 patients with indwelling urinary catheters,
concluding that female sex, age greater than 50 years, higher severity of illness, non-surgical illness, and no systemic antibiotics were independent risk factors for the development of CAUTI (defined then as bacteriuria of more than 10^2 CFU/ml).[7] Importantly, Garibaldi also reported that catheter dwell-time (i.e., number of days spent catheterized) was a significant risk factor for CAUTI, with a 7.4% risk of infection in the 24 hours following insertion, and a steady 8.1% risk increase each subsequent day for the first seven days.[7] Further studies in the 1980s reproduced these risk factors, adding catheter care violations and non-sealed catheter junctions as risk factors as well.[8]

Overall, there have been very few studies that focus on understanding CAUTI risk factors, including dwell-time of the catheter.[9-10] To the best of our knowledge, no study since 1974 has attempted to provide an estimate of the daily risk of maintaining a urinary catheter, a principle that could have significant implications in refining CAUTI prevention guidelines. Further, additional risk factors such as comorbidities need to be better identified. We conducted a retrospective review of data from electronic health records to help illuminate CAUTI risk factors.[11]

The objective of this study was to examine how the risk for CAUTI changes over time and identify the risk factors for CAUTI by analyzing data from a large electronic health record (EHR) dataset of routine nursing documentation.

Methods

Setting

The study was conducted at an urban academic health system comprising of two large academic medical centers, two community hospitals, and a pediatric hospital. Together the hospitals had over 2,500 beds. The Institutional Review Board reviewed the study and granted approval.

Patient and Public Involvement

This research was conducted in reaction to the efforts focused on reducing CAUTI rates, which is a concern to both providers and patients alike. However, the study is a retrospective analysis of data collected as part of care, therefore there was no direct involvement of patients in design, recruitment and conduct of the study.
Review of Electronic Health Record Nursing Documentation

We reviewed all infections associated with catheters that occurred between January 1, 2012 and March 31, 2016. For all patients hospitalized at the study sites during this time period, we identified “catheter days”, i.e., the number of calendar days during which the patient had an indwelling urinary catheter (IUC) as recorded in nursing flowsheet documentation in the EHR. CAUTI presence was extracted from Infection Prevention and Control logs as they are manually assigned after detailed review, using the definition that is set forth by National Healthcare Safety Network (NHSN) within the Center for Disease Control (CDC). Both flowsheet documentation and CAUTI presence logs contained patient medical record number and admission date, these two identifiers were used to link the IUC data with the CAUTI events. If multiple CAUTI events occurred during one IUC period, only the earliest CAUTI was included in our analysis (i.e., our analysis examined event-free survival for each IUC period). However, if there was a reinsertion, this was considered a new IUC period and therefore a CAUTI during this new period would be eligible for the study. All ages and all types of infections (bacterial and fungal) were included in the study.

Statistical Analysis

We calculate and report a CAUTI rate per 1000 catheter days using the full population of catheterizations, as is standard. For the subsequent analyses, the population is filtered to remove all catheterizations with an IUC duration of less than 3 days (this is to match the CDC criteria for defining CAUTIs) [12]. To address the issue of missing data, any catheterizations for patients who were missing covariates are removed (Supplementary Figure 1).

We performed a time-independent analysis to evaluate differences between catheterizations that resulted in a CAUTI and those that did not. Differences in continuous variables were assessed with a t-test and differences in categorical variables were assessed with a chi-squared test. The time-independent analysis was followed by survival analyses to characterize event-free survival — i.e., number of days between IUC insertion and either CAUTI occurrence or IUC removal with no CAUTI event. As CAUTI is defined as infection that occurs any time after the second day of catheter placement, it is impossible for a CAUTI to exist prior to day 3. Therefore, risk for CAUTI begins at day 3 by definition. In our survival analyses, day 3 is considered the start time.
A Kaplan-Meier estimate was computed to evaluate the instantaneous hazard rates for developing a CAUTI and the
time-dependent differences in subpopulations found to be significant in the time-independent analysis. The time-
dependent differences in infection-free survival rates are reported in the full population, the population stratified by
pediatric vs. adult patients, and stratified by female vs. male patients.

Finally, after testing the proportional hazard assumption and finding that it is not violated, we performed a Cox
Proportional Hazard analysis. To address potential biases we adjusted for a set of confounders. Univariate Cox
models were created to assess the effect of each variable’s effect on time-to-infection; overall Charlson Comorbidity
Index (CCI) score[13], the presence or absence of the 17 comorbidities that are included in CCI, sex, age, and
patient type (medical vs. surgical) were examined. CCI was computed for each patient using an automated method
described in [14]. The CCI assigns weights to the 17 different comorbidities and was originally designed to predict
10-year survival in patients (ie. the higher a patient’s CCI, the more likely they are to die). The 17 comorbidities
included were: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease,
dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, diabetes
with complications, paraplegia, renal disease, cancer, metastatic cancer, severe liver disease, HIV. The variables
found to be significant in the univariate models were included in the multivariate Cox Proportional Hazard model.

All statistical analyses were carried out using the R programming language [15], using the survival and survminer
packages.

Results

CAUTI Rates

From January 2012 to March 2016, there were 148,631 catheterizations for 115,710 patients. The 148,631
catheterization events for the 2012-2016 time period totaled 540,494 catheter days. We identified a CAUTI rate of
1.64 per 1000 catheter-days [95% CI: 1.63-1.65] for the total population. The pediatric population (0-17 years of
age) had a total of 23,531 catheter days and a CAUTI rate of 2.08 [95% CI: 1.56-2.78] per 1000 catheter-days. The
adult population (18+ years of age) had a total of 517,335 catheter days and a CAUTI rate of 1.61 [95% CI: 1.51-1.73] per 1000 catheter-days, representing a non-statistically significant difference with the pediatric population.

Time-Independent Analysis

To align with CDC CAUTI definitions and remove missing data, all catheterizations with missing data or IUC duration of less than 3 days were removed from the analysis. This filtration resulted in a cohort of 47,926 patients with 61,047 catheterizations and a total of 381,951 catheter days (16,254 pediatric catheter days and 365,697 adult catheter days). From this total population of patients with IUCs and without missing data, there were 861 CAUTI events (1.41% [1.32-1.51]). Overall median duration of IUC from first insertion was 7 days (IQR=10) for patients who developed a CAUTI and 4 days (IQR=4) for those who did not. Median duration of catheterization for all IUCs was 4 days (IQR = 4).

There were significant differences identified in terms of age, sex, and CCI between the patients that developed a CAUTI and those that did not (Table 1). The results indicate that pediatric patients and women are more prone to develop CAUTIs. We also see evidence that older but not elderly patients (ages 25-64) are also prone to develop CAUTIs.

Time-to-event analysis

The Kaplan-Meier curve for all catheterizations is displayed in Figure 1. CAUTI-free survival rate was 97.3% [CI: 97.1-97.6] at 10 days, 88.2% [CI:86.9-89.5], and 71.8% [CI: 66.3-77.8] at 60 days. The instantaneous hazard is depicted in Figure 2. From left to right, the number of patients with that many days of catheterization decreases, and hence the confidence-interval for the smoothed model widens. The B-spline smoothing model estimates that instantaneous hazard to be the highest at around 40 days.

Analyzing disease-free survival for different patient cohorts using a Kaplan-Meier estimate demonstrated that pediatric patients were at a higher risk of developing a CAUTI (log rank p=0.007) (Figure 3A).
infection-free probability estimates at 30 days were 0.88 [0.87-0.90] for adult and 0.87 [0.82-0.93] for pediatric patients with the largest difference in survival occurring between days 30 and 55. Pediatric females were found to be over 3 times as likely to develop a CAUTI than pediatric males. Additionally, females were found to be more likely to develop CAUTI than males (log-rank p<0.0001) (Figure 3B). The Kaplan-Meier infection-free probability estimates at 30 days were 0.84 [0.82-0.87] for female and 0.92 [0.90-0.93] for male patients with the largest difference in survival occurring between days 10 and 60.

Cox proportional hazards models identified additional risk factors for CAUTI. The univariate Cox proportional hazards models found the following variables as significantly affecting time-to-infection: age, sex, CCI, myocardial infarction, congestive heart failure, cerebrovascular disease, pulmonary disease, connective tissue disease, paraplegia, renal disease, and severe liver disease. The multivariate Cox model reduced the set of significant variables: congestive heart failure was associated with a hazard ratio 0.75 [0.64-0.89] (p<0.001), whereas cerebrovascular disease and paraplegia increased the risk by 1.78 [1.53-2.08] (p<0.001) and 1.40 [1.11-1.77] (p=0.005), respectively (Figure 4). The hazard for males was found to be 0.56 [0.48-0.64]).

Discussion

CAUTIs pose a significant burden on patients, both in terms of morbidity and mortality. Apart from the clear harm posed to patients, governmental pressure has helped hospitals across the country focus even more effort on CAUTI reduction. CAUTI rates are incorporated into both government quality ratings through the Centers for Medicaid and Medicare quality star ratings, as well as financial penalties through the Hospital Acquired Condition Reduction Penalty (HACRP) program.

However, while some CAUTI-reduction efforts have shown positive results,[3,16] CAUTI rates in the U.S. still increased by 6.0% from 2009 to 2013.[3] CAUTIs remain one of the most common nosocomial infections, however, there is little evidence on what specific factors lead to these infections. If we are able to identify factors that are associated with the development of CAUTIs, we will then be able to modulate our preventive strategy accordingly, specifically modifying the standard of care for hospital practice as well as implementing targeted electronic alerts, such as alerting at a higher frequency for pediatric patients.
Prompt removal of IUC at the earliest possibility has been a cornerstone of CAUTI reduction programs in the published literature, and the toolkit developed by the Agency for Healthcare Research and Quality to reduce CAUTIs also emphasizes on prompt removal of IUCs.[17] Nevertheless, evidence on the additive hazard of IUC duration in development of CAUTI had not been updated for more than three decades. Our study is the first to revisit this association for a very large cohort of patients and provide novel evidence about the various risk factors for CAUTI in hospitalized patients.

**Root Cause Analysis for CAUTI events**

In addition to the EHR-derived IUC data, we were able to obtain the records from a collection of root cause analysis (RCA) performed for patients who contracted a CAUTI. RCAs are routinely performed at healthcare institutions and have been previously found to help in understanding the underlying causes for infection [18]. Our study had RCA data available for 10% of the total CAUTIs in the study population. Analysis of the RCA data identified that the most common indications for catheterization were recording inputs and outputs, critical illness, peri-operative status, and diuresis. The most common contributing factors for CAUTI that were identified by the clinical teams and infection preventionists were comorbidities, lapses in catheter care protocols, active infection, fecal incontinence, and duration of IUC. The duration of IUC was identified as a contributing factor for 16.5% of the CAUTI cases, however, for almost 25% of the cases reviewed in the RCAs, the clinical teams and infection preventionists stated that the catheters could have been removed earlier.

**Contributions to the CAUTI risk factor literature**

Our study upholds previous findings and provides new insights as well. As has been previously reported, longer duration of catheterization and female sex are both risk factors for the development of CAUTI[7,19-22]. Interestingly, using the same adult age brackets (18-50 years old and over 50 years old) as the Garibaldi et al. 1974 study, we found that younger adults had a 1.3 [95% CI: 1.1-1.5] times greater hazard for developing a CAUTI (p = 0.007), which is the opposite of the results in the original study. When we adjust for life expectancy differences and look at patients ages 18-64 vs. patients ages 65+, the risk of CAUTI remained higher in younger patients than in older patients. However, when adding comorbidities to the analysis, age was no longer found to be a significant factor, implying that age in itself may not be a risk factor.
As the data for CAUTIs in pediatric patients is limited, the current study supplements available medical literature. Goudie et al [23] studied healthcare-associated infections in the pediatric population and found that the risk of CAUTIs in girls was more than three times higher than that in boys. Our study found a very similar significant difference between the sexes. In addition, our study showed that pediatric patients had a higher risk of being infected than their adult counterparts, suggesting that even more caution should be undertaken in children with catheters.

While there is little literature to compare to our findings regarding the CCI, there were both expected and unexpected findings with this data. Both stroke (cerebrovascular disease) and paraplegia being risk factors for CAUTI is understandable, as neurologic units have been shown to have higher rates of CAUTI as compared to other units. [24] As was demonstrated by Titsworth et al, introducing UTI bundles and practicing a higher-level vigilance in neurological intensive care units can decrease the rate of infection in this subset of patients. Although the CCI was created to predict mortality and not infection susceptibility, it was unexpected that the overall comorbidity score did not affect risk of CAUTI as we expect increased comorbidity burden to increase risk of infection. The most surprising result was congestive heart failure (CHF) was associated with a lower risk of CAUTI in our population. One possible explanation for this result is that many patients with CHF have a very specific indication for catheterization, namely diuresis, and are monitored vigilantly for euvolemic fluid status which prompts timely removal of the catheter. The current analysis does not distinguish between patients with a longstanding diagnosis of CHF and patients that are in the hospital for a CHF exacerbation, so this data cannot be extrapolated to infer that patients with CHF exacerbation have a lower risk of CAUTI, but this is an area that is important for future analysis.

While previous studies have reported on various metrics of CAUTI risk relative to IUC duration, our study demonstrates a nonlinear increase in the cumulative risk hazard as duration increases, suggesting that each extra day of catheterization incrementally increases the risk of CAUTI. As the RCA data revealed that almost one quarter of patients could have had their catheters removed earlier and the EHR-derived data identified the risk for CAUTI increases non-linearly each day, these results can help encourage automated alerts for the removal of IUCs and inform their timing.

Our study also has a number of limitations. First, the definition used for CAUTI was changed by the CDC in January 2015 and therefore the CAUTI population in our study is not homogeneous; for instance, non-bacterial forms of UTI could be counted as CAUTI in the data from 2012 to 2014, but not in the data from 2015 and
If we assume that the daily additional risk of CAUTI differs in fungal versus bacterial UTI, then this heterogeneity in the data may have confounded our results. Second, the capabilities of the EHR limited our ability to collect some granular data that may have supplemented the analysis. Lastly, some patients had more than one CAUTI catheterization event in our data. While typically these catheterizations occurred in different admissions, it is possible that patient-level factors may contribute to the risk of infection, i.e. not all of our data points are completely independent. We tried to model these patient-level factors using the covariates in the adjusted model, but this model may not have sufficiently addressed the issue of dependent data points. Despite these limitations, we do believe our study is generalizable as it includes a large, heterogeneous subset of patients at a tertiary care center in a large metropolitan area.

Conclusions

Using a very large EHR-derived dataset, our findings indicate that indwelling urinary catheter dwell-time is a significant risk factor for patients who develop CAUTIs, even when controlling for sex, age, and patient comorbidities. We also identify female sex, pediatric age, and neurological issues as risk factors for CAUTIs. Our study finds that approximately 12% of patients who have a catheter inserted for 30 days will develop a CAUTI. The findings of this study can help guide efforts for future CAUTI reduction programs.

Contributorship

Concept and design: Letica, Perotte, Salmasian, Vawdrey.

Acquisition, analysis, or interpretation of data: Letica, Perotte Salmasian, Youngerman.

Drafting of the manuscript: Calfee, Furuya, Green, Letica, Perotte, Salmasian, Vawdrey, Youngerman.

Critical revision of the manuscript for important intellectual content: Calfee, Furuya, Green, Letica, Perotte, Salmasian, Vawdrey, Youngerman.

Statistical analysis: Letica, Perotte, Salmasian.

Supervision: Perotte, Salmasian, Vawdrey.
Data Sharing

No additional data available.

Funding and Competing Interests Statement

There is no funding to report for this research. No competing interests declared for any author.

Acknowledgements

We are grateful to the reviewers of this manuscript for helping us greatly improve the manuscript through the peer-review process.

References


### Table 1: Descriptive Data for the Full Population of Catheterizations.

The table compares descriptive statistics for catheterizations where patients developed CAUTIs and did not.

<table>
<thead>
<tr>
<th></th>
<th>CAUTI developed (N=861)</th>
<th>No CAUTI developed (N=60,186)</th>
<th>p-value for group differences</th>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean (years)</td>
<td>60.2 (SD 21.4)</td>
<td>62.6 (SD 21.3 )</td>
<td>0.001†</td>
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<tr>
<td>0-17</td>
<td>49 (5.6%)</td>
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<td>18-24</td>
<td>14 (1.6%)</td>
<td>1,271 (2.1%)</td>
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<td>25-44</td>
<td>115 (13.4%)</td>
<td>6,741 (11.2%)</td>
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<td>45-64</td>
<td>253 (29.4%)</td>
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<td>65+</td>
<td>430 (49.9%)</td>
<td>32,928 (54.7%)</td>
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<td><strong>Sex</strong></td>
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<td>Male</td>
<td>335 (38.9%)</td>
<td>30,669 (51.0%)</td>
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<td><strong>Patient Type</strong></td>
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<td>613 (71.2%)</td>
<td>41,988 (69.8%)</td>
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<td><strong>Comorbidities</strong></td>
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<tr>
<td>Charlson Comorbidity Score</td>
<td>3.0 (SD 2.7)</td>
<td>2.6 (SD 2.6)</td>
<td>&lt;0.001†</td>
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†Student’s t-test, Chi-squared analysis.
Figure 1: **Kaplan-Meier survival curve for all catheterizations.** The x-axis begins on day 3 as only patients who had catheters inserted for at least two full days can develop a CAUTI, according to the CDC definition. The number of patients at risk after each 20 day interval is represented in the table below the figure. Minimal survival rate of .66 is reached on day 73 when 23 patients remain in the study sample.

Figure 2: **Instantaneous Hazard Curve.** The instantaneous hazard is derived using the Kaplan Meier estimates. The B-spline smoothing model estimates that instantaneous hazard to be the highest at around 40 days. The graph is truncated after the last CAUTI event occurs.

Figure 3: **Infection-free survival stratified by sex and age group.** (A) Kaplan-Meier survival curve comparing adult (18+ years old) versus pediatric (0-17 years old) groups (log-rank p=0.007). (B) Kaplan-Meier survival curve comparing males and females (log-rank p<0.0001)

Figure 4: **Hazard Ratios derived from the Cox Proportional Hazards Model.** The presence of a comorbidity is represented by a “1”, i.e. 1,771 patients had a severe liver disease diagnosis. Only comorbidities that were found to be significant in a univariate analysis are included in the multivariate model and figure.

**Supplementary Figure 1: Flowchart demonstrating how the 61,000 catheterizations were identified in the EHR database.** A total of 1,668 catheterizations were removed due to missing sex, age, or ICD-9 comorbidity data.
Figure 1: Kaplan-Meier survival curve for all catheterizations. The x-axis begins on day 3 as only patients who had catheters inserted for at least two full days can develop a CAUTI, according to the CDC definition.

The number of patients at risk after each 20 day interval is represented in the table below the figure.

Minimal survival rate of .66 is reached on day 73 when 23 patients remain in the study sample.
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Figure 4: Hazard Ratios derived from the Cox Proportional Hazards Model. The presence of a comorbidity is represented by a “1”, i.e. 1,771 patients had a severe liver disease diagnosis. Only comorbidities that were found to be significant in a univariate analysis are included in the multivariate model and figure.
All urinary catheter placements between January 1, 2012 – March 31, 2016 as identified through EHR nursing documentation

N= 148,631

All catheterizations with IUC duration < 3 days are removed as they are ineligible for CAUTIs as per CDC definition

N=85,916

All urinary catheter placements for patients admitted between January 1, 2012 – March 31, 2016 that are eligible for a CAUTI

N=62,715 (884 CAUTIs)

Final dataset of catheterization used for analysis

N=61,047 (861 CAUTIs)

Used to calculate the CAUTI per 1000 catheter days rate

All catheterizations for patients with missing data are removed

N=1,668 (23 CAUTIs)
### STROBE Statement—Checklist of items that should be included in reports of cohort studies

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Title and abstract** | 1   | *(a)* Indicate the study’s design with a commonly used term in the title or the abstract – Page 1  

*(b)* Provide in the abstract an informative and balanced summary of what was done and what was found – Page 2 |
| **Introduction** |  |  |
| **Background/rationale** | 2   | Explain the scientific background and rationale for the investigation being reported – Page 3-4 |
| **Objectives** | 3   | State specific objectives, including any prespecified hypotheses – Page 4 |
| **Methods** |  |  |
| **Study design** | 4   | Present key elements of study design early in the paper – Pages 4-5 |
| **Setting** | 5   | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – Page 4 |
| **Participants** | 6   | *(a)* Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. – Page 4. **Methods of follow-up not applicable.**  

*(b)* For matched studies, give matching criteria and number of exposed and unexposed. **Not applicable.** |
| **Variables** | 7   | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. Pages 4-6. |
### Data sources/measurement

For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. **Page 5.**

### Bias

Describe any efforts to address potential sources of bias. **Page 5**

### Study size

Explain how the study size was arrived at. **Page 4.**

### Quantitative variables

Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. **Page 5-6.**

### Statistical methods

(a) Describe all statistical methods, including those used to control for confounding. **Page 5.**

(b) Describe any methods used to examine subgroups and interactions. **Pages 5-6.**

(c) Explain how missing data were addressed. **Page 5, Figure S1.**

(d) If applicable, explain how loss to follow-up was addressed. **Not applicable.**

(e) Describe any sensitivity analyses. **Not Applicable**

### Results

#### Participants

(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. **Page 6, Figure S1.**

(b) Give reasons for non-participation at each stage. **Page 6, Figure S1.**

(c) Consider use of a flow diagram. **Figure S1.**

#### Descriptive data

(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. **Table 1.**
(b) Indicate number of participants with missing data for each variable of interest. Page 6, Figure S1.

(c) Summarise follow-up time (eg, average and total amount). Not applicable.

Outcome data 15* Report numbers of outcome events or summary measures over time. Page 7.

Main results 16 (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. Pages 6-8.

(b) Report category boundaries when continuous variables were categorized. Not Applicable

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. Figure 4.

Other analyses 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. Page 8, Figure 3.

Discussion

Key results 18 Summarise key results with reference to study objectives. Page 8-10.

Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. Page 10.

Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. Pages 10-11.

Generalisability 21 Discuss the generalisability (external validity) of the study results. Page 10.

Other information
Funding

Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. Not applicable.

*Give information separately for exposed and unexposed groups.
Identifying the risk factors for catheter-associated urinary tract infections: a large cross-sectional study of six hospitals

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</table>
| Complete List of Authors: | Letica-Kriegel, Allison; Massachusetts General Hospital, Department of Surgery  
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Identifying the risk factors for catheter-associated urinary tract infections: a large cross-sectional study of six hospitals

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Abstract

Motivation: Catheter-associated urinary tract infections (CAUTI) are a common and serious healthcare-associated infection. Despite many efforts to reduce the occurrence of CAUTI, there remains a gap in the literature about CAUTI risk factors, especially pertaining to the effect of catheter dwell-time on CAUTI development and patient comorbidities.

Objective: To examine how the risk for CAUTI changes over time. Additionally, to assess whether time from catheter insertion to CAUTI event varied according to risk factors such as age, sex, patient type (surgical vs. medical), and comorbidities.

Design: Retrospective cohort study of all patients who were catheterized from 2012-2016, including those who did and did not develop CAUTIs. Both pediatric and adult patients were included. Indwelling urinary catheterization is the exposure variable. The variable is interval, as all participants were exposed but for different lengths of time.

Setting: Urban academic health system of over 2,500 beds. The system encompasses two large academic medical centers, two community hospitals, and a pediatric hospital.

Results: The study population was 47,926 patients who had 61,047 catheterizations, of which 861 (1.41%) resulted in a CAUTI. CAUTI rates were found to increase non-linearly for each additional day of catheterization; CAUTI-free survival was 97.3% [CI: 97.1-97.6] at 10 days, 88.2% [CI: 86.9-89.5] at 30 days, and 71.8% [CI: 66.3-77.8] at 60 days. This translated to an instantaneous hazard ratio of .49%-1.65% in the 10-60 day time range. Paraplegia, cerebrovascular disease and female sex were found to statistically increase the chances of a CAUTI.

Conclusions: Using a very large data set, we demonstrated the incremental risk of CAUTI associated with each additional day of catheterization, as well as the risk factors that increase the hazard for CAUTI. Special attention should be given to patients carrying these risk factors, e.g. females or those with mobility issues.
Article Summary

Strengths and limitations of this study

- The analysis focused on a very large population of patients: four years of data across 61,000 catheterizations and over 47,000 patients.
- The methodology not only controls for age, sex, and patient type but patient comorbidities as well.
- The definition used for CAUTI was changed by the CDC in January 2015 and therefore the CAUTI population in our study is not homogeneous.
- The capabilities of the electronic health record limited our ability to collect some granular data that may have supplemented the analysis.

Introduction

Catheter-associated urinary tract infections (CAUTI) continue to be among the most common healthcare-associated infections in the United States. In 2011, there were an estimated 93,000 cases of CAUTI in U.S. acute care hospitals.[1] CAUTIs can lead to more serious complications such as sepsis and endocarditis, and it is estimated that over 13,000 deaths each year are associated with healthcare-associated UTIs.[2]

For an infection to be classified as a CAUTI under guidelines published by the U.S. Centers for Disease Control and Prevention (CDC), a patient must have: (a) had an indwelling urinary catheter for more than two days by the date of event (with “day one” being the day of catheter insertion); (b) one sign or symptom including fever, suprapubic tenderness, costovertebral angle tenderness, urinary frequency or urgency or dysuria; and (c) urine culture with more than 10^5 CFU/ml of one bacterial species (non-bacterial pathogens have been excluded since 2015). As it is estimated that 69% of CAUTI events are avoidable,[3] the U.S. Department of Health and Human Services spearheaded national efforts in 2009 to reduce CAUTI rate.[4] The efforts undertaken to reduce CAUTI rates include avoiding unnecessary catheterization, reducing duration of catheterization (e.g., by using reminder systems to encourage catheter removal when the catheter is no longer indicated), emphasizing antiseptic technique for insertion, and using hydrophilic-coated catheters.[5-6]

Despite advances in prevention guidelines, there remains a lack of knowledge concerning risk factors for CAUTI. A seminal study from Garibaldi and colleagues in 1974 examined 405 patients with indwelling urinary catheters,
concluding that female sex, age greater than 50 years, higher severity of illness, non-surgical illness, and no systemic antibiotics were independent risk factors for the development of CAUTI (defined then as bacteriuria of more than 10^2 CFU/ml).[7] Importantly, Garibaldi also reported that catheter dwell-time (i.e., number of days spent catheterized) was a significant risk factor for CAUTI, with a 7.4% risk of infection in the 24 hours following insertion, and a steady 8.1% risk increase each subsequent day for the first seven days.[7] Further studies in the 1980s reproduced these risk factors, adding catheter care violations and non-sealed catheter junctions as risk factors as well.[8].

Overall, there have been very few studies that focus on understanding CAUTI risk factors, including dwell-time of the catheter.[9-10] To the best of our knowledge, no study since 1974 has attempted to provide an estimate of the daily risk of maintaining a urinary catheter, a principle that could have significant implications in refining CAUTI prevention guidelines. Further, additional risk factors such as comorbidities need to be better identified. We conducted a retrospective review of data from electronic health records to help illuminate CAUTI risk factors.[11]

The objective of this study was to examine how the risk for CAUTI changes over time and identify the risk factors for CAUTI by analyzing data from a large electronic health record (EHR) dataset of routine nursing documentation.

Methods

Setting

The study was conducted at an urban academic health system comprising of two large academic medical centers, two community hospitals, and a pediatric hospital. Together the hospitals had over 2,500 beds. The Columbia University Irving Medical Center Institutional Review Board reviewed the study and granted approval.

Patient and Public Involvement

This research was conducted in reaction to the efforts focused on reducing CAUTI rates, which is a concern to both providers and patients alike. However, the study is a retrospective analysis of data collected as part of care, therefore there was no direct involvement of patients in design, recruitment and conduct of the study.
Review of Electronic Health Record Nursing Documentation

We reviewed all infections associated with catheters that occurred between January 1, 2012 and March 31, 2016. For all patients hospitalized at the study sites during this time period, we identified “catheter days”, i.e., the number of calendar days during which the patient had an indwelling urinary catheter (IUC) as recorded in nursing flowsheet documentation in the EHR. CAUTI presence was extracted from Infection Prevention and Control logs as they are manually assigned after detailed review, using the definition that is set forth by National Healthcare Safety Network (NHSN) within the Center for Disease Control (CDC). Both flowsheet documentation and CAUTI presence logs contained patient medical record number and admission date, these two identifiers were used to link the IUC data with the CAUTI events. If multiple CAUTI events occurred during one IUC period, only the earliest CAUTI was included in our analysis (i.e., our analysis examined event-free survival for each IUC period). However, if there was a reinsertion, this was considered a new IUC period and therefore a CAUTI during this new period would be eligible for the study. All ages and all types of infections (bacterial and fungal) were included in the study.

Statistical Analysis

We calculate and report a CAUTI rate per 1000 catheter days using the full population of catheterizations, as is standard. For the subsequent analyses, the population is filtered to remove all catheterizations with an IUC duration of less than 3 days (this is to match the CDC criteria for defining CAUTIs) [12]. To address the issue of missing data, any catheterizations for patients who were missing covariates are removed (Supplementary Figure 1).

We performed a time-independent analysis to evaluate differences between catheterizations that resulted in a CAUTI and those that did not. Differences in continuous variables were assessed with a t-test and differences in categorical variables were assessed with a chi-squared test. The time-independent analysis was followed by survival analyses to characterize event-free survival — i.e., number of days between IUC insertion and either CAUTI occurrence or IUC removal with no CAUTI event. As CAUTI is defined as infection that occurs any time after the second day of catheter placement, it is impossible for a CAUTI to exist prior to day 3. Therefore, risk for CAUTI begins at day 3 by definition. In our survival analyses, day 3 is considered the start time.
A Kaplan-Meier estimate was computed to evaluate the instantaneous hazard rates for developing a CAUTI and the time-dependent differences in subpopulations found to be significant in the time-independent analysis. The time-dependent differences in infection-free survival rates are reported in the full population, the population stratified by pediatric vs. adult patients, and stratified by female vs. male patients.

Finally, after testing the proportional hazard assumption and finding that it is not violated, we performed a Cox Proportional Hazard analysis. To address potential biases we adjusted for a set of confounders. Univariate Cox models were created to assess the effect of each variable’s effect on time-to-infection; overall Charlson Comorbidity Index (CCI) score[13], the presence or absence of the 17 comorbidities that are included in CCI, sex, age, and patient type (medical vs. surgical) were examined. CCI was computed for each patient using an automated method described in [14]. The CCI assigns weights to the 17 different comorbidities and was originally designed to predict 10-year survival in patients (ie. the higher a patient’s CCI, the more likely they are to die). The 17 comorbidities included were: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, diabetes with complications, paraplegia, renal disease, cancer, metastatic cancer, severe liver disease, HIV. The variables found to be significant in the univariate models were included in the multivariate Cox Proportional Hazard model.

All statistical analyses were carried out using the R programming language [15], using the survival and survminer packages.

**Results**

**CAUTI Rates**

From January 2012 to March 2016, there were 148,631 catheterizations for 115,710 patients. The 148,631 catheterization events for the 2012-2016 time period totaled 540,494 catheter days. We identified a CAUTI rate of 1.64 per 1000 catheter-days [95% CI: 1.63-1.65] for the total population. The pediatric population (0-17 years of age) had a total of 23,531 catheter days and a CAUTI rate of 2.08 [95% CI: 1.56-2.78] per 1000 catheter-days. The
adult population (18+ years of age) had a total of 517,335 catheter days and a CAUTI rate of 1.61 [95% CI: 1.51-1.73] per 1000 catheter-days, representing a non-statistically significant difference with the pediatric population.

**Time-Independent Analysis**

To align with CDC CAUTI definitions and remove missing data, all catheterizations with missing data or IUC duration of less than 3 days were removed from the analysis. This filtration resulted in a cohort of 47,926 patients with 61,047 catheterizations and a total of 381,951 catheter days (16,254 pediatric catheter days and 365,697 adult catheter days). From this total population of patients with IUCs and without missing data, there were 861 CAUTI events (1.41% [1.32-1.51]). Overall median duration of IUC from first insertion was 7 days (IQR=10) for patients who developed a CAUTI and 4 days (IQR=4) for those who did not. Median duration of catheterization for all IUCs was 4 days (IQR = 4).

There were significant differences identified in terms of age, sex, and CCI between the patients that developed a CAUTI and those that did not (Table 1). The results indicate that pediatric patients and women are more prone to develop CAUTIs. We also see evidence that older but not elderly patients (ages 25-64) are also prone to develop CAUTIs.

**Time-to-event analysis**

The Kaplan-Meier curve for all catheterizations is displayed in Figure 1. CAUTI-free survival rate was 97.3% [CI: 97.1-97.6] at 10 days, 88.2% [CI:86.9-89.5] at 30 days, and 71.8% [CI: 66.3-77.8] at 60 days. The instantaneous hazard is depicted in Figure 2. From left to right, the number of patients with that many days of catheterization decreases, and hence the confidence-interval for the smoothed model widens. The B-spline smoothing model estimates that instantaneous hazard to be the highest at around 40 days.

Analyzing disease-free survival for different patient cohorts using a Kaplan-Meier estimate demonstrated that pediatric patients were at a higher risk of developing a CAUTI (log rank p=0.007) (Figure 3A). The Kaplan-Meier
infection-free probability estimates at 30 days were 0.88 [0.87-0.90] for adult and 0.87 [0.82-0.93] for pediatric patients with the largest difference in survival occurring between days 30 and 55. Pediatric females were found to be over 3 times as likely to develop a CAUTI than pediatric males. Additionally, females were found to be more likely to develop CAUTI than males (log-rank p<0.0001) (Figure 3B). The Kaplan-Meier infection-free probability estimates at 30 days were 0.84 [0.82-0.87] for female and 0.92 [0.90-0.93] for male patients with the largest difference in survival occurring between days 10 and 60.

Cox proportional hazards models identified additional risk factors for CAUTI. The univariate Cox proportional hazards models found the following variables as significantly affecting time-to-infection: age, sex, CCI, myocardial infarction, congestive heart failure, cerebrovascular disease, pulmonary disease, connective tissue disease, paraplegia, renal disease, and severe liver disease. The multivariate Cox model reduced the set of significant variables: congestive heart failure was associated with a hazard ratio 0.75 [0.64-0.89] (p<0.001), whereas cerebrovascular disease and paraplegia increased the risk by 1.78 [1.53-2.08] (p<0.001) and 1.40 [1.11-1.77] (p=0.005), respectively (Figure 4). The hazard for males was found to be 0.56 [0.48-0.64]).

Discussion
CAUTIs pose a significant burden on patients, both in terms of morbidity and mortality. Apart from the clear harm posed to patients, governmental pressure has helped hospitals across the country focus even more effort on CAUTI reduction. CAUTI rates are incorporated into both government quality ratings through the Centers for Medicaid and Medicare quality star ratings, as well as financial penalties through the Hospital Acquired Condition Reduction Penalty (HACRP) program.

However, while some CAUTI-reduction efforts have shown positive results,[3,16] CAUTI rates in the U.S. still increased by 6.0% from 2009 to 2013.[3] CAUTIs remain one of the most common nosocomial infections, however, there is little evidence on what specific factors lead to these infections. If we are able to identify factors that are associated with the development of CAUTIs, we will then be able to modulate our preventive strategy accordingly, specifically modifying the standard of care for hospital practice as well as implementing targeted electronic alerts, such as alerting at a higher frequency for pediatric patients.
Prompt removal of IUC at the earliest possibility has been a cornerstone of CAUTI reduction programs in the published literature, and the toolkit developed by the Agency for Healthcare Research and Quality to reduce CAUTIs also emphasizes on prompt removal of IUCs.[17] Nevertheless, evidence on the additive hazard of IUC duration in development of CAUTI had not been updated for more than three decades. Our study is the first to revisit this association for a very large cohort of patients and provide novel evidence about the various risk factors for CAUTI in hospitalized patients.

Root Cause Analysis for CAUTI events
In addition to the EHR-derived IUC data, we were able to obtain the records from a collection of root cause analysis (RCA) performed for patients who contracted a CAUTI. RCAs are routinely performed at healthcare institutions and have been previously found to help in understanding the underlying causes for infection [18]. Our study had RCA data available for 10% of the total CAUTIs in the study population. Analysis of the RCA data identified that the most common indications for catheterization were recording inputs and outputs, critical illness, peri-operative status, and diuresis. The most common contributing factors for CAUTI that were identified by the clinical teams and infection preventionists were comorbidities, lapses in catheter care protocols, active infection, fecal incontinence, and duration of IUC. The duration of IUC was identified as a contributing factor for 16.5% of the CAUTI cases, however, for almost 25% of the cases reviewed in the RCAs, the clinical teams and infection preventionists stated that the catheters could have been removed earlier.

Contributions to the CAUTI risk factor literature
Our study upholds previous findings and provides new insights as well. As has been previously reported, longer duration of catheterization and female sex are both risk factors for the development of CAUTI[7,19-22]. Interestingly, using the same adult age brackets (18-50 years old and over 50 years old) as the Garibaldi et al. 1974 study, we found that younger adults had a 1.3 [95% CI: 1.1-1.5] times greater hazard for developing a CAUTI (p = 0.007), which is the opposite of the results in the original study. When we adjust for life expectancy differences and look at patients ages 18-64 vs. patients ages 65+, the risk of CAUTI remained higher in younger patients than in older patients. However, when adding comorbidities to the analysis, age was no longer found to be a significant factor, implying that age in itself may not be a risk factor.
As the data for CAUTIs in pediatric patients is limited, the current study supplements available medical literature. Goudie et al [23] studied healthcare-associated infections in the pediatric population and found that the risk of CAUTIs in girls was more than three times higher than that in boys. Our study found a very similar significant difference between the sexes. In addition, our study showed that pediatric patients had a higher risk of being infected than their adult counterparts, suggesting that even more caution should be undertaken in children with catheters.

While there is little literature to compare to our findings regarding the CCI, there were both expected and unexpected findings with this data. Both stroke (cerebrovascular disease) and paraplegia being risk factors for CAUTI is understandable, as neurologic units have been shown to have higher rates of CAUTI as compared to other units. [24] As was demonstrated by Titsworth et al.,[25] introducing UTI bundles and practicing a higher-level vigilance in neurological intensive care units can decrease the rate of infection in this subset of patients. Although the CCI was created to predict mortality and not infection susceptibility, it was unexpected that the overall comorbidity score did not affect risk of CAUTI as we expect increased comorbidity burden to increase risk of infection. The most surprising result was congestive heart failure (CHF) was associated with a lower risk of CAUTI in our population. One possible explanation for this result is that many patients with CHF have a very specific indication for catheterization, namely diuresis, and are monitored vigilantly for euvolemic fluid status which prompts timely removal of the catheter. The current analysis does not distinguish between patients with a longstanding diagnosis of CHF and patients that are in the hospital for a CHF exacerbation, so this data cannot be extrapolated to infer that patients with CHF exacerbation have a lower risk of CAUTI, but this is an area that is important for future analysis.

While previous studies have reported on various metrics of CAUTI risk relative to IUC duration, our study demonstrates a nonlinear increase in the cumulative risk hazard as duration increases, suggesting that each extra day of catheterization incrementally increases the risk of CAUTI. As the RCA data revealed that almost one quarter of patients could have had their catheters removed earlier and the EHR-derived data identified the risk for CAUTI increases non-linearly each day, these results can help encourage automated alerts for the removal of IUCs and inform their timing.

Our study also has a number of limitations. First, the definition used for CAUTI was changed by the CDC in January 2015 and therefore the CAUTI population in our study is not homogeneous; for instance, non-bacterial forms of UTI could be counted as CAUTI in the data from 2012 to 2014, but not in the data from 2015 and
If we assume that the daily additional risk of CAUTI differs in fungal versus bacterial UTI, then this heterogeneity in the data may have confounded our results. Second, the capabilities of the EHR limited our ability to collect some granular data that may have supplemented the analysis. Lastly, some patients had more than one CAUTI catheterization event in our data. While typically these catheterizations occurred in different admissions, it is possible that patient-level factors may contribute to the risk of infection, i.e. not all of our data points are completely independent. We tried to model these patient-level factors using the covariates in the adjusted model, but this model may not have sufficiently addressed the issue of dependent data points. Despite these limitations, we do believe our study is generalizable as it includes a large, heterogeneous subset of patients at a tertiary care center in a large metropolitan area.

Conclusions

Using a very large EHR-derived dataset, our findings indicate that indwelling urinary catheter dwell-time is a significant risk factor for patients who develop CAUTIs, even when controlling for sex, age, and patient comorbidities. We also identify female sex, pediatric age, and neurological issues as risk factors for CAUTIs. Our study finds that approximately 12% of patients who have a catheter inserted for 30 days will develop a CAUTI. The findings of this study can help guide efforts for future CAUTI reduction programs.
Data Sharing

No additional data available.

Funding and Competing Interests Statement

There is no funding to report for this research. No competing interests declared for any author.

Acknowledgements

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References


### Table 1: Descriptive Data for the Full Population of Catheterizations

The table compares descriptive statistics for catheterizations where patients developed CAUTIs and did not.

<table>
<thead>
<tr>
<th></th>
<th>CAUTI developed (N=861)</th>
<th>No CAUTI developed (N=60,186)</th>
<th>p-value for group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-17</td>
<td>49 (5.6%)</td>
<td>2,836 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>14 (1.6%)</td>
<td>1,271 (2.1%)</td>
<td><strong>0.025</strong></td>
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<tr>
<td>25-44</td>
<td>115 (13.4%)</td>
<td>6,741 (11.2%)</td>
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</tr>
<tr>
<td>45-64</td>
<td>253 (29.4%)</td>
<td>16,410 (27.3%)</td>
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</tr>
<tr>
<td>65+</td>
<td>430 (49.9%)</td>
<td>32,928 (54.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>335 (38.9%)</td>
<td>30,669 (51.0%)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
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<td><strong>Patient Type</strong></td>
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<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>613 (71.2%)</td>
<td>41,988 (69.8%)</td>
<td><strong>0.383</strong></td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Charlson Comorbidity Score</td>
<td>3.0 (SD 2.7)</td>
<td>2.6 (SD 2.6)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>

Student’s t-test, Chi-squared analysis.
Figure 1: Kaplan-Meier survival curve for all catheterizations. The x-axis begins on day 3 as only patients who had catheters inserted for at least two full days can develop a CAUTI, according to the CDC definition. The number of patients at risk after each 20 day interval is represented in the table below the figure. Minimal survival rate of .66 is reached on day 73 when 23 patients remain in the study sample.

Figure 2: Instantaneous Hazard Curve. The instantaneous hazard is derived using the Kaplan Meier estimates. The B-spline smoothing model estimates that instantaneous hazard to be the highest at around 40 days. The graph is truncated after the last CAUTI event occurs.

Figure 3: Infection-free survival stratified by sex and age group. (A) Kaplan-Meier survival curve comparing adult (18+ years old) versus pediatric (0-17 years old) groups (log-rank p=0.007). (B) Kaplan-Meier survival curve comparing males and females (log-rank p<0.0001)

Figure 4: Hazard Ratios derived from the Cox Proportional Hazards Model. The presence of a comorbidity is represented by a “1”, i.e. 1,771 patients had a severe liver disease diagnosis. Only comorbidities that were found to be significant in a univariate analysis are included in the multivariate model and figure.

Supplementary Figure 1: Flowchart demonstrating how the 61,000 catheterizations were identified in the EHR database. A total of 1,668 catheterizations were removed due to missing sex, age, or ICD-9 comorbidity data.
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147x91mm (300 x 300 DPI)
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All urinary catheter placements between January 1, 2012 – March 31, 2016 as identified through EHR nursing documentation

N= 148,631

All catheterizations with IUC duration < 3 days are removed as they are ineligible for CAUTIs as per CDC definition

N=85,916

All urinary catheter placements for patients admitted between January 1, 2012 – March 31, 2016 that are eligible for a CAUTI

N=62,715 (884 CAUTIs)

Final dataset of catheterization used for analysis

N=61,047 (861 CAUTIs)

Used to calculate the CAUTI per 1000 catheter days rate

All catheterizations for patients with missing data are removed

N=1,668 (23 CAUTIs)
STROBE Statement—Checklist of items that should be included in reports of cohort studies

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong> 1</td>
<td><em>(a)</em> Indicate the study’s design with a commonly used term in the title or the abstract – Page 1</td>
</tr>
<tr>
<td></td>
<td><em>(b)</em> Provide in the abstract an informative and balanced summary of what was done and what was found – Page 2</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
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<tr>
<td><strong>Background/rationale</strong> 2</td>
<td>Explain the scientific background and rationale for the investigation being reported – Page 3-4</td>
</tr>
<tr>
<td><strong>Objectives</strong> 3</td>
<td>State specific objectives, including any prespecified hypotheses – Page 4</td>
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<tr>
<td><strong>Methods</strong></td>
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<tr>
<td><strong>Study design</strong> 4</td>
<td>Present key elements of study design early in the paper – Pages 4-5</td>
</tr>
<tr>
<td><strong>Setting</strong> 5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – Page 4</td>
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<tr>
<td><strong>Participants</strong> 6</td>
<td><em>(a)</em> Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. – Page 4. Methods of follow-up not applicable.</td>
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<tr>
<td></td>
<td><em>(b)</em> For matched studies, give matching criteria and number of exposed and unexposed. Not applicable.</td>
</tr>
<tr>
<td><strong>Variables</strong> 7</td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. Pages 4-6.</td>
</tr>
<tr>
<td>Section</td>
<td>Code</td>
</tr>
<tr>
<td>----------------------------------------------</td>
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</tr>
<tr>
<td>Data sources/measurement</td>
<td>8*</td>
</tr>
<tr>
<td>Bias</td>
<td>9</td>
</tr>
<tr>
<td>Study size</td>
<td>10</td>
</tr>
<tr>
<td>Quantitative variables</td>
<td>11</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12</td>
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</tbody>
</table>

### Results

<table>
<thead>
<tr>
<th>Section</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>13*</td>
<td><em>(a)</em> Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. <strong>Page 6, Figure S1.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(b)</em> Give reasons for non-participation at each stage. <strong>Page 6, Figure S1.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(c)</em> Consider use of a flow diagram. <strong>Figure S1.</strong></td>
</tr>
<tr>
<td>Descriptive data</td>
<td>14*</td>
<td><em>(a)</em> Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. <strong>Table 1.</strong></td>
</tr>
</tbody>
</table>
(b) Indicate number of participants with missing data for each variable of interest. **Page 6, Figure S1.**

(c) Summarise follow-up time (e.g., average and total amount). **Not applicable.**

<table>
<thead>
<tr>
<th>Outcome data</th>
<th>15*</th>
<th>Report numbers of outcome events or summary measures over time. <strong>Page 7.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Main results</td>
<td>16</td>
<td><em>(a)</em> Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included. <strong>Pages 6-8.</strong></td>
</tr>
<tr>
<td><em>(b)</em> Report category boundaries when continuous variables were categorized. <strong>Not Applicable</strong></td>
<td></td>
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<tr>
<td><em>(c)</em> If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. <strong>Figure 4.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other analyses</td>
<td>17</td>
<td>Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses. <strong>Page 8, Figure 3.</strong></td>
</tr>
</tbody>
</table>

**Discussion**

| Key results | 18  | Summarise key results with reference to study objectives. **Page 8-10.** |
| Limitations | 19  | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. **Page 10.** |
| Interpretation | 20  | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. **Pages 10-11.** |
| Generalisability | 21  | Discuss the generalisability (external validity) of the study results. **Page 10.** |

**Other information**
| Funding    | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. **Not applicable.** |

*Give information separately for exposed and unexposed groups.*