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Role of Transfusions in the Development of Hospital-Acquired Urinary Tract-Related Bloodstream Infection Among United States Veterans

M. Todd Greene, PhD, MPH[1,2], **Sanjay Saint, MD, MPH**[1,2], **David Ratz, MS**[1], **Latoya Kuhn, MPH**[1], **Jennifer Davis, MHSA**[1], **Payal K. Patel, MD, MPH**[1,2], and **Mary A.M. Rogers, PhD**[2]

[1]Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan;

[2]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

Abstract

Background.—Urinary tract-related bloodstream infection (BSI) is associated with substantial morbidity, mortality and financial costs. We examined the role of red blood cell transfusions on developing this condition among United States Veterans.

Methods: We conducted a matched case-control study among adult inpatients admitted to 4 Veterans Affairs hospitals. Cases were patients with a positive urine culture obtained 48 hours or more after admission and a blood culture obtained within 14 days of the urine culture, which grew the same organism. Controls included patients with a positive urine culture who were at risk for BSI but did not develop one (control group 1) and patients without a positive urine culture who were present in the facility at the time of case diagnosis (control group 2).

Results.—Compared to control group 1, receipt of red blood cells was not significantly associated with urinary tract-related BSI (OR = 1.03, 95% CI 1.00 – 1.07, p=0.07). However, we detected increased odds of urinary tract-related BSI when compared to patients without infection (control group 2) (OR = 1.11, 95% CI 1.06 – 1.17, p<0.001).

Conclusions.—Given the heightened risk of urinary tract-related BSI associated with receiving a greater number of red blood cell transfusions, adhering to recommendations to transfuse the minimum amount of blood products necessary may minimize the risk of this infection among Veterans.

INTRODUCTION

Knowing the contributors of bloodstream infection (BSI) is a crucial precursor to developing patient safety practices for prevention. The urinary tract has been considered a contributor to dissemination of microorganisms to the bloodstream; the percentage of patients with bacteriuria who subsequently develop bacteremia is estimated at 3%.[1] The incidence of nursing home-acquired BSI was reported at a similar rate of 0.3 per 1000 resident-days but, when BSI occurs, the urinary tract accounts for 50% of such episodes.[2] In acute care hospitals, 21% of BSIs are reported to be secondary to a urinary source.[3] This is important

Corresponding Author: M. Todd Greene, PhD, MPH, 2800 Plymouth Rd. NCRC Bldg. 16, Rm 470C, Ann Arbor, Michigan 48109, Fax: (734) 936-5216, Telephone: (734) 936-4795, mtgreene@med.umich.edu.

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because treating patients with BSI is challenging and mortality rates among patients with urinary tract-related BSI have been estimated between 13 and 30%.[4,5]

Previously identified risk factors for urinary tract-related BSI include age,[6,7] male sex,[7–9] urinary tract disease,[6,10] urinary tract procedure,[9] chronic kidney disease,[11] malignancy,[7] neutropenia,[10] elevated serum creatinine,[12] low serum albumin,[12] diabetes mellitus,[7,12] liver disease,[10] dementia,[11] cigarette use,[7] indwelling urethral catheters,[6,9,13] immunosuppressant therapy,[7,9,10] and red blood cell transfusion.[14]

As blood transfusion practices among hospitalized patients have changed considerably over the past 20 years[15] and male sex has consistently been found to confer increased risk of developing urinary tract-related BSI,[16] we were particularly interested in examining the role of red blood cell transfusions on developing this disease among predominantly male, U.S. Veterans. Additionally, although numerous risk factors for urinary tract-related BSI have been previously identified, findings have been derived from single-site studies. We therefore conducted a multi-site, matched case-control study on adult Veteran patients hospitalized at 4 Veterans Affairs (VA) hospitals to examine factors that may alter the risk of urinary tract-related BSI.

METHODS

Setting

Patients were identified at 4 diverse Veteran's Affairs Medical Centers (1 in the South and 3 in the Midwest) from 1/1/2000 to 12/31/2014. The VA Ann Arbor Healthcare System Institutional Review Board approved this study.

Case Definition

Nosocomial urinary tract-related bloodstream infections in adult patients (18 years of age or older) were defined as: (a) a positive urine culture and blood culture with the same organism during their hospital stay, (b) the urine culture must have been obtained 48 hours or more after admission, (c) the blood culture must have been obtained on the same day or after the urine culture, but within 14 days of the urine culture, and (d) the urine culture must show growth of at least 10^3 colony-forming units (CFUs)/mL of the single organism. Manual record review was performed for all cases to identify and exclude cases that displayed evidence of primary BSI with hematogenous spread to the kidney (e.g., central line-associated BSI and endocarditis). We had 2 registered nurses separately perform chart abstraction of the cases to identify and exclude cases of primary bloodstream infection. A physician with experience in infectious disease-related studies reviewed a random sample of cases and also adjudicated any discordant views between the registered nurses.

Control Selection

All controls were selected using incidence density sampling. Controls were matched to each case by calendar time (within 90 days) when the BSI occurred in the case, gender, and hospital. A 1:4 ratio of cases to controls was used for matching whenever possible.

Control Group 1

Control group 1 included all adult patients with a positive urine culture (as defined above) who were at risk for a BSI, but did not develop one during their hospital stay (i.e., negative blood culture or no blood culture ordered). The explicit goal for this control group was to determine factors that influenced the spread of a microorganism in the urinary tract to the bloodstream. The exposure period for these controls was similar to that of the matched cases. That is, if the BSI occurred 10 days after the UTI in the case, then the matched control exposure period would likewise be the 10-day period after UTI.

Control Group 2

The risk set for control group 2 included all adult patients without a positive urine culture (as defined above) who were present in the facility at the time of case diagnosis. These were patients who had negative urine cultures or did not have a urine culture ordered. Since a substantial number of patients may well have had a positive urine culture, even in the absence of symptomatic, clinical UTI, this second control group was included to avoid the control requirement that a urinalysis was ordered. The exposure period was the time from admission to BSI for the respective matched case.

Data Collection

Demographic, clinical, microbiological, and blood bank data were extracted from the VA electronic medical record. All urine and blood cultures were ordered and collected at the clinical discretion of healthcare providers and conventional microbiological methods were used for identification of microorganisms from cultures. Comorbid conditions were defined using Elixhauser comorbidity codings via International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Statistical Analysis

Preliminary analyses included an assessment of means and standard deviations for continuous variables and percentages for categorical variables. Differences in the frequency of identified microorganisms (*genus)* between cases and controls (control group 1) were assessed using Chi-square tests. To account for the matched design, conditional logistic regression was used to assess adjusted associations between the cases and each control group separately. The full model contained the following explanatory variables: age, race, surgical procedures (cardiovascular, digestive, and urologic), cancer, diabetes mellitus, renal failure, liver disease, medications (antibacterial, statins, and immunosuppressants), and units of red blood cells, platelets and plasma received. We used α=0.05 (2-tailed) for all statistical tests. Statistical analyses were performed using SAS V9.4 (SAS Institute).

RESULTS

Of the 569 patients that met the case definition, 67 were deemed to be “seeding” cases after medical chart review, 2 had a prior BSI with the same organism prior to admission, and 1 had no urine CFU data leaving 499 eligible cases for analysis. The majority of cases (66%) had their urine and blood culture collections on the same day, while they were 1 day apart

for 10%, and 2 or more days apart for 24%. The median time between admission and BSI was 12 days.

Descriptive characteristics for all 3 groups can be found in Table 1. For control group 1, 482 (97.0%) cases reached our goal of 1:4 case-control ratio (1959 total matches). Among the cases, 65.8% had urine culture values of 10^5 CFU/mL or greater (i.e., more stringent than our 10^3 CFU/mL inclusion criteria), while 57.8% of the controls reached the same threshold. Cases were more likely to have renal failure (p=0.002) and malignancy (p=0.02), to undergo cardiovascular (p<0.001) and digestive system (p<0.001) procedures, and to receive red blood cell products (p<0.001). Cases also spent more days in the ICU (p=0.004) and were more likely to die during hospitalization (p<0.001). For control group 2, 488 (98.4%) cases reached the 1:4 matching ratio (1967 total matches). Compared to control group 2, cases were older (p<0.001), more likely to have renal failure (p<0.001) and cancer (p=0.001), undergo cardiovascular (p<0.001), digestive system (p<0.001) and urologic procedures (p<0.001), and receive red blood cell products (p<0.001). Cases were also more likely to spend more time in the ICU (p<0.001), have longer length of stay (p<0.001) and die during hospitalization (p<0.001).

Microorganism percentages for cases and controls are presented in Table 2. The most common microorganisms were *Enterococcus* spp. (18.1%), *Staphylococcus* spp. (17.5%), *Candida* spp. (16.7%), and *Escherichia coli* (14.6%). Cases were more likely to be infected with *Staphylococcus* spp. (p<0.001). The breakdown of *Staphylococcus sp.* identified among cases was as follows: *Staphylococcus epidermidis* 67/182 (36.8%); coagulase negative *Staphylococcus* (*sp.* unknown) 58/182 (31.9%); *Staphylococcus aureus* 57/182 (31.3%). A total of 15/57 (26.3%) *Staphylococcus aureus* organisms identified among cases were methicillin resistant and 3/57 (5.3%) were methicillin sensitive.

Multivariable conditional logistic regression results comparing cases to both control groups are shown in Table 3. After adjusting for age, race, comorbidities, surgical procedures, medications received, and other blood product receipt, receipt of red blood cell transfusion was not significantly associated with increased odds of urinary tract-related BSI, when comparing cases to control group 1 (adj OR = 1.03, 95% CI = 1.00–1.07, p =0.07) and significantly associated with increased odds of urinary tract-related BSI, when comparing cases to control group 2 (adj OR = 1.11, 95% CI = 1.06–1.17, p <0.001).

Because transfusions are within the hypothesized causal pathway between surgery (via blood loss) and BSI, in secondary analysis, we excluded all surgical procedures from our multivariable models. Compared to both control groups, cases receiving red blood cell transfusions had significantly increased odds of developing urinary tract-related BSI (adj OR = 1.05, 95% CI = 1.02–1.09, p =0.002; adj OR = 1.17, 95% CI = 1.12–1.23, p <0.001; relative to control groups 1 and 2 respectively).

DISCUSSION

Several important findings emerged from our study. First, *Staphylococcus spp.*, and *Escherichia coli* were the most common pathogens identified in our cohort of US Veterans

with urinary tract-related BSI.[17] Second, some of our findings confirm previously identified risk factors for the development of urinary tract-related BSI. Third, red blood cell transfusions during hospitalization were associated with urinary tract-related BSI.

Prior studies have identified Enterobacteriaceae,[7] *Enterococcus spp.,*[5,10] *and E. coli*[6] as the most commonly isolated microorganisms in patients with urinary tract-related BSI. In the present study, the most common microorganisms isolated in urine cultures were *Enterococcus spp*. However, similar to a prior study of urinary tract-related BSI among Veterans,[7] we found that *Enterococcus spp*. were more common in controls than cases. Conversely, *Staphylococcus spp*. -- the second most common microorganisms in the present study -- were more frequently isolated in the cases. Although isolated less frequently overall, Saint and colleagues also found that *Staphylococcus sp*. were more frequently isolated in Veterans with urinary tract-related BSI.[7] Taken together, these findings suggest a potentially unique role of *Staphylococcus sp*. in the development of urinary tract-related BSI among Veterans specifically. This has important implications for Veteran care, as complicated urinary tract infection caused by *Staphylococcus sp*. is often caused by antibiotic-resistant strains and is strongly associated with urinary catheterization.[18] Furthermore, catheter-associated urinary tract infection caused by methicillin-resistant *Staphylococcus aureus* disseminates to bacteremia more frequently and rapidly compared to infections due to other bacteria.[18–20] In the present study, 64.9% of cases had an indwelling urinary catheter at some point between hospital admission and the date of urinary tract-related BSI. Furthermore, prior studies have shown that urinary catheter utilization is higher in VA settings compared to non-VA settings.[21,22]

Our study both confirms and extends previous work on the identification of risk factors for urinary tract-related BSI. A recent systematic review indicated that male sex, neutropenia, malignancy, liver disease, receipt of immunosuppressant medications, and red blood cell transfusions were the most consistently identified risk factors conferring greater risk of developing urinary tract-related BSI.[16] In our study of predominantly male U.S. Veterans with urinary tract-related BSI, compared to control group 1, our findings confirm the previously identified associations between malignancy, and receipt of immunosuppressant medications. Additionally, we detected an association between renal failure and increased risk of urinary tract-related BSI; an association detected in one previous study.[10] Urologic procedures are also a known risk factor for urinary tract-related BSI.[9,10] Our findings support the associations previously detected between urologic procedures and also suggest that patients undergoing other surgical procedures (specifically cardiovascular and digestive) may be at increased risk of developing urinary tract-related BSI. The statistically significant associations detected in our study when comparing cases to control group 1 were also detected when comparing to control group 2, which helps to rule out possibility that identified associations were confounded by urinalysis orders.

There was a dose-response in the odds of urinary tract-related BSI when compared to patients without infection (i.e., control group 2); for each unit of red blood cells, the odds of BSI increased by 11%. The primary mechanism by which this occurs may be immunomodulation[23] which was first recognized in the 1970s, when transfusions were used as immunosuppressants. Since then, red blood cell transfusions have been shown to be

associated with the incidence of BSI in hospitalized patients,[24,25] particularly in surgical patients. In our study, red blood cell transfusions appear to be within the causal pathway between surgery and urinary tract-related BSI. A larger prospective study would be necessary to separate the effects of transfusion from those of surgery and the procedures associated with the surgery. In addition, we found that, for nonsurgical patients, the odds of urinary tract-related BSI were increased after the use of red blood cell transfusions. Similarly, a previous study indicated that patients receiving red blood cell transfusions had nearly 5-times greater odds of developing urinary tract-related BSI compared to those not receiving transfusions.[14] In that study, however, the majority of patients were women. Red blood cell transfusions tend to be more common in women because the threshold for administration is not sex-specific and women normally have lower hemoglobin levels than men. In our present study, nearly all the patients were male and the use of blood products was closely associated with surgical procedures (rather than iron deficiency anemia). For the surgical patients, we could not completely distinguish whether the increased risk of BSI was due to the surgical procedures or the blood products. However, for the nonsurgical patients, red blood cell transfusion was associated with BSI.

Another mechanism for the association between transfusion and infection is through the introduction of microorganisms, although this is less likely to occur. In healthy individuals, blood does transiently contain microorganisms;[26,27] however, donated blood in the U.S. is tested for human immunodeficiency virus, hepatitis B and C, human T-lymphotropic virus, and syphilis, with periodic testing for West Nile virus and Chagas disease in certain areas. There are ongoing improvements in pathogen reducing treatments for blood products.[28] Unfortunately, additional data regarding the specific blood products were not available in this dataset. More recent evidence indicates that characteristics of blood donors may affect the response of the recipients,[29,30] including age and sex of the blood donor.

Despite underlying gender differences, our study does provide additional support of the connection between receipt of red blood cell transfusion and healthcare-associated infection generally. As such, judicious use of blood transfusions may help to enhance patient safety. A meta-analysis of randomized controlled trials has shown that restrictive transfusion strategies were associated with reduced risk of healthcare associated infections (particularly for serious infections) compared to liberal transfusions strategies.[31] Recent updates to clinical practice guidelines from the AABB (formerly the American Association of Blood Banks) indicate that restrictive strategies in which the transfusion is not indicated until the hemoglobin is 7g/dL are safe in most hemodynamically stable hospitalized adult patients.[32] These guideline updates are in concert with the American Society of Hematology recommendation for the Choosing Wisely® initiative to only transfuse the minimum amount of red blood cell units necessary.[33] In line with these recommendations, blood transfusions have decreased among U.S. Veterans between 2000 and 2010.[34]

Our study has several limitations. First, it may not always be clear whether a positive urinary culture in a patient who is bacteremic represents urinary tract-related BSI or hematogenous seeding of a primary BSI or bacteremia from an alternate source - particularly among the cases with positive cultures with microorganisms not traditionally viewed as primary uropathogens. The retrospective nature of our study affected our ability to determine

whether positive urine culture reflected a primary urinary infectious nidus or seeding from a hematogenous site. We addressed this by conducting manual chart reviews and excluding cases felt to have a clear competing BSI source. Second, we did not confirm that isolates from the urine and blood were identical organisms using antimicrobial resistance patterns or molecular typing methods. Third, although this was a multi-site study performed in 4 VA hospitals, the generalizability of our findings to all Veterans may be limited. Fourth, because the characteristics of blood donors vary, each unit of blood is slightly different in composition. Furthermore, there may be differences in preservatives and storage duration for the blood products, which we could not discern in this study.

Limitations notwithstanding, our multi-center case-control study of U.S. Veterans has findings relevant to hospital infection prevention policy and clinical practice. We found that certain patients – those with malignancy, renal failure, undergoing surgical procedures, or receiving immunosuppressant medications – are at higher risk for developing BSI and thus efforts to reduce modifiable risk factors (such as implementing strategies to reduce urinary catheters[35]) are warranted. Additionally, patients with a suspected urinary tract source of BSI may warrant empiric antibacterial coverage of common pathogens, such as Staphylococcus species. Finally, endeavoring to transfuse the minimum amount of blood products necessary in a hospitalized patient remains a prudent approach.

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Table 1.

Descriptive Characteristics of Cases and Controls

Characteristic	Cases (n=499)	Control 1 (n=1959)	Control 2 (n=1967)	p*	p**
Demographics					
Male sex	492 (98.6)	1939 (99.0)	1940 (98.6)	0.47	0.96
Age (Mean/SD)	67.2 (12.3)	67.1 (12.1)	61.8 (13.3)	0.95	<0.001
Race					
White	281 (56.3)	1126 (57.5)	1210 (61.5)	0.76	0.10
Black	175 (35.1)	654 (33.4)	600 (30.5)	-	-
Other	43 (8.6)	179 (9.1)	157 (8.0)	-	-
Length of stay (Mean/SD)	46.8 (89.0)	39.3 (50.2)	25.0 (29.5)	0.07	<0.001
BMI^ (Mean/SD)	26.2 (6.9)	26.3 (7.2)	27.4 (6.6)	0.72	0.001
ICU days prior to BSI (Mean/SD)	12.2 (63.8)	3.9 (8.9)	1.8 (5.3)	0.004	<0.001
Died during hospitalization	121 (24.2)	159 (8.1)	55 (2.8)	<0.001	<0.001
Comorbidities					
Diabetes	137 (27.4)	542 (27.7)	535 (27.2)	0.92	0.91
Renal failure	93 (18.6)	259 (13.2)	189 (9.6)	0.002	<0.001
Liver disease	43 (8.6)	141 (7.2)	133 (6.8)	0.28	0.15
Malignancy	50 (10.0)	134 (6.8)	117 (5.9)	0.02	0.001
Procedures					
Cardiovascular	195 (39.1)	452 (23.1)	360 (18.3)	<0.001	<0.001
Digestive	130 (26.1)	344 (17.6)	247 (12.6)	<0.001	<0.001
Urologic	34 (6.8)	72 (3.7)	39 (2.0)	0.002	<0.001
Medications≠					
Antibiotics	149 (29.9)	693 (35.4)	476 (24.2)	0.02	009
Immunosuppressants	72 (14.4)	207 (10.6)	144 (7.3)	0.02	<0.001
Statins	142 (28.5)	593 (30.3)	503 (25.6)	0.43	0.19

Characteristic	Cases (n=499)	Control 1 (n=1959)	Control 2 (n=1967)	p*	p**
Receipt of Blood Products					
Red blood cells	194 (38.9)	581 (29.7)	376 (19.1)	<0.001	<0.001
Platelets	38 (7.6)	83 (4.2)	64 (3.3)	0.002	<0.001
Plasma	61 (12.2)	156 (8.0)	115 (5.8)	0.003	<0.001

Data presented as n (%) unless noted. BMI = body mass index; ICU = intensive care unit; BSI = bloodstream infection; p-values derived from Chi-square (categorical variables) or t-test (continuous variables).

*Cases v. control group 1.

**Cases v. control group 2.

^BMI data missing for 31 cases, 132 controls from control group 1 and 232 controls from control group 2.

≠Medication received 2 days prior to BSI date. Control group 1 included all adult patients with a positive urine culture who were at risk for a BSI, but did not develop one during their hospital stay (i.e., negative blood culture or no blood culture ordered). Control group 2 included all adult patients without a positive urine culture (i.e., negative urine culture

Table 2.

Distribution of microorganisms among cases and control group 1

Microorganism	Cases(n=499)	Control Group 1 (n=1959)	Total (n=2458)	p-value
Staphylococcus Spp.	182 (36.5)	249 (12.7)	431 (17.5)	<0.001
Escherichia coli	96 (19.2)	262 (13.4)	358 (14.6)	0.001
Candida Spp.	51 (10.2)	359 (18.3)	410 (16.7)	<0.001
Pseudomonas Spp.	45 (9.0)	172 (8.8)	217 (8.8)	0.87
Klebsiella Spp.	42 (8.4)	144 (7.4)	186 (7.6)	0.42
Enterococcus Spp.	29 (5.8)	416 (21.2)	445 (18.1)	<0.001
Proteus Spp.	18 (3.6)	91 (4.6)	109 (4.4)	0.31
Enterobacter Spp.	15 (3.0)	43 (2.2)	58 (2.4)	0.29
Other*	21 (4.2)	223 (11.4)	244 (9.9)	<0.001

Acinetobacter spp., Alcaligenes spp., Streptococcus spp., Bacillus spp., Burkholderia cepacia, Citrobacter spp., Corynebacterium spp., Diptheroids spp., Gardnerella vaginalis, Hafnia alvei, Lactobacillus spp., Morganella morganii, Providencia spp., Legionella pneumophilia, Serratia spp.
Control group 1 included all adult patients with a positive urine culture (as defined above) who were at risk for a BSI, but did not develop one during their hospital stay (i.e., negative blood culture or no blood culture ordered).

Table 3.

Predictors of hospital-acquired urinary tract-related bloodstream infection

	Cases v Control 1		Cases v Control 2	
Characteristic	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age	1.00 (0.99–1.01)	0.60	1.03 (1.02–1.04)	<.0.001
Race				
White (ref)	ref	-	ref	-
Black	1.06 (0.84–1.34)	0.62	1.29 (1.01–1.65)	0.04
Other/unreported	1.02 (0.70–1.50)	0.91	1.25 (0.84–1.88)	0.27
Surgical Procedures				
Cardiovascular	1.99 (1.58–2.50)	<0.001	2.26 (1.75–2.92)	<0.001
Digestive	1.54 (1.19–1.99)	0.001	1.90 (1.43–2.51)	<0.001
Urologic	1.79 (1.15–2.79)	0.01	3.27 (1.93–5.54)	<0.001
Comorbidities				
Diabetes mellitus	0.99 (0.78–1.25)	0.90	0.96 (0.75–1.23)	0.72
Renal failure	1.39 (1.04–1.86)	0.03	1.48 (1.08–2.05)	0.02
Liver disease	1.17 (0.80–1.72)	0.43	1.62 (1.08–2.44)	0.02
Malignancy	1.42 (1.00–2.04)	0.05	1.44 (0.97–2.12)	0.07
Medications received *				
Antibiotics	0.68 (0.53–0.86)	0.001	0.99 (0.77–1.27)	0.95
Immunosuppressants	1.38 (1.02–1.89)	0.04	2.15 (1.52–3.04)	<0.001
Statin	1.00 (0.79–1.28)	0.98	1.13 (0.87–1.47)	0.37
Blood products **				
Red blood cells	1.03 (1.00–1.07)	0.07	1.11 (1.06–1.17)	<0.001
Platelets	0.98 (0.86–1.12)	0.77	0.93 (0.81–1.07)	0.29
Plasma	1.00 (0.95–1.05)	0.89	0.98 (0.92–1.05)	0.55

OR - odds ratio, CI - confidence interval.

* Medications modeled as being administered during the hospital stay 2 days prior to the index date (i.e., the bloodstream infection date of the case) within each matched case-control set.

** Number of transfusions. Control group 1 included all adult patients with a positive urine culture who were at risk for a BSI, but did not develop one during their hospital stay (i.e., negative blood culture or no blood culture ordered). Control group 2 included all adult patients without a positive urine culture (i.e., negative urine culture or no urine culture ordered) who were present in the facility at the time of case diagnosis.