The Epidemiology of Symptomatic Catheter-associated Urinary Tract Infections in the Intensive Care Unit: A 4-year Single Center Retrospective Study

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Purpose: Catheter-associated urinary tract infection (CAUTI) occurs frequently in critical illness with significant morbidity, mortality, and additional hospital costs. The epidemiology of symptomatic ward-acquired CAUTI (within 48 hours of intensive care unit [ICU] admission) has not been carefully examined. The objective of our study was to identify the patient characteristics and microbiology of symptomatic CAUTI in critical illness.

Materials and Methods: A 4-year retrospective observational study (2013-2016) was conducted at a single adult ICU with 30 beds in a tertiary hospital in Northeast China. The enrolled patients were over 18 years of age and had been diagnosed as having symptomatic CAUTIs in the ICU from January 2013 to December 2016. The information of clinicopathological characteristics (such as age, sex, underlying diseases, hospital admission diagnosis, ICU admission source, severity of illness, duration of urinary catheterization, use of antibiotics, duration of ICU stay, and ICU mortality) was recorded in an electronic database by senior clinicians who were blinded to the study purpose and design. Microbiological data were retrieved from the computerized hospital database.

Results: Between January 2013 and December 2016, 4115 patients were admitted to the ICU. Ninety-eight symptomatic CAUTI cases were enrolled in this study, including 29 patients who had ward-acquired CAUTI and 69 patients who had ICU-acquired CAUTI. Patients with ward-acquired symptomatic CAUTI had significantly shorter overall ICU length of stay and shorter urinary catheterization time, and the overall ICU mortality was significantly higher in patients who had ICU-acquired symptomatic CAUTI. More third-generation cephalosporins and carbapenems were used prior to CAUTI in the patients with ICU-acquired symptomatic CAUTI. Escherichia coli and Acinetobacter baumannii were the most common bacteria causing ward-acquired and ICU-acquired CAUTI, respectively. There were a higher number of cases of non-Candida albicans infections in patients with ICU-acquired symptomatic CAUTI than in patients with ward-acquired symptomatic CAUTI.

Conclusion: Clinical characteristics, microbiological characteristics, and prognosis were different between ward-acquired and ICU-acquired symptomatic CAUTI. Patients with ICU-acquired symptomatic CAUTI had higher overall ICU mortality.

Keywords: catheter-associated urinary tract infections; intensive care unit; critical illness; candiduria; bacteriuria

INTRODUCTION

Catheter-associated urinary tract infection (CAUTI) occurs frequently in critical illness with significant morbidity, mortality, and additional hospital costs.[1,2] Many studies have been conducted to investigate the epidemiology, surveillance, and prevention of intensive care unit (ICU) acquired CAUTI.[3-5]) Owing to impaired consciousness and/or systemic inflammation, the diagnosis of CAUTI can be challenging in critically ill patients.[6,7] The diagnoses of CAUTI have been different across previous studies.[2] Moreover, an observational study was conducted on critically ill patients to determine the epidemiology of bacteriuria and candiduria, but asymptomatic and symptomatic bacteriuria/candiduria could not be differentiated.[8]

In contrast, the epidemiology of symptomatic ward-acquired CAUTI in critical illness (within 48 hours of ICU admission) has not been carefully examined. The objective of our study was to identify the patient characteristics and microbiology of symptomatic CAUTI in critical illness. The differences between ICU- and ward-acquired CAUTI, as well as differences between ICU-acquired symptomatic bacteriuria and candiduria, were also analyzed.

MATERIALS AND METHODS

Study Population

A 4-year retrospective study was conducted at The First Affiliated Hospital of China Medical University. All adult patients admitted to the selected ICUs between January 2013 and December 2016 were included in this study.

Inclusion and exclusion criteria

The enrolled patients were over 18 years of age and had been diagnosed as having symptomatic CAUTIs in

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Table 1. Comparison of characteristics of critically ill patients with ward- and ICU-acquired symptomatic CAUTI.

Variables [a]	Ward-acquired (n =29)	ICU-acquired (n = 69)	*P*-value
Age, year; median (IQR)	69 (61, 80)	65.8 (53, 79)	.50
Sex, male; n (%)	13 (44.83)	36 (52.17)	.51
Underlying diseases; n (%)			
Diabetes mellitus	12 (41.38)	24 (34.78)	.54
Chronic liver disease	1 (3.45)	2 (2.9)	.86
Chronic renal disease	6 (20.69)	9 (13.04)	.25
Chronic respiratory disease	7 (24.14)	11 (15.94)	.34
Chronic cardiovascular disease	17 (58.62)	35 (50.72)	.48
Solid tumor	8 (27.59)	16 (23.19)	.68
Hospital admission diagnosis; n (%)			
Cardiovascular disease	5 (17.24)	9 (13.04)	.59
Trauma	1 (3.45)	7 (10.14)	.27
Sepsis	8 (27.59)	35 (50.72)	.04
Gastrointestinal/liver disease	6 (20.69)	4 (5.8)	.03
Respiratory disease	4 (13.79)	3 (4.35)	.10
Neurologic disease	3 (10.34)	6 (8.7)	.75
Others [b]	2 (6.9)	5 (7.25)	N/A
ICU admission sources; n (%)			
Surgery	11 (37.93)	33 (47.83)	.73
Medicine	12 (41.38)	19 (27.54)	.18
Emergency Department	6 (20.69)	17 (24.64)	.67
Severity of illness; median (IQR)			
APACHE II score [c]	16.38 (13, 20)	18.36 (14, 23)	.19
SOFA score [c]	5.72 (3, 7)	7 (5, 10)	.08
Duration of urinary catheterization prior to CAUTI, days; median (IQR)	4 (3, 7)	9 (5, 21)	< .001
Antibiotic use prior to CAUTI; n (%)			
Third generation cephalosporin	7 (24.14)	32 (46.38)	.04
Levofloxacin or moxifloxacin	9 (31.03)	23 (33.33)	.825
Carbapenems	6 (20.69)	30 (43.48)	.033
Vancomycin or linezolid	5 (17.24)	16 (23.19)	.167
Antifungal drugs	6 (20.69)	24 (34.78)	.513
ICU Outcomes			
ICU LOS, days; median (IQR)	17.14 (6, 22)	39.01 (17, 50)	< 0.001
ICU LOS after CAUTI, days; median (IQR)	16.59 (6, 22)	25.86 (9, 31)	.16
ICU mortality; n (%)	2 (6.9)	24 (34.78)	.01

Abbreviations: ICU, Intensive care unit; IQR, interquartile range; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; SOFA score, Sequential Organ Failure Assessment score; LOS, length of stay; CAUTI, Catheter-Associated Urinary Tract Infections.

[a] Continuous variables were compared by independent samples t-test. Mann-Whitney *U* test was employed to analyze variables with non-normal distribution. Chi-square and Fisher exact tests were used to determine whether differences existed between groups of categorical variables.

[b] Other includes renal disease, metabolic disorder, poisoning

[c] Values of APACHE II score and SOFA score were recorded at the admission of ICU

ICU. Patients with symptomatic CAUTI were defined as follows:(1) when a patient who had an indwelling urinary catheter for more than 2 days developed one or more of the following symptoms: fever > 38°C, urgency, frequency, suprapubic tenderness, or dysuria;(2) positive urine cultures containing ≥ 105 colony forming units per mL of no more than two microorganisms; and (3) a clinician diagnosis of CAUTI in the patient's record. The exclusion criteria were as follows: (1) patients who were re-admitted to the ICU, (2) patients who were transferred from the ICU of another hospital, or (3) patients who stayed in the ICU longer than 6 months.

Procedures

There has been an electronic database in the ICU of our hospital since 2012, and patients who were catheterized upon admission or during their stay in ICU were screened daily for the acquisition of CAUTIs. Patients diagnosed as having symptomatic CAUTIs were recorded prospectively. In this study, we retrospectively collected the clinical information of patients diagnosed as symptomatic CAUTIs from the electronic database. The clinicopathological characteristics including age, sex, underlying diseases (such as diabetes mellitus, chronic liver disease, chronic renal disease, chronic respiratory disease, chronic cardiovascular disease, and solid tumor), hospital admission diagnosis (such as cardiovascular disease, trauma, sepsis, gastrointestinal/liver disease, respiratory disease, neurologic disease), and the severity of illness were recorded in an electronic database by senior clinicians who were blinded to the study purpose and design. The duration of urinary catheterization, use of antibiotics, duration of ICU stay, and ICU mortality were also collected. Microbiological data were retrieved from the computerized hospital database. The study was approved by the ethics committee of The First Hospital of China Medical University for screening, inspection, and data collection of the patients.

Evaluations

Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score were used to evaluate the severity of illness on ICU admission. The ICU admission sources were grouped as follows: surgery ward, medical ward, and emergency department. Ward-acquired CAUTI was defined as the first positive urine culture occurring within 48 hours of ICU admission, and ICU-acquired CAUTI was defined as the first positive urine culture occurring after 48 hours of ICU stay.(8) Sepsis was defined as the presence of both infection and

Table 2. Microbiological characteristics of ward- and ICU-acquired symptomatic CAUTI.

Pathogens [a]	Ward-acquired (n =32)	ICU-acquired (n =76)	*P*-value
Enterobacteriaceae; n (%)	8 (25)	11 (14.5)	.19
Escherichia coli	7 (21.9)	5 (6.6)	.03
Klebsiella pneumonia	1 (3.1)	4 (5.3)	.63
Enterobacter	0 (0)	2 (2.6)	N/A
Pseudomonas aeruginosa; n (%)	1 (3.1)	3 (3.9)	.83
Enterococcus; n (%)	4 (12.5)	10 (13.2)	.96
E. faecalis	0 (0)	2 (2.6)	N/A
E. faecium	4 (12.5)	8 (10.5)	.77
Acinetobacter baumannii; n (%)	2 (6.3)	11 (14.5)	.23
Corynebacterium diphtheroides; n (%)	0 (0)	2 (2.6)	N/A
Burkholderia cepacia; n (%)	0 (0)	1 (1.3)	N/A
Candida spp.; n (%)	17 (53.1)	35 (46.1)	.50
Candida albicans	14 (43.8)	17 (22.4)	.03
Candida glabrata	2 (6.3)	8 (10.5)	.48
Candida parapsilosis	1 (3.1)	4 (5.3)	.63
Candida tropicalis	0 (0)	4 (5.3)	N/A
Candida guilliermondii	0 (0)	1 (1.3)	N/A
Candida lusitaniae	0 (0)	2 (2.6)	N/A
Trichosporon asahii; n (%)	0 (0)	2 (2.6)	N/A

Abbreviations: ICU, Intensive care unit; CAUTI, Catheter-Associated Urinary Tract Infections.

[a] Chi-square and Fisher exact tests were used to determine whether differences existed between groups of categorical variables.

a systemic inflammatory response.[9] Duration of ICU stay and ICU mortality were evaluated as patient outcomes.

Statistical analysis

Continuous data are reported as medians and interquartile ranges (IQR). Categorical data are presented as frequency distributions. Differences in continuous variables between groups were compared using the t-test and Mann-Whitney U test. Chi-squared and Fisher exact tests were used to determine whether differences existed between groups of categorical variables. All the tests were 2-tailed, and a P value < 0.05 was determined to represent statistical significance. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Between January 2013 and December 2016, 4115 patients were admitted to the ICU; 107 patients were diagnosed as having symptomatic CAUTI. Four patients who were re-admitted to the ICU, three patients who were transferred from the ICU of another hospital, and two patients who stayed in the ICU longer than 6 months were excluded. For subsequent analysis, 98 patients with symptomatic CAUTI were enrolled. For each patient, if CAUTI occurred multiple times during the ICU stay, only the first epidemiological recording was considered in the analysis.

Characteristics of critically ill patients with ward- and ICU-acquired symptomatic CAUTI

Table 1 shows the characteristics of the 29 patients with ward-acquired symptomatic CAUTI and the 69 patients with ICU-acquired symptomatic CAUTI. In terms of age, sex, underlying diseases, and admission source or illness severity, no significant differences were found between the two groups. The patients with ward-acquired symptomatic CAUTI had a significantly shorter overall ICU length of stay (LOS) (median ICU LOS, 17.14 days [IQR 6-22] vs. 39.01 days [IQR 17-50], P < .001); however, there was no significant difference in ICU LOS after CAUTI between both groups. The overall ICU mortality was significantly higher in patients who had ICU-acquired symptomatic CAUTI than in those who had ward-acquired symptomatic CAUTI (34.78% vs. 6.9%, P = .01). In terms of the diagnosis at hospital admission, the ICU-acquired symptomatic CAUTI group had a higher number of patients with sepsis, and the ward-acquired symptomatic CAUTI group had a higher number of patients with gastrointestinal/liver disease. The duration of urinary catheterization prior to CAUTI in the group of ward-acquired symptomatic CAUTI was significantly shorter than that in the ICU-acquired group (median, 4 days [IQR 3-7] vs. 9 days [IQR 5-21], P < .001).

Antibiotic use prior to CAUTI is described in **Table 1**. More third-generation cephalosporins (46.38% vs. 24.14%, P =.04) and carbapenems (43.48 vs. 20.69%, P = .033) were used prior to CAUTI in patients with ICU-acquired symptomatic CAUTI. There was no significant difference between groups in the use of levofloxacin or moxifloxacin, vancomycin or linezolid, and antifungal drugs prior to CAUTI.

Microbiological characteristics of ward- and ICU-acquired symptomatic CAUTI

For each patient, when multiple isolates were obtained, only the first isolate was considered in the analysis. **Table 2** presents pathogens causing ward- and ICU-acquired symptomatic CAUTI. Thirty-two pathogens were isolated from 29 ward-acquired CAUTI patients. Of these, 25% (8/32) were from the Enterobacteriaceae family, with Escherichia coli being the most frequently occurring bacteria (7/15 isolated bacterial strains, 46.7%) (**Table 2**). Furthermore, 53.1% were identified as Candida spp., with Candida albicans being the most frequently occurring yeast (14/17 isolated Candida spp., 82.4%) (**Table 2**). Seventy-six pathogens were isolated from 69 ICU-acquired CAUTI cases. Candida spp. were the most frequently isolated microorganism (46.1%), with C. albicans infection representing 22.4% (17/76) of cases. There was a higher number of non-C. albicans infection cases in patients with ICU-acquired CAUTI than in those with ward-acquired CAUTI (18/35 vs.

Table 3. Comparison between critically ill patients with ICU-acquired candiduria and with ICU-acquired bacteriuria.

Variables [a]	Candiduria (n = 31)	Bacteriuria (n = 32)	*P*-value
Age, year; median (IQR)	67.48 (60,78)	62.75 (49,79)	.26
Gender, male; n (%)	13 (41.9)	21 (65.63)	.06
Underlying diseases; n (%)			
Diabetes mellitus	13 (41.9)	9 (28.13)	.25
Chronic liver disease	2 (6.5)	0 (0)	N/A
Chronic renal disease	4 (12.9)	4 (12.5)	.96
Chronic respiratory disease	6 (19.4)	5 (15.6)	.70
Chronic cardiovascular disease	17 (54.8)	14 (43.8)	.38
Solid tumor	6 (19.4)	8 (25)	.59
Hospital admission diagnosis; n (%)			
Cardiovascular disease	7 (22.6)	1 (3.1)	.02
Trauma	2 (6.5)	5 (15.6)	.25
Sepsis	16 (51.6)	14 (43.8)	.53
Gastrointestinal/liver disease	1 (3.2)	3 (9.4)	.32
Respiratory disease	0 (0)	3 (9.4)	N/A
Neurologic disease	4 (12.9)	2 (6.3)	.37
Others [b]	1 (3.2)	4 (12.5)	N/A
ICU admission source; n (%)			
Surgery	13 (41.9)	16 (50)	.52
Medicine	8 (25.8)	10 (31.3)	.63
Emergency Department	10 (32.3)	6 (12.8)	.22
Severity of illness; median (IQR)			
APACHE II score [c]	18.8 (15, 22)	18.13 (12.75, 23)	.71
SOFA score [c]	7(4.5, 9.5)	6.8 (4.75, 10)	.79
ICU Outcomes			
ICU LOS, days; median (IQR)	39.1 (16, 54)	41.4 (18.5, 57)	.77
ICU LOS after CAUTI, days; median (IQR)	28.7 (9, 42)	25.1 (9, 25)	.50
ICU mortality, n (%)	11 (35.5)	10 (31.3)	.72

Abbreviations: ICU, Intensive care unit; IQR, interquartile range; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; SOFA score, Sequential Organ Failure Assessment score; LOS, length of stay; CAUTI, Catheter-Associated Urinary Tract Infections.

[a] Continuous variables were compared by independent samples t-test. Mann-Whitney U test was employed to analyze variables with non-normal distribution. Chi-square and Fisher exact tests were used to determine whether differences existed between groups of categorical variables.

[b] Other includes renal disease, metabolic disorder, poisoning

[c] values of APACHE II score and SOFA score were recorded at the admission of ICU

3/17, $P = .02$); specifically, cases of Candida glabrata (10.5%), Candida parapsilosis (5.3%), and Candida tropicalis (5.3%) infection were noted in ICU-acquired CAUTI patients. However, E. coli infection comprised only 6.6% of the cases (5/76) in ICU-acquired CAUTI patients, which was lower than that in ward-acquired CAUTI patients (21.9%, $P = .03$). Finally, 3 (10.3%) ward-acquired CAUTI patients and 7 (10.1%) ICU-acquired CAUTI patients had polymicrobial infection.

ICU-acquired symptomatic candiduria and ICU-acquired symptomatic bacteriuria

Of the 69 patients with ICU-acquired symptomatic CAUTI, 2 patients had Trichosporon asahii infection, and 4 exhibited both candiduria and bacteriuria during their ICU admissions and were excluded from this comparison. As shown in **Table 3**, no significant differences were observed between the two groups in terms of age, sex, underlying diseases, admission source, illness severity, or outcome. In terms of the diagnosis at hospital admission, cardiovascular disease was more frequent among the patients with ICU-acquired symptomatic candiduria than among those with ICU-acquired symptomatic bacteriuria.

DISCUSSION

In this study, we reported the epidemiology of symptomatic CAUTI diagnosed in critically ill patients. Although many studies concerning the epidemiology, surveillance, and prevention of CAUTI have focused on ICU-acquired CAUTI, few studies have investigated the difference between symptomatic ICU-acquired and ward-acquired CAUTI in critically ill patients.

For example, Aubron et al. compared the clinical characteristics of critically ill patients who had ward- and ICU-acquired positive urine cultures.[8] They found that age, Acute Physiology and Chronic Health Evaluation (APACHE) III score, underlying diseases (chronic liver disease or hepatic failure), primary diagnosis (trauma or neurological findings), microbiological patterns, and the hospital or ICU LOS were significantly different between groups. However, they were unable to differentiate between asymptomatic and symptomatic bacteriuria/candiduria.[8] Asymptomatic bacteriuria is defined as bacteriuria in patients without urinary tract signs or symptoms.[10] The differentiation between symptomatic and asymptomatic urinary tract infections (UTI) is clinically important, because asymptomatic catheter-associated bacteriuria and funguria rarely result in adverse outcomes (e.g., pyelonephritis, perinephric abscess, and bacteremia) and generally do not require treatment. Patients with candiduria are mostly asymptomatic; a large multicenter study showed that only 4% of patients had symptomatic UTI.[11] Bacteriuria in indwelling urinary catheterized patients is usually asymptomatic.[12] In January 2009, the National Healthcare Safety Network (NHSN), the Centers for Disease Control and Prevention's surveillance system on patients' safety, significantly revised the definition of CAUTI: symptomatic and bacteremic cases were included as CAUTI but asymptomatic bacteriuria was removed.[13,14]

We compared the ICU and ward-acquired symptomat-

ic CAUTI cases in critical illness. Our results showed that the overall ICU LOS was significantly shorter in patients who had ward-acquired symptomatic CAUTI, whereas the overall ICU mortality was significantly higher in patients who had ICU-acquired symptomatic CAUTI (no significant difference was found in terms of the disease severity on ICU admission). This difference could be explained by the prevalence of different kinds of diseases in the two groups: the ICU-acquired symptomatic CAUTI group had a higher number of patients with sepsis than did the ward-acquired group.

In previous studies, gram-negative bacilli were reported to be the most commonly isolated bacterial pathogens in ICU-acquired positive urine cultures, with E. coli being the most frequently isolated bacteria.[5,15] The comparison between ICU and ward-acquired symptomatic CAUTI in critical illness showed that E. coli was more prevalent in ward-acquired symptomatic CAUTI, whereas Acinetobacter baumannii was more prevalent in ICU-acquired CAUTI in our study population. Acinetobacter baumannii isolated from patients in the ICU may be highly resistant to multiple antibiotic classes. The difference in the pathogenic bacteria spectrum between the two groups can be potentially explained by the longer ICU LOS, prolonged catheterization period, and more frequent use of broad-spectrum antibiotics in the group of ICU-acquired CAUTI.[16-18]) Recently, some studies indicated that CAUTI might be associated with microbial biofilm, and the biofilm formation might be related to the production of drug-resistant bacteria in CAUTI.[17-18]

In our study, Candida spp. were the most commonly isolated microorganisms in both ward- and ICU-acquired symptomatic CAUTI. Aubron et al. reported that 55% of the positive urine cultures in critical illness were caused by Candida spp.;[8] our results were consistent with their results. Compared with previous studies that reported that C. albicans and other Candida species cause 1/3 of all ICU-acquired UTIs, this rate is regarded as high.[19]) During the period of critical illness, high rates of candiduria have been related to the frequent use of systemic antibiotics.[20,21] Previous studies showed that risk factors for candiduria include female sex, advanced age, ICU hospitalization, surgery, and preexisting diabetes mellitus.[22,23] However, in the present study, a comparison of ICU-acquired candiduria with bacteriuria showed no significant differences between groups in terms of the aforementioned risk factors.

As mentioned earlier, patients with ICU-acquired candiduria had a longer ICU LOS and higher APACHE III score in a previous study.[8] Our results showed that there were no significant differences between ICU-acquired candiduria and bacteriuria in terms of illness severity or ICU LOS. Finally, there was a higher number of cases of non-C. albicans infection in patients with ICU-acquired symptomatic CAUTI. Interestingly, in contrast to our findings, C. albicans has been reported to be the most common Candida spp. in ICU-acquired CAUTI cases in other studies.[22,24]

Although candiduria reporting has been eliminated from the 2015 NHSN definition of CAUTI,[25] the diagnosis of CAUTI with Candida and whether to treat catheter-related candiduria in critical illness are still controversial. A meta-analysis that included 11 studies and 2745 ICU patients with CAUTI suggested that 34% of CAUTI cases in ICU patients were caused by fungal sources. In Infectious Disease Society of America-2016 guidelines,[26] barring high-risk patients (neutropenic patients and patients undergoing urologic manipulation), patients with asymptomatic candiduria are not recommended to undergo treatment with antifungal agents. Antifungal agents are recommended in patients with symptomatic candiduria.[26]

The results of our study also showed that, in terms of the diagnosis at hospital admission, cardiovascular disease was more frequent among patients with ICU-acquired symptomatic candiduria than among those with ICU-acquired symptomatic bacteriuria. There are no similar reports in previous literature. This correlation needs to be confirmed by further studies in a larger sample.

There are several limitations in our study. First, there was a lack of representativeness; the present study was only performed in one tertiary-care hospital, although it included multiple ICU populations. Second, due to the retrospective nature of our study, we depended on the clinicians' judgment to investigate the cause of fever. These limitations might introduce bias in the results.

CONCLUSIONS

This is the first study to analyze the differences between ward- and ICU-acquired symptomatic CAUTI in critical illness. The clinical characteristics, microbiological characteristics, and prognosis were different between the two groups. No significant differences between ICU-acquired symptomatic candiduria and bacteriuria were found. Our study's findings suggest that both ICU-acquired symptomatic candiduria and bacteriuria should receive more attention because ICU-acquired symptomatic CAUTI might be associated with poor prognosis.

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CONFLICTS ON INTEREST

The authors report no conflict of interest.

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