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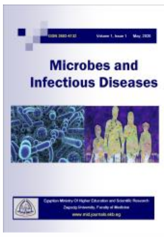


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**Original article**

# Multidrug-resistant urinary tract pathogens isolated from Egyptian catheterized ICU inpatients during coronavirus disease 2019 pandemic

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**ABSTRACT**

**Background:** The CDC recommended conducting insistent surveillance for catheter-associated urinary tract infection (CAUTI) helping in the early identification of patients based on the frequency of catheter use and potential risk. One of the largest problems facing public health is the COVID-19 pandemic. **Aim:** This study aimed to highlight the frequency of CAUTI, and antibiotic susceptibility profile of isolated bacteria recovered from COVID-19 patients and to compare resistance patterns with CAUTI cases during the pre-COVID period. **Study design:** This study included prospective and retrospective parts and included two ICUs at Zagazig University Hospitals that was transformed into an isolation hospital during Coronavirus disease 2019 pandemic. **Methods:** Patients included were clinically suspected of having catheter-associated urinary tract infection during two different stages; the pre-COVID period and the COVID-19 second wave. **Results:** This study was conducted on 479 catheterized hospitalized patients at Zagazig University ICUs (362 inpatients hospitalized pre–COVID-19 period, and 117 inpatients hospitalized during the second COVID-19 wave). The CAUTI rate during the COVID-19 second wave was statistically higher significant than the CAUTI rate during the per-COVID-19 period. **Conclusion:** The current study demonstrated an increased frequency of CAUTI among catheterized ICU patients during the second COVID-19 pandemic wave. The rates of carbapenem-resistant *Enterobacteriaceae*, MDR *A. baumannii*, and ESBL- *Pseudomonas aeruginosa* were significantly increased. These findings may indicate the increased risk of CAUTI and increased prevalence of isolated MDRO during the COVID-19 second wave.

## Introduction

Acute-care hospitals are burdened by coronavirus illness (COVID-19 pandemic) and its management has been changing over the progression of the pandemic with new research guidelines and repetitive reformulation [1]. The massive bearing of COVID-19 on healthcare-associated infections (HAIs) in 2020 clarified that catheter-associated urinary tract infection (CAUTI) has shown an overall 19% increase across different hospital departments, with a particularly higher increase of about 30% in ICUs [2].

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There is no doubt that even developed countries' hospitals were striving to face the unprecedented challenge due to a high flood of critically ill COVID-19 positive while already suffering from the shortage of suppliers during the international travel restrictions [3]. It has been observed that nearly 60% of patients in an intensive care unit (ICU) had urinary catheters. Urinary tract infections accounted for nearly one-third of all healthcare-associated infections, the majority of which are related to catheter use [4,5].

Healthcare-associated infections (HAIs) impacts are not only limited to public health but the economic and social status of patients and their families as well; this is due to the long hospital stays, possible debilities, and high death rate [6]. Additionally, evidence suggests that coinfections and secondary infections resulted in a higher mortality rate during the COVID-19 era in a considerable number of hospitalized patients [7].

Overconsumption of antibiotics during the COVID-19 era offered a chance for the bacterial pathogens especially those recovered from patients admitted to the ICU to develop resistance mechanisms resulting in increased prevalence of multidrug-resistant organisms (MDROs) and extensively drug-resistant (XDR) organisms [8].

The picture in our hospitals was not unlike. The frequency of CAUTI among hospitalized COVID-19 patients was increasing with ensuing increased complications and prolonged hospital stay. Raising the alarm for undertaking this research during the second wave of COVID-19.

This study aimed to assess the prevalence of CAUTI and its associated risk factors in COVID-19 patients. The antibiotic susceptibility profile and resistance pattern of isolated bacteria recovered from CAUTI patients during the second COVID-19 wave were compared to cases during the pre-COVID period.

## Methods and methods

### Study settings and design

This survey study was carried out over 10 months including retrospective and prospective divisions; five months each. The retrospective part of the study was conducted by data collection from a laboratory information system (LIS) and medical records of CAUTI patients admitted to ICU during a five-month pre-COVID period from June 2019 to October 2019. The prospective part of the study was conducted during the second wave of the COVID-19 pandemic from October 2020 to February 2021 at a tertiary care hospital at Zagazig University, Egypt. This study was carried out at the intensive care units (ICUs) of Zagazig University Isolation Hospitals, bacteriology laboratory at medical microbiology and immunology department, molecular biology central laboratories, and clinical pathology laboratories, Faculty of Medicine, Zagazig University.

The Institutional Review Board (IRB), Faculty of Medicine, Zagazig University, approved the study. (IRB reference number: ZUIRB# 1097/ 2021). It was conducted by the updated Declaration of Helsinki. All study participants gave informed consent or in the case of unconscious ones, their legal guardians did.

### Participants

This research included one retrospective and one prospective division. Representative samples were collected from hospitalized, urinary catheterized COVID-19 ICU inpatients. Patients included in the current work had confirmed COVID-19 and urinary catheterized with an indwelling urethral urinary catheter in place within the 48-hours before the sample collection, and had focal symptoms or fever. In case of refusal of the patient or his family to participate in the study, patients were excluded. Our ICU policy as regard insertion and maintenance of catheters was the same pre and during COVID-19.

By use of the online tool Open epi version 3.1, the sample size was estimated [9]. A retrospective sample of medical records of ICU inpatients was included covering the second half of 2019 as the pre-COVID-19 period.

Each participant had a thorough history-taking as well as a clinical assessment that concentrated on the related risk factors such as age, insidious comorbidities, invasive medical procedures, urinary catheter days, use of empirical antibiotics, and immunomodulatory treatment. According to relevant local guidelines, the following lab tests were performed for all patients including complete blood count (CBC), liver function tests, renal function tests, coagulation profile, D-dimer, ferritin level, and inflammatory markers in serum such as C-reactive proteins (CRP), procalcitonin (PCT), and interleukin-6 (IL-6).

Diagnostic criteria, investigations, and treatment of all enrolled participants were performed following relevant local guidelines, protocols, and regulations.

Steroids (dexamethasone) and tocilizumab (actemra) were given as indicated in cases with severe COVID-19 and those who exhibit hyper-inflammatory syndrome with higher IL-6 serum levels [10].

**Specimens collection**

In a sterile, leak-proof universal container, fresh urine samples were aseptically taken from catheterized study participants. The samples were taken from the sampling port of a sterile closed urine drainage system, then were instantly transferred to the microbiology laboratory for processing.

Urine samples were subjected to direct wet mount and cultured on blood agar, MacConkey, Cystine Lactose Electrolyte Deficient (CLED) agar, and Sabouraud dextrose agar (SDA) plates. All media were supplied in powder form (Oxoid, UK). Viable bacterial counting was performed on blood agar using a semi-quantitative standard loop technique [11]. Bacterial colony count ≥100,000 CFU/ml (colony-forming units per milliliter) was considered a significant Bacteriuria. If > 2 organisms type with no predominant organism, possible contamination was assumed and the sample was excluded.

**Identification and antimicrobial susceptibility**

Separate bacterial colonies were subjected to Gram staining and identified by VITEK2 compact system (BioMérieux, Marcy l'Etoile, France) using the appropriate Vitek 2 identification cards (GP/GN/Yeast) [13].

Antimicrobial susceptibilities were performed using a VITEK 2 Compact AST-GN AST 204 (BioMérieux, Marcy l'Etoile, France). MIC (Minimal Inhibitory concentration) breakpoints were interpreted according to the Clinical and Laboratory Standards Institute guidelines (CLSI, 2018) [14]. *Staphylococcus aureus (S. aureus)* ATCC 29213 and *Escherichia coli* ATCC 25922 were used as quality control strains for the VITEK2 Gram-positive and Gram-negative antibiotic susceptibility test card, respectively.

The antibiotics used for Gram-negative susceptibility testing were: ampicillin (AMP), amoxicillin /clavulanic acid (AMC), amikacin (AK), gentamicin (GEN), cefotaxime (CTX), ceftazidime (CAZ), cefepime (FEP), ciprofloxacin (CIP), norfloxacin (NOR), nitrofurantoin (F), ertapenem (ETP), imipenem (IPM), meropenem (MEM), fosfomycin (FOS), trimethoprim-sulfamethoxazole (SXT) and piperacillin/tazobactam (TZP).

For Gram-positive susceptibility testing, the following antibiotics were used: cefoxitin (FOX), oxacillin (OX), vancomycin (VA), trimethoprim-sulfamethoxazole (SXT), nitrofurantoin (F), ciprofloxacin (CIP), moxifloxacin (MOX), levofloxacin (LEV), gentamicin (GEN), quinupristin/dalfopristin (QDA), rifampicin (RD), linezolid (LNZ) tetracycline (TE), tigecycline (TGC), and erythromycin (E).

According to **Magiorakos et al.** [15], MDR organisms were defined as being isolates that are non-susceptible to one or more agents in three or more antimicrobial categories, while XDR organisms were defined as isolates non-susceptible to one or more agents in all but two or fewer categories.

**Reverse transcription real-time polymerase chain reaction (RT-PCR) for SARS-Cov2 detection**

Under complete aseptic conditions, nasopharyngeal and oropharyngeal swabs were obtained by trained healthcare personnel at the isolation units. The two swabs from each participant were placed in a collection tube containing three ml of the viral transport medium (VTM, Ref: 1/V T01.001.0001) and were sent immediately to the Faculty of Medicine's Scientific & Medical Research Center at Zagazig University.

For viral RNA extraction, a commercial Kit, QIAamp® Viral RNA mini kit (Qiagen, cat. no. 52906) was used as per the manufacturer's guidelines. One-step RT-qPCR was done using a real-time PCR kit (Primer design Ltd, Ref: Z-Path-COMD-19-CE, UK) in Stratagene Mx3000P qPCR System (Agilent). The PCR targets are the RNA-dependent RNA polymerase (*RdRP*) gene of SARS-CoV-2.

The reaction mixture included 8 µl sample extract, 10 µl 2X RT-qPCR Master Mix, and 2 µl of COVID-19 Primers. A positive control template and a negative amplification control using water free of nuclease were used in each run. Reverse transcription (complementary DNA; cDNA; formation) was carried out in the one-step process. The mix was heated for10 min at 55 °C, followed by initial denaturation by heating at 95°C for 2 min. Then, 45 amplification cycles were done (each cycle consisting of a denaturation phase at 95°C for 10 sec., annealing, and extension phases at 60°C for 1 min.). (*Ct*) values were recorded for each sample. If samples had a *Ct* value ≥40 or if no cycle threshold

(*Ct)* values were reported, the analyzed samples were considered negative [16].

**Statistical analysis**

SPSS software was used to statistically analyze the collected data (Statistical Package for the Social Sciences software version 25). The mean value and standard deviation (SD) were used to represent quantitative variables, whereas absolute numbers and percentages were used to represent categorical variables. A Chi-square test ($\chi^2$) was used for comparing proportions. Results with *p* (probability) values of 0.05 or less, were considered statistically significant. CAUTI rate was calculated using the following formula: No of CUITIs identified/No of indwelling urinary catheter days x1000 [17].

**Results**

The current research was conducted on 479 catheterized hospitalized patients in Zagazig University ICUs (362 inpatients hospitalized during pre–COVID-19 period and 117 inpatients hospitalized during the second COVID-19 wave). 69% (331/479) of included patients fulfilled the criteria of the CDC NHSN (Center for Disease Control and Prevention-National Healthcare Safety Network) definition of CAUTI [17], including the identification of maximum 2 organisms with a colony count >100,000 CFU/mL, in the presence of fever or localized symptoms in a patient who had an indwelling urethral urinary catheter in place at the time the specimen was collected. The demographic and associated clinical manifestations of studied patients showed in **table (1).**

The proportions of CAUTI among catheterized patients in both groups were calculated. The CAUTI rate among catheterized patients during the pre-COVID-19 period was 64.6 % (234/362). While the proportion of CAUTI among catheterized COVID-19 patients during the second wave was 82.9% (97/117). The CAUTI rate during the COVID-19 second wave was statistically higher significant than the CAUTI rate during the per-COVID-19 period **(Table 2).**

From 234 CAUTI cases in the pre-COVID-19 period, 250 isolates were isolated, while 107 isolates were recovered from 97 CAUTI cases during the COVID-19 second wave. The total number of isolated was higher than the number of CAUTI cases due to the presence of mixed infections.

Among 250 urinary isolates recovered from CAUTI patients during the pre-COVID-19 period, 26.4 % were CRE (Carbapenem-resistant *Enterobacteriaceae)*, 2.4 % were ESBL *P. aeruginosa (*Extended-spectrum beta-lactamase *Pseudomonas aeruginosa)*, 1.2 % were MDR *A. baumannii* (Multidrug-resistant *Acinetobacter baumannii*), and 5.6% were VREF (Vancomycin-resistant *Enterococcus faecium*).

On the other hand, from 107 urinary isolates recovered from CAUTI patients during the second wave of COVID-19, 64.5 % were *CRE*, 7.5% were ESBL *P. aeruginosa*, 10.3 % were MDR *A. baumannii*, and 6.5 % were VREF **(Table 3).** The presence of CRE, ESBL *P. aeruginosa*, and MDR *A. baumannii* was significantly increased during the COVID-19 second wave.

Candiduria represents 7.2% vs. 1.9% among CAUTI patients during the pre-COVID-19 period and second COVID-19 wave, respectively.

**Table 1.** Demographic and associated clinical manifestations of studied patients.

| **Characteristics** | **Before COVID-19 (n= 362 patients)** | **COVID-19 second wave (n= 117 patients)** |
|---|---|---|
| **Age (years), Mean ± SD**<br>**Range** | 43.45 ± 14.9<br>(18 -78) | 62.67 ± 11.08<br>(39 – 83) |
| **Sex, Number (%)** | | |
| Male | 228 (62.9%) | 64 (54.7%) |
| Female | 134 (37.1%) | 53 (45.3%) |
| **Underling comorbidities, Number (%)** | | |
| Obesity | 137 (37.8%) | 56 (47.8%) |
| Diabetes Mellitus | 144 (39.8%) | 39 (33.3%) |
| Hypertension | 109 (30.1%) | 45 (38.5%) |
| Hypothyroidism | 25 (6.9%) | 9 (7.7%) |
| Chest disease | 198 (54.7) | 42 (35.9%) |
| Heart disease | 127 (35.1%) | 35 (29.9%) |
| Kidney Disease | 90 (24.8%) | 23 (19.6%) |
| Malignancy | 39 (10.8%) | 2 (1.7%) |
| Trauma | 217 (59.9%) | 0 |
| **Mechanical ventilation, Number (%)**<br>(Both non-invasive, and invasive) | 218 (60.2%) | 106 (90.6%) |
| **Length of ICU stay (days), Mean ± SD**<br>**Range** | 31.32 ± 21.8<br>(5 -93) | 23.36 ± 15.7<br>(4 – 70) |
| **Urinary catheter days, Mean ± SD**<br>**Range** | 31.32 ± 21.8<br>(5 -93) | 23.36 ± 15.7<br>(4 – 70) |
| **Empiric antibiotic on admission Number (%)** | 362 (100%) | 117 (100%) |
| **Immunomodulatory treatment Number (%)** | 47 (12.9%) | 117 (100%) |
| **Death rate** | 102 (28.2%) | 98 (83.7%) |

**Table 2.** The proportions of CAUTI (CAUTI rate) among catheterized patients in both groups.

| | **Before COVID-19** | **Second Wave** | **Total** | ***p* value** |
|---|---|---|---|---|
| **CAUTI cases** | 234 (64.6%) | 97 (82.9%) | 331 | <0.001* |
| **NON-CAUTI cases** | 128 (35.4%) | 20 (17.1%) | 148 | |
| **Total no of cases** | 362 | 117 | 479 | |

Chi-square test ($\chi^2$): ***p value* <0.001 highly-significant
CAUTI: Catheter-associated urinary tract infection

**Table 3.** The resistant pattern of urinary isolates of CAUTI in both groups.

| Isolated organisms | Before COVID-19 | Second wave | *p* value |
|---|---|---|---|
| **CSE** | 122 (48.8%) | 6 (5.6%) | <0.001** |
| **Non-ESBL producer *P. aeruginosa*** | 8 (3.2%) | 1 (0.9%) | 0.21 NS |
| ***A. baumannii (non-MDR)*** | 7 (2.8%) | 1 (0.9%) | 0.27 NS |
| **Vancomycin sensitive *enterococci*** | 6 (2.4%) | 2 (1.9%) | 0.75 NS |
| ***Candida*** | 18 (7.2%) | 2 (1.9%) | 0.04* |
| **CRE** | 66 (26.4%) | 69 (64.5%) | <0.001** |
| **ESBL *P. aeruginosa*** | 6 (2.4%) | 8 (7.5%) | 0.23* |
| **MDR *A. baumannii*** | 3 (1.2%) | 11 (10.3%) | <0.001** |
| ***VREF*** | 14 (5.6%) | 7 (6.5%) | 0.72 NS |
| **Total no of isolates** | 250 | 107 | |

Chi-square test ($\chi^2$): * *p value* <0.05 = significant ** *P value* <0.001 highly-significant
*CSE: Carbapenem-sensitive Enterobacteriaceae*
*ESBL P. aeruginosa: Extended-spectrum beta-lactamase Pseudomonas aeruginosa*
*MDR A. baumannii: Multidrug-resistant Acinetobacter baumannii*
*CRE: Carbapenem-resistant Enterobacteriaceae*
*VREF: Vancomycin-resistant Enterococcus faecium*
**N.B.** Total no of isolates is higher than CAUTI cases due to the presence of mixed infections.

## Discussion

The COVID-19 pandemic influenced antibiotic resistance in variable ways. During the first wave, the COVID-19 pandemic represents great stress on ICUs, interfering with the implementation of antibiotic stewardship and infection preventive measures. This possibly promoted the emergence of more resistance among hospitalized patients. On the other hand, restricted travel and social distancing possibly reduced the transmission of resistant bacteria in the community [18].

An increase in the incidence of antimicrobial resistance and the predominance of MDROs, poses collateral damage to the current status of the COVID-19 pandemic. The cause behind is multifactorial and is principally related to high rates of antimicrobial agent consumption used as a prophylactic treatment or for treatment of co- or secondary infections among COVID-19 patients low rate of [19].

The proportion of CAUTI in catheterized COVID-19 patients during the second wave was higher than in catheterized non–COVID-19 patients (82.9% vs. 64.6%). Similarly, to our results, a previous study in the USA reported CAUTI rates 83% higher in COVID-19 areas compared to non-COVID-19 areas [20]. The increased proportion of CAUTI may be attributed to the longer duration of indwelling urinary catheter days in COVID-19 patients, the presence of co-morbidities, understaffing, and lack of strict adherence to infection prevention and control practices during the COVID-19 outbreak.

Moreover, the susceptibility to hospital infections may be higher among critically-ill COVID-19 patients due to lymphopenia, impaired immune functions [21], and using steroids as a part of standard treatment for acute respiratory distress syndrome in COVID-19 patients [22].

By comparing the resistance pattern of urinary isolates of CAUTI in the pre–COVID-19 period and second wave of COVID-19, our findings demonstrated a highly significant increase ($p<0.001$) in CRE and MDR *A. baumannii* during the second wave of COVID-19. When compared to CAUTI patients in the pre-COVID-19 period, the rate of ESBL- *P. aeruginosa* was significantly greater in the second wave of COVID-19 (7.5% vs. 2.4%) ($p = 0.05$).

On the other hand, the rate of Vancomycin-sensitive *Enterococci* and VRE did not significantly alter between the pre-COVID-19 and COVID-19 periods, according to our study.

These findings were different from the previous study in Taiwan that showed no significant changes between the pre–COVID-19 period and pandemic period for organisms associated with CAUTIs [19]. The increase in the rate of CRE, MDR *A. baumannii*, and ESBL- *P. aeruginosa* in our study may reflect the impact of intense use of carbapenems and third-generation cephalosporins in our institute.

Patients admitted to ICUs frequently need high levels of support, including supplemental oxygen or ventilation, intravenous fluids, prone positioning, and strict input/output monitoring. Using invasive devices such as central venous catheters, ventilators, and indwelling urinary catheters is markedly increased among hospitalized COVID-19 patients. This may attribute to an increase in rates of device-associated infections patients including CAUTI in these patients [20].

In the current research, the outcome revealed that COVID-19 patients during the second wave had a shorter length of hospital stay coupled with short catheter days in contrast to ICU-admitted patients before COVID-19. Our findings were in agreement with a British study that proved that COVID-19 ICU patients were expected to stay in ICU for an average of 12.4 (13.4) days [24]. Another study in the Netherlands showed similar findings [25].

This short ICU stay for Covid-19 patients can be attributed to either death of these patients or being better with no need for ICU or supplemental oxygen and being shifted to complete their treatment in a non-ICU COVID-19-specific ward. Longer ICU stay before COVID-19 may be attributed to the difference in the type of admitted patients The majority of patients admitted to ICUs in the pre-COVID period, required longer ICU stays including patients with trauma, accidents, shock, or end-stage organ failure.

Large increases in CAUTI as well as other device-associated infections among COVID-19 patients requiring intensive care have been reported in different studies. This possibly may be attributed to the decreased contact time of healthcare workers with COVID-19 patients, which may interfere with the proper implementation of infection control measures and the application of CDC guidelines for insertion and maintenance of utilized devices [23].In our institute, high rate of CAUTI could be attributed to high work pressure and understaffing that caused defective implementation of aseptic techniques during insertion and maintenance of urinary catheter including defective hand hygiene or using same gloves for more than one patients. Delayed removal or emptying of urinary catheters and incorrect positioning of catheter could be also participating factors.

Using antimicrobials wisely following antimicrobial stewardship principles, as well as accurate diagnosis and application of strict infection control measures may be helpful strategies to reduce the occurrence of MDROs during this pandemic [19].

This research settled that the CAUTI rate and resistance pattern of isolated uropathogens within our hospital was greatly affected by the COVID-19 pandemic. Through our results, we highlight the desperate need for activating the role of the infection control team in close monitoring of processes and assessing outcomes and infections related to the utilization of indwelling urinary catheters and other invasive devices during the pandemic.

**Conclusion**

Current research demonstrated an increase in the CAUTI rate among catheterized ICU patients during the second COVID-19 pandemic wave. Moreover, a significant increase in MDR and XDR organisms, including CRE, MDR *A. baumannii,* and ESBL- *P. aeruginosa* was observed. This is due to suboptimal aseptic practices during catheter insertion, overuse of broad-spectrum antibiotics, and immunosuppressive agents associated with other risk factors in immunocompromised COVID-19 patients.

**Conflict of interest**

None.

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