Trends of antimicrobial resistance in patients with complicated urinary tract infection: Suggested empirical therapy and lessons learned from a retrospective observational study in Oman

Yousuf AL Mamari, Hiba Sami, Khurram Siddiqui, Hashim Ba Tahir, Zaaima AL Jabri, Zakariya AL Muharrmi, Syed Gauhar A. Rizvi, Meher Rizvi

Medical Student / Senior Clerk MD Program, College of Medicine and Health Sciences, Sultan Qaboos University; Department of Surgery, Division of Urology, College of Medicine and Health Sciences, Sultan Qaboos University; Department of Medicine, Division of Infectious Diseases, College of Medicine and Health Sciences, Sultan Qaboos University; Departments of Microbiology and Immunology and Family Medicine and Public Health, College of Medicine and Health Sciences, Sultan Qaboos University Hospital, Muscat, Oman; Department of Microbiology, Jawaharlal Nehru Medical College, AMU, Aligarh, Uttar Pradesh, India

Abstract

Background: Complicated urinary tract infection (cUTI) is defined as an infection associated with structural, functional, or metabolic abnormalities of the genitourinary tract. These infections are caused frequently by multidrug-resistant Gram-negative bacilli. The rapid emergence of extended-spectrum beta-lactamase (ESBL), AmpC, and carbapenemase (CR) producers has made the treatment of such infections increasingly more challenging.

Objectives: The aims of the present study were threefold: to assess the clinical profile, trends in etiology, and antimicrobial susceptibility profile in cUTI over the past 10 years at a tertiary care center in Oman as an interrupted time series on the one hand and to develop guidelines for empirical management of such cases on the other.

Materials and Methods: We conducted a retrospective analysis of cUTI in patients presenting at Sultan Qaboos University Hospital over 3 years (2008, 2013, and 2018) covering a span of 10 years. Data were obtained from the patient’s electronic records in the hospital information system. Analysis was done using the Statistical Package for Social Sciences program (SPSS), version 23.

Results: Among the 650 cases of cUTI, 284 (44%) were males and 366 (56%) were females, with dysuria being the most common symptom (34%). The biggest risk factor for developing cUTI was diabetes (35%). The predominant pathogen was Escherichia coli (53%), followed by Klebsiella spp. (16%), Enterococcus faecalis (7%), Pseudomonas aeruginosa (7%), Candida spp. (2%), and Enterobacter cloacae (2%). Over the years, E. coli emerged as the predominant ESBL and AmpC producer, Acinetobacter baumannii as the multidrug-resistant bug, and Klebsiella pneumoniae as the major carbapenem-resistant Enterobacterales (CRE) producer. Nitrofurantoin emerged as the most effective drug for cystitis. Aminoglycosides, piperacillin-tazobactam, and carbapenems demonstrated the highest activity with an overall resistance of less than 10%. Higher resistance (30%) was observed against cephalosporins, fluoroquinolones, and trimethoprim/sulfamethoxazole. Analysis of the

Access this article online

Quick Response Code:

Website: www.urologyannals.com

DOI: 10.4103/ua.ua_67_22

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: AL Mamari Y, Sami H, Siddiqui K, Tahir HB, AL Jabri Z, Al Muharrmi Z, et al. Trends of antimicrobial resistance in patients with complicated urinary tract infection: Suggested empirical therapy and lessons learned from a retrospective observational study in Oman. Urol Ann 2022;14:345-52.
INTRODUCTION

Urinary tract infections (UTIs) are among the most frequently acquired bacterial infections both in the community and the health-care settings.\(^1\)\(^,\)\(^2\) Approximately 40%–50% of women experience at least one episode of UTI during their lifetime.\(^3\) UTI is traditionally classified into two groups, complicated and uncomplicated. Complicated urinary tract infection (cUTI) is defined as an infection associated with structural, functional, or metabolic abnormalities of the genitourinary tract.\(^4\)\(^,\)\(^5\) These underlying conditions interfere with host defense mechanisms, thus increasing the risk of acquiring not only recurrent but also multidrug-resistant (MDR) UTI.\(^6\) The increased prevalence of MDR Enterobacteriales, which limits available treatment options for infections caused by these organisms, as well as the lack of new antibiotics, provides good justification for using older antibiotics like fosfomycin, which have been shown to retain some activity against MDR bacteria.\(^7\) As uropathogens are rapidly acquiring resistance, treating such infections is becoming increasingly more challenging. Focused local antibiograms are useful tools to inform empirical management. While abundant studies have focused on antimicrobial susceptibility pattern in simple community-acquired UTI, there are fewer studies on cUTI. The aims of the present study were threefold: to assess the clinical profile, trends in etiology, and antimicrobial susceptibility profile in cUTI over the past 10 years at a tertiary care center in Oman as an interrupted time series on the one hand and to develop guidelines for empirical management of such cases on the other.

10-year trend threw up some unexpected results. As expected, resistance increased from 2008 to 2013. Surprisingly, however, antimicrobial resistance in 2018 was lower against majority of the antimicrobials compared to 2013.

Conclusion: There is a paucity of data for developing evidence-based guidelines management of cUTI. Targeted antibiograms and not cumulative antibiograms are essential for promoting appropriate prescribing and optimizing patient care. The welcome decline in resistance may be attributed cascade reporting, introduction of more ID physicians. Another possibility is increased utilization of fluoroquinolones which spared the other groups of antimicrobials. Judicious heterogeneous mixing of antimicrobials should be spearheaded in both cystitis and pyelonephritis so that there is no undue pressure on one drug. We strongly recommend carbapenem-sparing protocols in treatment of cUTI when anticipating augmented resistance due to AmpC production. Synergistic combinations such as piperacillin-tazobactam plus aminoglycosides/fluoroquinolones may be prescribed. In sepsis, however, carbapenems are the drugs of choice.

Keywords: Antimicrobial resistance, complicated urinary tract infections, empirical therapy, Oman

MATERIALS AND METHODS

Study design

This study retrospectively analyzed the clinical profile, bacterial etiology, and antimicrobial resistance in patients presenting with cUTI at Sultan Qaboos University Hospital (SQUH), Oman, over a 10-year time period. The clinical profile and laboratory data of 3 years 2008, 2013, and 2015 were obtained through the electronic patient record from the Hospital Information System (HIS). The rationale for analyzing antimicrobial susceptibility profile as an interrupted time series over 3 years separated by a gap of 5 years was to assess the trends in antimicrobial resistance over the three different timelines. The microbiology laboratory has been following cascade reporting since the last 15 years, restricted formulary was adopted in 2012, and two more ID physicians joined early in the second decade of this century. Ethical approval was obtained from the Research and Ethics Committee, College of Medicine and Health Sciences, Sultan Qaboos University, Oman.

Study group

All consecutive, nonduplicate cases of complicated UTI were included in the study. Relevant information pertaining to demographic profile of patients, presentation, comorbid conditions, prior episodes of UTI, and prior antibiotic treatment in the last 3 months were elicited. cUTI was defined as an infection associated with structural, functional, or metabolic abnormalities of the genitourinary tract. Midstream urine samples were collected from patients with recurrent UTI, nosocomial UTI

Address for correspondence: Dr. Meher Rizvi, Department of Microbiology and Immunology, College of Medicine and Health Sciences, Sultan Qaboos University Hospital, Muscat, Oman.
E-mail: rizvimeher@squ.edu.om
Received: 26.04.2022, Accepted: 27.06.2022, Published: 07.09.2022
(symptoms developing at least 48 hours after admission), postmenopausal women, patients with comorbidities such as diabetes, renal failure, and sickle cell disease, patients with impaired voiding (vesicoureteral reflux), obstruction, immunosuppressed status (chemotherapy, renal transplant), thalassemia, patients with in situ devices, G6PD deficiency and congestive heart failure and were transported to the Microbiology Laboratory for culture and sensitivity. Samples from catheterized patients were collected only if the clinical picture merited it.

The processing of urine samples was performed as per standard guidelines. The identification and antimicrobial susceptibility of the isolates were carried out by BD Phoenix automated system (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) as per the Clinical and Laboratory Standards Institute guidelines. Extended-spectrum beta-lactamases (ESBLs) were defined as those strains that hydrolyzed cephalosporins and monobactams from the third and fourth generations, but not cephamycins or carbapenems. They can be inhibited by clavulanic acid (sulbactam or tazobactam). Isolates were identified as AmpC if they were resistant to cephalothin, cefazolin, cefotixin, most penicillins, and β-lactamase inhibitor-β-lactam combinations. MDR was defined as nonsusceptibility to at least one antimicrobial agent in three or more antimicrobial categories.

**Statistical analysis**

Patients’ clinical profile (epidemiologic, demographic, and clinical presentation), bacterial etiology, and the antimicrobial resistance profile were analyzed using SPSS v 23.0 Window (IBM Inc., SPSS Inc., Chicago, IL USA). The categorical data such as etiological profile of pathogens causing UTIs were presented in percentages whereas continuous data such as age was expressed as mean ± standard deviation. The trends of antibiotic resistance were analyzed by forming a linear regression line to trace the trend over a decade to analyze the changes in sensitivity over time. As this was a descriptive study, no hypothesis testing was done and no parametric and nonparametric tests were applied.

**RESULTS**

**Patient characteristics**

During the 10-year period, a total of 4437 patients spanning all age groups presented to SQUH with complaints of UTI. Among these, 650 (14.6%) cases with positive urine cultures qualified the criteria of cUTI. There was a strong female predominance right from childhood to around fifth decade. The males predominated in the extremes of age: neonates (n = 71.4% were males in this age group) and those 60 years or older (n = 56.7%). Majority (68%) were treated in the outpatient department while the remaining (32%) were hospitalized. Significant comorbidities in the hospitalized cases were diabetes (35%), obstruction (16%), and renal failure (11%) while the highest health-care associated risk factors were in situ devices 24% [Table 1].

**Clinical findings**

A significant number of cases were symptomatic (n = 73%). Dysuria was the most common presenting symptom, 218 cases (34%), followed by fever, 191 (23%) patients, while flank pain, abdominal pain, increase in frequency, hematuria, and suprapubic pain were observed in 97 (15%), 84 (13%), 71 (11%), 57 (9%), and 43 (7%) patients, respectively. The immunocompromised and those suspected to have catheter-associated urinary tract infection (CAUTI) made up the asymptomatic cases. G6PD deficiency was present in 31 (4.7%) cases.

**Etiology**

The most common pathogen across all the three study periods was *Escherichia coli* (n = 346, 53%), followed by *Klebsiella* spp. (n = 106, 16%), *Enterococcus faecalis* (n = 44, 7%), *Pseudomonas aeruginosa* (n = 47, 7%), *Candida* spp. (n = 15, 2%), *Enterobacter cloacae* (n = 15, 2%), and other miscellaneous bacteria, n = 77, which constituted 12%. Bacterial etiology over the 3 years (2008, 2013, and 2018) is given in Figure 1. *E. coli* and *Klebsiella* spp. predominated in diabetics and in patients with CAUTI [Figure 1]. The prevalence of *E. coli* was lowest (47%) in CAUTI while *P. aeruginosa* the highest (15%).

**Table 1: Demographic characteristics of patients with complicated urinary tract infection**

| Characteristics            | n (%)         |
|----------------------------|---------------|
| Total number of cases (patients) | 650 (14.6)    |
| Sex                        |               |
| Female                     | 366 (56)      |
| Male                       | 284 (44)      |
| Age (years), mean±SD (median) | 50.73±23.23 (57) |
| ≤30                        | 191 (29.3)    |
| 30–60                      | 239 (36.7)    |
| ≥60                        | 160 (24.6)    |
| Hospitalized               | 208 (32)      |
| Outpatient                 | 442 (68)      |
| Comorbidities              | 504 (77.5)    |
| Diabetes                   | 229 (35)      |
| In situ devices            | 159 (24.4)    |
| Urinary obstruction        | 104 (16)      |
| Renal failure              | 67 (10)       |
| Immunosuppression          | 58 (8.9)      |
| Sickle cell anemia         | 39 (6)        |
| Impaired voiding           | 28 (4.3)      |
| Congestive heart failure   | 17 (2.6)      |
| Thalassemia                | 5 (0.6)       |

SD: Standard deviation
Al Mamari, et al.: Trends of antimicrobial resistance in complicated UTI

The resistance patterns of different bacteria recovered from cUTI patients were evaluated over time against representative antibiotics. Both *E. coli* and *K. pneumoniae* isolates exhibited more than 30% resistance to cefuroxime, ceftriaxone, ceftazidime, and cefepime, cotrimoxazole, and ciprofloxacin while resistance rates to imipenem, meropenem, and amikacin were low. The change in antimicrobial resistance profile in the two dominant pathogens *E. coli* and *Klebsiella* spp. as well as in *Pseudomonas* and *Enterococcus* is shown in Figure 2. Interestingly, declining resistance trends were observed in 2018 compared to 2013.

On tracing the trends in antimicrobial resistance in *E. coli* over the three time lines, ciprofloxacin displayed rising resistance over the years. However, this was not the case for the other antimicrobials. Compared to 2013, a noticeable decline in resistance was observed in 2018 to aminoglycosides, amoxicillin-clavulanic acid, cephalosporins, cotrimoxazole, piperacillin/tazobactam, nitrofurantoin, and carbapenems. The reverse was true for *Klebsiella pneumoniae* in which resistance escalated against amikacin, amoxicillin-clavulanic acid, cotrimoxazole, nitrofurantoin, and carbapenems. Overall, a decline in resistance was observed against ciprofloxacin and all generations of cephalosporins. In *Pseudomonas*, a declining resistance trend was observed in 2018 as compared to 2013 against most of the antibiotics except imipenem. A promising declining trend in resistance was observed in *Enterococcus* for nitrofurantoin.

There was no prevalence of ESBL and MDR Gram-negative bacilli in 2008 but inhibitor-resistant TEMs were circulating as evidenced by 21% resistance to amoxicillin-clavulanic acid and (6%) to piperacillin-tazobactam. The 19% resistance to ceftazidime in 2008 may also point to ESBLs which remained undetected. In the last 5 years, *E. coli* emerged as the largest producer of ESBLs, 89/346 (26%), followed by *Klebsiella* spp., 19/106 (18%). Difference in susceptibility to nitrofurantoin, piperacillin-tazobactam, and cotrimoxazole was noticeable between *E. coli* and *Klebsiella*, with the latter being more resistant to the first two, and *E. coli* displayed higher resistance to cotrimoxazole. MDR isolates predominated in *Acinetobacter baumannii*, n = 2 (29%), and *Klebsiella* spp. at 14 (13%) followed by *P. aeruginosa*, 2 (4%), and *E. coli*, 4 (1%). CRE were not present in 2008 but showed a rise in 2013 and further increased in 2018 in the case of *Klebsiella* isolates.

**DISCUSSION**

cUTIs are frequent bacterial infections which merit empirical antimicrobial treatment, especially in the vulnerable group of patients such as elderly, diabetic, and immunocompromised. Timely institution of appropriate antimicrobials in cUTI is critical to avoid life-threatening situations. In an era of increasing AMR, selecting an appropriate antimicrobial is becoming increasingly challenging. One has to critically weigh the attraction of prescribing a broad-spectrum antibiotic at that point against the knowledge that the same antibiotic will in all probability be rendered ineffective for the next 3 months. It should become common knowledge that using a
broad-spectrum drug in the first episode of cUTI leaves the patient vulnerable to future difficult-to-treat infections and naturally a worse outcome. To combat this situation, evidence-based empiric antimicrobial prescribing etiquettes need to be promoted where the clinicians are armed with a sound knowledge of epidemiology and local levels of antimicrobial resistance. Treatment should rely on appropriately prepared targeted antibiograms and not on cumulative antibiograms. We believe that cumulative antibiograms may not be as useful as targeted antibiograms in not only shedding light on the true susceptibility profile but also may have limited clinical utility when selecting...
appropriate empiric antibiotic for a site-specific infection such as the urinary tract. While a large number of studies shed light on the susceptibility patterns in simple UTI, there is a paucity of relevant information in complicated UTI. Relying on the susceptibility pattern of uncomplicated UTIs to treat cUTI may lead to poor patient outcomes as cUTIs have a unique clinical as well as antimicrobial susceptibility profile.

This study was conducted to evaluate the trends in demography, bacterial etiology, antimicrobial resistance, and underlying risk factors in cUTI over 10 years (2008–2018). The prevalence of cUTI was higher in females, although the difference between the two genders was not significant P < 0.05. Females approaching menopause (50–59) were at the greatest risk for developing cUTI compared to all other age groups represented in the study, as has been reported in several studies.\(^\text{[12]}\)

The clinical presentation of symptomatic infection in cUTI ranged from mild-to-moderate symptoms such as fever, dysuria, frequency, urgency, and hematuria to severe systemic manifestations such as urosepsis.\(^\text{[13]}\)

In our study, we identified diabetes as the most significant comorbid condition and risk factor associated with cUTI, with 31% of patients being diabetic. Similar reports have emanated from the American Diabetes Association and other studies from Oman.\(^\text{[14,15]}\) A study from China by Li et al. reported diabetes as the second most common comorbidity (20.2%) after kidney stones.\(^\text{[12]}\) This variation may be related to lower prevalence of diabetes and a higher prevalence of kidney stones in the study population.

UTI in diabetes if not treated in a timely manner may be complicated by pyelonephritis, renal abscess, bacteremia, and sepsis. The role of diagnostic stewardship cannot be highlighted enough as choice of correct antibiotics with the least possible potential to development of resistant strains in the community is of critical importance. Appropriate samples sent in a timely manner not only guide individual treatment but also lead to development of appropriate antibiograms which can play a pivotal role in guiding appropriate empiric management. This will lead to better patient outcome as well as impede the development of antimicrobial resistance.

\textit{In situ} devices were found to be the second most common risk factor (22% cases) for cUTI. This prevalence was lower than that reported in some studies (25.6%) while higher (17.5%) than some other centers.\(^\text{[16,17]}\) The decision to treat CAUTI should rely on the clinical condition and not culture positivity. Majority of these presented as asymptomatic bacteriuria, which again raises the issue of whether they should be treated or not. Similar concerns have been raised by others.\(^\text{[18]}\) The high level of CAUTI suggests that infection prevention and control efforts should be intensified.

\textit{E. coli} (53%) was the predominant pathogen in our study which corroborates with other studies who have reported a prevalence of 48%–65%.\(^\text{[12,18]}\) The prevalence of \textit{E. coli} was lower in comparison to its prevalence in uncomplicated UTI.\(^\text{[20,21]}\) \textit{K. pneumoniae} (16%) and \textit{P. aeruginosa} (7%) were the next common isolates. Other studies have reported \textit{Enterococcus} spp. (11%–14%) as the second most common cause of cUTI.\(^\text{[12,21]}\) The prevalence of \textit{P. mirabilis} was surprisingly low in our study compared with other studies (2%–4.6%).\(^\text{[12,18,21]}\) This may be because the males in this region are all circumcised and thus protected from \textit{P. mirabilis} which usually multiplies in the preputial sacs of uncircumcised men. Thus, circumcision may protect young boys from UTI apart from its other benefits.\(^\text{[22]}\)

There is a global increase in antimicrobial resistance among uropathogens. Threefold increase in the prevalence of ESBL-producing Enterobacterales has been reported worldwide.\(^\text{[23,24]}\) Identification of the underlying conditions and judicious use of appropriate antimicrobials is essential to prevent serious life-threatening conditions, such as urosepsis and renal failure. The increasing resistance to fluoroquinolones observed in \textit{E. coli} (43%) and \textit{K. pneumoniae} (30%) precludes their empirical use as IDSA guidelines discourage empirical use of fluoroquinolones if the local resistance is more than 10%.\(^\text{[24]}\) The high carriage of ESBLs (26%) in \textit{E. coli} precludes using cephalosporins as empirical agents too. Thus, these excellent broad-spectrum antimicrobials, many with good oral bioavailability unfortunately, cannot be advised as first-line empirical agents in cUTI alone. In such situations, a single dose of a long-acting third-generation cephalosporin like ceftriaxone followed by oral fluoroquinolones can be prescribed. In mild infections, fluoroquinolone-sparing strategies can be followed: single shot of ceftriaxone followed by cotrimoxazole, amoxicillin-clavulanic acid, or cefixime.

A high rate of resistance to beta-lactam/beta-lactamase inhibitor combinations (amoxicillin-clavulanic acid [39%] and piperacillin-tazobactam [17%]) in \textit{E. coli} suggests the presence of inhibitor resistance TEMs as well as plasmid-mediated (resistance to amoxicillin-clavulanic acid) and derepressed AmpC (resistance to piperacillin-tazobactam) ß-lactamases. It is known that ESBL and AmpC beta-lactamase induction increases after
exposure to β-lactams and fluoroquinolones.\textsuperscript{12,27,28} Thus, a prior history of exposure to these two groups should alert prescribers of potential resistance and empirical treatment be started with some other group. We strongly recommend carbapenem sparing protocols in treatment of cUTI when anticipating augmented resistance due to AmpC production. Instead of resorting to carbapenems, synergistic combinations such as piperacillin-tazobactam plus aminoglycosides/fluoroquinolones may be prescribed. In septic cases, however, piperacillin-tazobactam may be replaced by carbapenems. It is however essential that subsequent treatment be guided by urine culture and sensitivity results. This will optimize both the treatment and curtail emergence of resistance.

In our center, nitrofurantoin with 3% resistance continues to be an excellent choice in cystitis as majority of cases are due to \textit{E. coli}. \textit{Klebsiella} species are not as sensitive to it and demonstrated a resistance of 43%. Aminoglycosides with a low resistance of 7% may be recommended as the first-line antimicrobials for pyelonephritis in patients with no underlying renal dysfunction. This group has excellent tissue penetration and efficacy against multiple drug-resistance strains. In the case of underlying renal dysfunction, piperacillin/tazobactam with an overall resistance of 12% and \textit{E. coli}-specific resistance of 7% is an excellent alternative. It is also recommended as a second-line treatment option according to European guidelines.\textsuperscript{29} Carbapenems should ideally be considered third-line treatment options as we should prescribe carbapenems judiciously and preserve them for more severe infections like urosepsis. The first-line empirical treatments recommended by most guidelines for complicated UTI are aminoglycosides, cephalosporin (especially second and third generations), and fluoroquinolones.\textsuperscript{30-32}

On tracing the trends in resistance of \textit{E. coli} over the three time lines, an interesting result was observed in our study. As is usually the case, we expected to observe a rising trend in antimicrobial resistance over the years with maximal resistance in 2018. While ciprofloxacin followed this expected pattern, this was not the case for the other antimicrobials. Compared to 2013, a noticeable and heartening decline in resistance was observed in 2018 to aminoglycosides, amoxicillin-clavulanic acid, cephalosporins, cotrimoxazole, piperacillin/tazobactam, nitrofurantoin, and carbapenems. A significant reason for this may be an increased prescription of fluoroquinolones which spared the other antimicrobials resulting in improved susceptibility. Strangely, the reverse was true for \textit{K. pneumoniae} in which resistance had escalated against amikacin, amoxicillin-clavulanic acid, cotrimoxazole, nitrofurantoin, and carbapenems. However, it was good to see a decline in resistance to all generations of cephalosporins and ciprofloxacin. This suggests that there was a general decline in prescription of cephalosporins which led to an improved susceptibility profile.

Implementing antimicrobial stewardship, cascade reporting, preparing and broadcasting targeted antibiograms to the concerned departments leads to optimal patient care on the one hand and declining antimicrobial resistance on the other. Adherence to local targeted antibiograms and guidelines will further help to prevent the spread of drug-resistant bacteria.

**CONCLUSION**

Given the high antimicrobial resistance in cUTI, following evidence-based guidelines for the management of complicated UTI is essential. In most centers, nitrofurantoin may be considered the drug of choice for cystitis as both Gram-positive and Gram-negative bacteria continue to be susceptible to it and its use is associated with minimal collateral damage. However, the same cannot be said for cotrimoxazole as its resistance exceeds 20% in most centers. In the same vein, we do not recommend empiric use of cephalosporins and fluoroquinolones even in complicated UTI, due to high-level resistance and significant collateral damage. Judicious heterogeneous mixing of antimicrobials should be spearheaded in both cystitis and pyelonephritis so that there is no undue pressure on one drug. In severe cUTI cases, amikacin with its excellent pharmacodynamics and pharmacokinetics and piperacillin/tazobactam may be preferred empirical choices to be de-escalated subsequent to culture reports. Taking relevant history pertaining to prior infections and antimicrobial treatment, deferring treatment till microbiology reports are available, if possible, and not treating asymptomatic cases except pregnant and select group of immunocompromised patients like fresh renal transplant cases are useful strategies in optimizing patient outcomes.

This study did not address the clinical dilemma of treating or not treating patients with recurrent UTI, persistent UTI, or lower urinary tract symptoms (LUTS), where urine analysis and culture reports are often negative. Next-generation sequencing (NGS) and expanded quantitative urine culture (EQUC) will undoubtedly shed much-needed light on whether such patients need antimicrobial therapy and, if so, what therapy. These tests will undoubtedly provide greater clarity regarding the optimal management of these challenging conditions.
REFERENCES

1. Gastmeier P, Kampf G, Wischniewski N, Hauer T, Schulgen G, Schumacher M, et al. Prevalence of nosocomial infections in representative German hospitals. J Hosp Infect 1998;38:37-49.

2. Laupland KB, Ross T, Pitout JD, Church DL, Gregson DB. Community-onset urinary tract infections: A population-based assessment. Infection 2007;35:150-3.

3. Engel JD, Schaeffer AJ. Evaluation of and antimicrobial therapy for recurrent urinary tract infections in women. Urol Clin North Am 1998;25:685-701.

4. Solomkin JS, Hemsell DL, Sweet R, Tally F, Bartlett J. Evaluation of new anti-infective drugs for the treatment of intra-abdominal infections. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis 1992;15 Suppl 1:S33-42.

5. Bergan T (ed): Urinary Tract Infections Infectiology. Basel, Karger, 1997, vol 1, pp 19-26. doi: 10.11159/000061991.

6. Stamm WE, Norrby SR. Urinary tract infections: Disease panorama and challenges. J Infect Dis 2001;183 Suppl 1:S1-4.

7. Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant Gram-negative bacteria causing urinary tract infections: A review. J Chemother 2017;29:2-9.

8. CLSI. 2021. Performance standards for antimicrobial susceptibility testing, M100, 31st ed. Clinical and Laboratory Standards Institute, Wayne, PA.

9. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Gertzings SE, Rice JC, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis 2010;50:625-63.

10. Fair WR, Cough J, Wehtner N. Prostatic antibacterial factor. Identity and significance. Urology 1976;7:169-77.

11. Beyer I, Mergam A, Benoit F, Thurnissen C, Pepersack T. Management of urinary tract infections in the elderly. Z Gerontol Geriat 2001;34:153-7.

12. Ll X, Chen Y, Gao W, Ye H, Shen Z, Wen Z, et al. A 6-year study of complicated urinary tract infections in southern China: Prevalence, antibiotic resistance, clinical and economic outcomes. Ther Clin Risk Manag 2017;13:1479-87.

13. Nicolle LE, AMMI Canada Guidelines Committee*. Complicated urinary tract infection in adults. Can J Infect Dis Med Microbiol 2005;16:349-60.

14. Prapajap K. Urinary Tract Infection in Diabetes. Microbiology of Urinary Tract Infections – Microbial Agents and Predisposing Factors. IntechOpen; 2018. Available from: https://www.intechopen.com/chapters/64419. [Last accessed on 2022 Apr 06].

15. Al Riyami A, Elaty M, Morsi M, Al Kharusi H, Al Shukaily W, Jaju S. Oman world health survey: Part 1 – Methodology, sociodemographic profile and epidemiology of non-communicable diseases in Oman. Oman Med J 2012;27:425-43.

16. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370:1198-208.

17. Zarb P, Coignard B, Griskevičienė J, Muller A, Vankerkhoven V, Weis K, et al. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. Euro Surveill 2012;17:20316.

18. Verhamme KM, Dieleman JP, Bleumink GS, van der Lei J, Surkenboom MC, Artibani W, et al. Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care-the Triumph project. Eur Urol 2002;42:323-8.

19. Muhammad A, Khan SN, Ali N, Rehman MU, Ali I. Prevalence and antibiotic susceptibility pattern of uropathogens in outpatients at a tertiary care hospital. New Microbes New Infect 2020;36:100716.

20. Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. JAMA 1999;281:736-8.

21. Zilberberg MD, Shorr AF. Secular trends in gram-negative resistance among urinary tract infection hospitalizations in the United States, 2000-2009. Infect Control Hosp Epidemiol 2013;34:940-6.

22. Glennon J, Ryan PJ, Keane CT, Rees JP. Circumcision and periurethral carriage of Proteus mirabilis in boys. Arch Dis Child 1988;63:556-7.

23. Raphael E, Glymour MM, Chambers HF. Trends in prevalence of extended-spectrum β-lactamase producing Enterobacteriaceae in outpatients attending community health centers in Bánlytre, Malawi. Trop Med Infect Dis 2021;6:179.

24. Al Riyami A, Elaty MA, Morsi M, Al Kharusi H, Al Shukaily W, Jaju S. Microbiology of urinary tract infection in diabetics. Microbiology of Urinary Tract Infections – Microbial Agents and Predisposing Factors. IntechOpen; 2018. Available from: https://www.intechopen.com/chapters/64419. [Last accessed on 2022 Apr 06].

25. Bonkat, R. Bartoletti, F. Bruyère, et al. European association of urology (EAU) guidelines on urological infections 2021. Avail-able at https://uroweb.org/guideline/urological-infections.2015.00128. [Last accessed on 2021 Nov 17].

26. Ramadan MF, Morsi M, Al Kharusi H, Al Shukaily W, Jaju S. Microbiology of urinary tract infection in diabetics. Microbiology of Urinary Tract Infections – Microbial Agents and Predisposing Factors. IntechOpen; 2018. Available from: https://www.intechopen.com/chapters/64419. [Last accessed on 2022 Apr 06].

27. Al Riyami A, Elaty MA, Morsi M, Al Kharusi H, Al Shukaily W, Jaju S. Oman world health survey: Part 1 – Methodology, sociodemographic profile and epidemiology of non-communicable diseases in Oman. Oman Med J 2012;27:425-43.

28. Zilberberg MD, Shorr AF. Secular trends in gram-negative resistance among urinary tract infection hospitalizations in the United States, 2000-2009. Infect Control Hosp Epidemiol 2013;34:940-6.

29. Grabe M, Bartoletti R, BJerkund-Johansen TD, Cai T, Çek M, Koves B, et al. Induction of plasmid-mediated AmpC β-lactamase producing Enterobacteriaceae. PLoS One 2019;14:e0218589.

30. Zilberberg MD, Shorr AF. Secular trends in gram-negative resistance among urinary tract infection hospitalizations in the United States, 2000-2009. Infect Control Hosp Epidemiol 2013;34:940-6.

31. Zilberberg MD, Shorr AF. Secular trends in gram-negative resistance among urinary tract infection hospitalizations in the United States, 2000-2009. Infect Control Hosp Epidemiol 2013;34:940-6.

32. Zilberberg MD, Shorr AF. Secular trends in gram-negative resistance among urinary tract infection hospitalizations in the United States, 2000-2009. Infect Control Hosp Epidemiol 2013;34:940-6.