Original Article

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

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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

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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

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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 Enterobacterales, 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.

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

(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.[8] 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).[9] Isolates were identified as AmpC if they were resistant to cephalothin, cefazolin, cefoxitin, most penicillins, and β-lactamase inhibitor-β-lactam combinations.[10] MDR was defined as nonsusceptibility to at least one antimicrobial agent in three or more antimicrobial categories.[11]

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

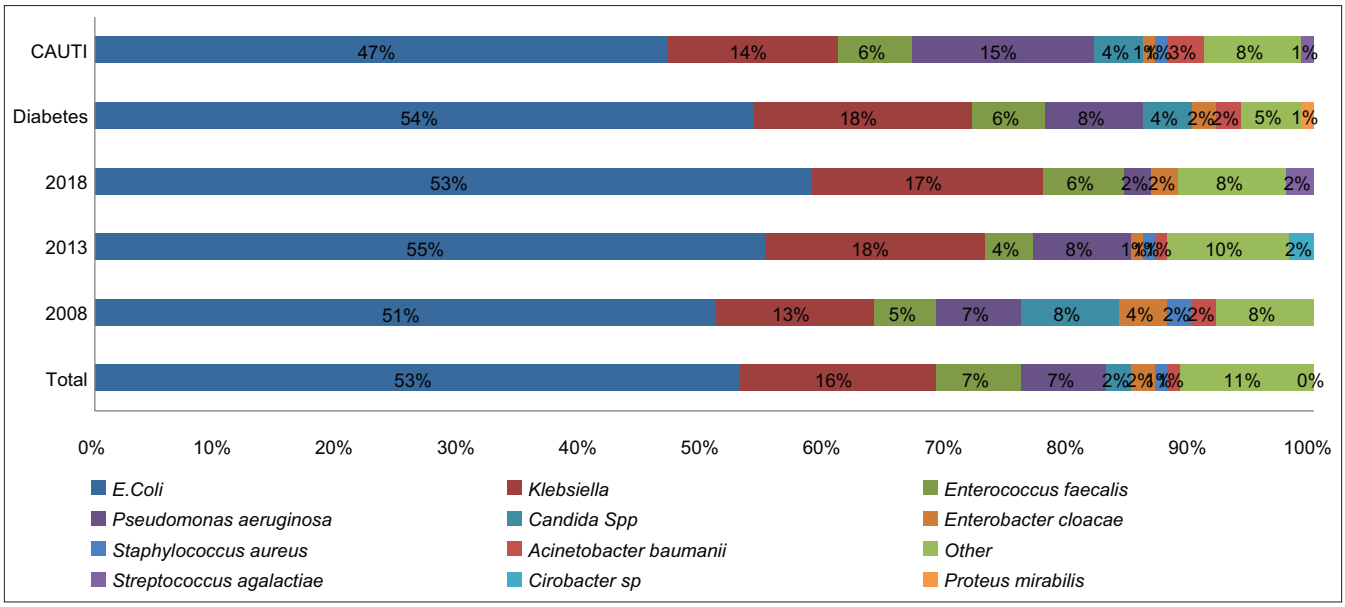

Figure 1: Comparison of distribution of bacterial isolates in cUTI patients over the three time lines 2008, 2013, and 2018, in diabetics and in CAUTI. cUTI: Complicated urinary tract infection, CAUTI: Catheter-associated urinary tract infection

Antimicrobial resistance

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 cephalosporins (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

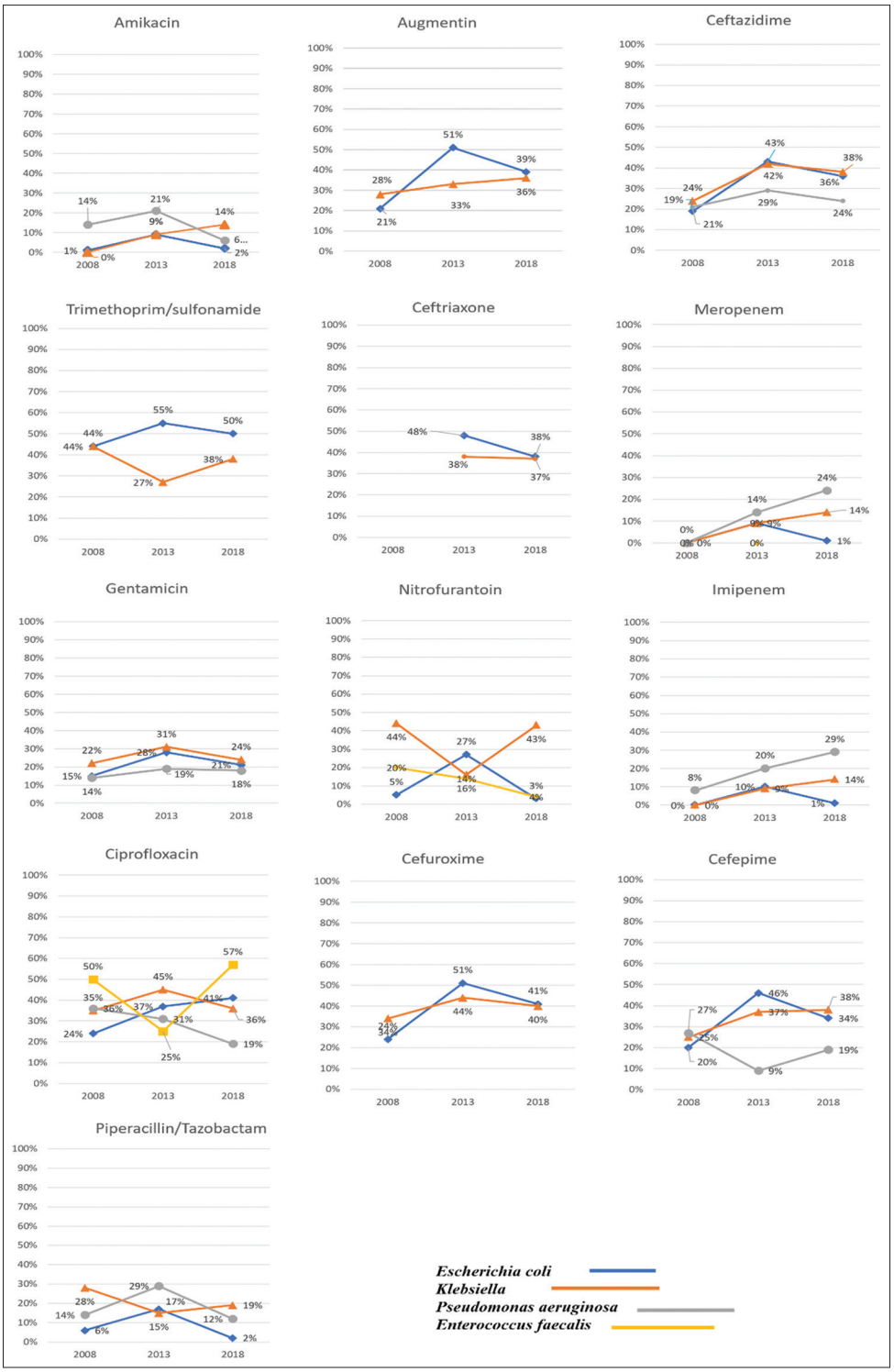

Figure 2: Prevalence ESBLs and multidrug resistance producers over the three time periods (2008–2018). ESBL: Extended-spectrum beta-lactamase

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.[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.[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.[14,15] A study from China by Li *et al*. reported diabetes as the second most common comorbidity (20.2%) after kidney stones.[12] This variation may be related to lower prevalence of diabetes and a higher prevalence of kidney stones in the study population. UTI in diabetics 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.

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.[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.[9] The high level of CAUTI suggests that infection prevention and control efforts should be intensified.

E. coli (53%) was the predominant pathogen in our study which corroborates with other studies who have reported a prevalence of 48%–65%.[12,18] The prevalence of *E. coli* was lower in comparison to its prevalence in uncomplicated UTI.[19,20] *K. pneumoniae* (16%) and *P. aeruginosa* (7%) were the next common isolates. Other studies have reported *Enterococcus* spp. (11%–14%) as the second most common cause of cUTI.[12,21] The prevalence of *P. mirabilis* was surprisingly low in our study compared with other studies (2%–4.6%).[12,18,21] This may be because the males in this region are all circumcised and thus protected from *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.[22]

There is a global increase in antimicrobial resistance among uropathogens. Threefold increase in the prevalence of ESBL-producing Enterobacterales has been reported worldwide.[23-25] 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 *E. coli* (43%) and *K. pneumoniae* (30%) precludes their empirical use as IDSA guidelines discourage empirical use of fluoroquinolones if the local resistance is more than 10%.[26] The high carriage of ESBLs (26%) in *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 *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) β-lactamases. It is known that ESBL and AmpC beta-lactamase induction increases after

exposure to β-lactams and fluoroquinolones.[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 *E. coli*. *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 *E. coli*-specific resistance of 7% is an excellent alternative. It is also recommended as a second-line treatment option according to European guidelines.[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.[30-32]

On tracing the trends in resistance of *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 *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.

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Conflicts of interest
There are no conflicts of interest.

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