Original Article

Management of community-acquired urinary tract infection in a tertiary care setting: A prospective study

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ABSTRACT

Background and Objectives: Carbapenems and beta-lactam-beta-lactamase inhibitors are empirical drugs of choice in the treatment of urinary tract infection (UTI); however, de-escalation of therapy is necessary to ensure compliance. **Objectives:** The objective is to study the impact of antibiotic susceptibility report on the management of community-acquired UTI. **Materials and Methods:** Patients were classified prospectively as uncomplicated UTI (UC-UTI) and complicated UTI (C-UTI), and symptoms, microbiology, antibiotic susceptibility pattern, and treatment modification following culture report were analyzed. Extended spectrum beta-lactamase (ESBL) prevalence in patients was compared among naive and those who received empirical treatment before presentation. Patients with a history of recurrent UTI were given prophylaxis and all were followed up for 1 month. SPSS version 20 package was used for statistical analysis. **Results:** Nearly 75% of the study population had C-UTI. Around 70% of C-UTI and 50% of UC-UTI had ESBL-producing Gram-negative enterobacteriace. In UC-UTI, failed empirical treatment before presentation at our center was significantly associated with positive ESBL producer status. Sensitivity to amikacin and carbapenems was over 90%; nitrofurantoin and piperacillin-tazobactam followed at around 70%. Following culture report, a significant number of C-UTI were de-escalated to oral regimens. **Conclusions:** Despite the high prevalence of ESBL-producing pathogens in community-acquired UTI, once systemic signs of sepsis are controlled, de-escalation is possible in the majority of patients.

Key words: De-escalation of therapy, extended spectrum beta lactamase, urinary tract infection

INTRODUCTION

In India, the prevalence of extended spectrum beta-lactamase (ESBL)-producing enterobacteriaceae in community-acquired urinary tract infection (UTI) ranges between 23% and 60%.[1-3]

Beta-lactam-beta-lactam inhibitors (BL-BLIs) and carbapenems are used only for hospitalized patients. Outpatients (OPs) are generally treated with oral antibiotics such as fluoroquinolones and cephalosporins

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despite high levels of resistance being reported. Failure of OP therapy leads to hospitalization and increased morbidity.

Culture and antibiotic susceptibility reports play a key role in successful treatment. We undertook a study to determine the impact of urine culture in managing patients with UTI, both uncomplicated UTI (UC-UTI) and complicated UTI (C-UTI).

MATERIALS AND METHODS

The study was done at a tertiary care center, between September 2012 and August 2013. Institutional Review Board and Ethics Committee approval was obtained for the study. The study group included patients presenting with a history of either urinary symptoms and/or fever with pyuria (>10–15 leukocytes/μL) and/or imaging evidence of UTI (cystitis, pyelonephritis, etc.). Details noted at registration included age, gender, comorbidity, urinary symptoms, and fever. The antibiotics used by the patients empirically without performing urine culture before presentation at our center were documented.

Urine sample was sent for microscopy and culture for all patients. For patients with a history of prior empirical treatment, it was ensured that patients were off antibiotics for at least 12 h before sending samples for culture. Blood culture was done when systemic sepsis was suspected. Bacterial colony count more than 10^5 colony-forming unit (CFU)/ml in naive and between 10^2 and 10^5 CFU/ml in those with a history of empirical prior treatment was taken as significant bacteriuria.[4]

Microbiology

Clean-catch midstream specimen was collected in a sterile wide-mouth leak-proof container to hold about 50 ml specimen and transported to the microbiology laboratory. Conventional methods such as semi-quantitative culture using calibrated loop/surface streak method with incubation at 35–37°C for 24 h were followed.[5] Culture isolates were further identified using standard biochemical reactions wherever applicable. Antibiotic sensitivity testing was done by the modified Kirby–Bauer disc diffusion method using commercial media from HiMedia, Mumbai, India, according to the Clinical and Laboratory Standards Institute guidelines.[6] Antibiotic discs were procured from HiMedia, Mumbai, India. ESBL detection and phenotypic confirmation were done by testing the strain against ceftazidime and ceftazidime/clavulanic acid. A difference of >5 mm diameter of the zone of inhibition for ceftazidime/clavulanic acid in comparison to ceftazidime was considered indicative of ESBL production. *Escherichia coli* ATCC 25922 for ESBL negative and *Klebsiella pneumoniae* 700603 for ESBL positive were used as reference strains.

Antibiotic protocol

Initial antibiotic regimen for OPs with acute cystitis, quinolones, co-trimoxazole, or nitrofurantoin was given. For inpatients (IPs) with systemic sepsis or pyelonephritis, carbapenems or BL/BLIs: cefoperazone-sulbactam or piperacillin-tazobactam were given.

Once the culture report was obtained, the antibiotics were modified.

Modification of antibiotic regimen

In culture-positive cases, the antibiotic regimen was either the same (appropriate and already narrow spectrum/cannot be de-escalated), de-escalated (on appropriate drug but switched to narrow spectrum drug), or changed (not on appropriate drug and changed as per susceptibility report). The de-escalation/change of antibiotics was in the following order of preference: quinolones, amoxicillin-clavulanate, co-trimoxazole, nitrofurantoin, cephalosporins, amikacin, BL-BLIs, ertapenem, or meropenem/imipenem.

In patients with ESBL producers, de-escalation of antibiotics was done after clinical improvement, i.e., defervescence, stabilization of hemodynamics, and reduction in total white cell counts. Ertapenem was preferred over amikacin in patients with renal insufficiency. Nitrofurantoin was deferred in patients with pyelonephritis and renal failure. Antibiotics were administered for a total duration of 3–7 days in UC-UTI and 14 days for C-UTI.

In culture-negative cases, the same antibiotic was continued in responders. For nonresponders, the antibiotic was switched either to another oral agent or to ertapenem depending on the severity of the UTI.

In those with a history of recurrent UTI (>3 episodes/year), after the complete course of antibiotics for the current infection, prophylactic antibiotic was given based on culture report (nitrofurantoin, co-trimoxazole, or cranberry juice extract) for 3 months.

All patients were followed up for a month for relapse of symptoms. Those patients with recurrence of urinary symptoms had repeat urine culture and treated appropriately.

Exclusion criteria were other causes of fever, lack of laboratory evidence of UTI by urine analysis or imaging, asymptomatic bacteriuria, an indwelling catheter, instrumentation, and onset of symptoms within 48 h of discharge from the hospital.

For analysis, all the patients were classified as follows:

1. UC-UTI (only premenopausal women)
2. C-UTI (men, postmenopausal women, diabetes mellitus, pregnancy, or ureteric obstruction due to stricture or stone).

Analysis was done for the two groups with respect to symptoms, organism isolated, antibiotic susceptibility, and treatment modification following culture report. ESBL prevalence was analyzed in subgroups of (i) naïve (not taken any antibiotics prior to presentation) and (ii) failed treatment (taken empirical antibiotics without urine culture).

Statistical analysis using SPSS version 20 (IBM Armonk, New York, USA)package was performed. Proportions were tested with Chi-square test; ANOVA was used for testing of means and Kruskal–Wallis test for median as appropriate.

RESULTS

A total of 150 patients were registered for the study. More than two-thirds, i.e., 104 (69.3%) were women. The median age was 57 years (range: 16–90 years) for either sex (Kruskal–Wallis test, P = not significant [NS]); a third of the patients were in the sixth and seventh decades. Majority of the patients in the third decade were women (18 out of 19) ($P < 0.05$). Diabetes as a comorbid condition was present in nearly half of the study population (48%).

At the time of registration, 41% (62/150) of the patients had taken antibiotics on an empirical basis. These included quinolones (20%), nitrofurantoin (8%), and cephalosporins (8%). A quarter of the patients had taken two or more antibiotics (quinolones ± cephalosporins ± a third agent); a third was unaware of the name of the antibiotics.

The C-UTI group comprised 116 patients (77.3%) and UC-UTI group comprised 34 patients (22.6%). UTI manifested as only fever without urinary symptoms in 33% of C-UTI and 17% of UC-UTI (P = NS) patients. Symptoms' wise, there was no significant difference between patients with C-UTI and UC-UTI.

Complicated urinary tract infection

Among 116 patients, culture was positive in 98 patients (84%). Culture negativity was lower though NS in naïve patients (7/66, i.e., 10.6%) compared to those who had failed empirical treatment (11/50, i.e., 22%). *E. coli* was the most common organism isolated [Table 1]; 10% had isolated Gram-positive, mixed, or candidal infection. Overall, ESBL status was positive in 70% of Gram-negative isolates. In naïve patients, ESBL production was positive in 67% compared to 48% of failed treatment patients (P = NS).

The isolates were maximally susceptible to amikacin, carbapenems (95%), least to amoxicillin clavulanate, cephalosporins, quinolones, co–trimoxazole, and cefoperazone-sulbactam (30%–45%), and moderately to piperacillin tazobactam (80%) and nitrofurantoin (76%).

Nearly 42% of the patients were given carbapenems and 41% of BL/BLIs as initial antibiotic regimen. Following culture report, 22% of the patients continued on carbapenems, 8.6% on BL/BLIs, and the rest were de-escalated to oral drugs, namely, co-trimoxazole, nitrofurantoin, quinolones, and cephalosporins in that order of frequency. For ESBL producers, de-escalation was done within 3 days in 47% of patients, 5 days in 33%, and in 7 days in the remaining 20% of patients. For non-ESBL producers, the de-escalation was done as soon as the report was available.

Pie chart [Figure 1] shows culture reports resulted in significant de-escalation in the C-UTI group ($P < 0.0001$ and relative risk [RR]: 4.8; 95% confidence interval [CI]: 1.9–12.3).

Totally 21 patients received prophylaxis. Three out of the remaining 95 patients (3%) relapsed in the follow-up period.

Uncomplicated urinary tract infection

Among the 34 patients, pathogens were isolated in 25 patients (73.5%). Culture negativity was similar in naïve (5/22, i.e., 22.7%) versus failed empirical treatment patients (4/12, i.e., 33%).

E. coli was the most common organism in 80% of the patients [Table 1]. Overall, ESBL-producing Gram-negative

Table 1: Microbiology of isolates in culture specimens of the patients

Organism	C-UTI, *n* (%)	UC-UTI, *n* (%)
Escherichia coli	80 (81.6)	20 (80)
Klebsiella species	6 (6.1)	2 (8)
Proteus species	1 (1)	0
Enterobacter species	1 (1)	1 (4)
Enterococcus faecalis	3 (3)	0
Streptococcus agalactiae	1 (1)	0
Candida species	2 (2)	0
Mixed (Gram positive/Gram negative)	4 (4)	2 (8)
Total	98	25

C-UTI: Complicated urinary tract infection, UC-UTI: Uncomplicated urinary tract infection

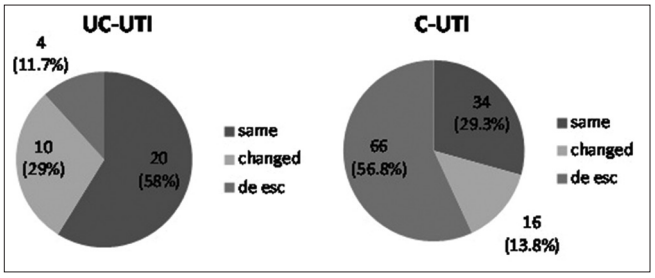

Figure 1: Modification of management following culture report. UC-UTI: Uncomplicated urinary tract infection, C-UTI: Complicated urinary tract infection, Same: No change in antibiotic after culture and sensitivity report, Changed: Changed antibiotic to different class as per culture and sensitivity report, De esc: De-escalated antibiotic after culture and sensitivity report

Enterobacteriaceae were isolated in 50% of the UC-UTI patients. Among naïve patients, the prevalence of ESBL producers was 29.4% compared to 100% in the failed treatment group ($P < 0.0001$ and RR: 4; 95% CI: 1.8–10.0).

The isolates showed maximal susceptibility to amikacin (90%) followed by carbapenems (80%), piperacillin-tazobactam (72%), nitrofurantoin (68%), and least to amoxicillin-clavulanate, cephalosporins, quinolones, co–trimoxazole, and cefoperazone-sulbactam (40%–60%) in this order.

As an initial antibiotic regimen, quinolones were used in 41.2%, BL-BLIs in 17.6%, followed by cephalosporins in 9%, co-trimoxazole in 8.8%, and ertapenem in 5.9% of the patients. Following the culture report, quarter each of the total UC-UTI study population was on one of the following agents, namely, quinolones, nitrofurantoin, or co-trimoxazole [Figure 1]. Around 17% were continued on ertapenem. The remaining 8% received cephalosporins. De-escalation was done after 2 days of carbapenem therapy in all patients with ESBL producers. De-escalation was done immediately after the sensitivity report in non-ESBL producers. The pie chart illustrates significant change of antibiotics following culture report in UC-UTI ($P < 0.05$). Three patients received prophylaxis. Of the remaining 31 patients, 1 patient relapsed (3.2%) in the follow-up period.

DISCUSSION

Our study has attempted to assess the impact of urine culture report on the management of community-acquired UTI, C-UTI as well as UC-UTI. The majority of the study population was C-UTI because of the tertiary care center setting. Furthermore, most of the C-UTI and UC-UTI patients were hospitalized. Surprisingly, there were no significant differences between symptomatology between both groups. UTIs present with symptoms in the majority; however, around 17% of UC-UTI and 33% of C-UTI in our series presented with only fever.

The most common organism was *E. coli* in both groups as has been shown in various studies. The ESBL prevalence was higher though NS in C-UTI at 70% compared to 50% in UC-UTI. The prevalence of ESBL producers in UC-UTI at our center may be an overestimation, considering nearly half of the patients who were included in the study had failed prior empiric treatment. The prevalence of ESBL-producing organisms was 30% in the naïve UC-UTI patients comparable to other studies done on community basis.

Interestingly, 100% of the patients with UC-UTI who had failed prior empiric treatment were positive for ESBL production. Treatment failure with usual empirical choices such as quinolones and cephalosporins in young women indicates that ESBL-producing pathogen needs confirmation in a larger study. On the other hand, treatment failure was not predictive of the prevalence of ESBL producers in C-UTI.

An antibiotic is recommended as empiric treatment when resistance rates are below 20%.[7] As per our data, carbapenems and amikacin have the lowest resistance rates. Carbapenems are the drugs of choice in infections secondary to ESBL-producing organisms. Although we had de-escalated to noncarbapenem agents, it was done only after the clinical condition of the patient improved in case of positive ESBL status. In patients with UTI secondary to non-ESBL producers, de-escalation was done immediately irrespective of clinical status.

We believe only carbapenems can be recommended in an IP setting for both UC-UTI and C-UTI.

Amikacin as an empiric choice while awaiting cultures has been recommended by a group in GB Pant hospital, New Delhi.[8] Christian Medical College, Ludhiana's antibiotic policy recommends the usage of amikacin only as an add-on agent to carbapenems or BL-BLIs in ICU settings.[9] Amikacin probably can be used empirically in acute cystitis, but not in patients who have systemic symptoms.

BL-BLIs have been generally successful in the treatment of UTI caused by ESBL producers. Among BL-BLIs, it is noteworthy that sensitivity rates to cefoperazone-sulbactam are much lower compared to that of piperacillin-tazobactam. It probably reflects the extensive usage of the former drug in UTI. Although BL-BLIs can be used for de-escalation, 3 to 4 times a day dosing makes it inappropriate for OP therapy.

Although the successful treatment of UTI is nearly guaranteed by the usage of carbapenems, it is unnecessary. In our series, 85% of the UC-UTI group and 70% of the C-UTI group were de-escalated to oral regimens (co-trimoxazole/nitrofurantoin) after culture report. In rest of the patients, wherein the isolates are sensitive to only intravenous agents, amikacin or ertapenem in case of renal insufficiency may be preferred because of once daily dosing for the completion of treatment as OP.

Our observations suggest that urine culture is mandatory for all categories of UTI in the Indian subcontinent irrespective of OP/IP setting for the following reasons:

1. To identify ESBL producer status and plan treatment accordingly
2. Although less frequent, to identify Gram-positive, mixed, or fungal infections and treat appropriately.

Although ESBL producer status rates are high in OP settings, noncarbapenem drugs can be used for OP management of acute cystitis. Despite the very high sensitivity rate to amikacin and once a day dosing, the acceptability of parenteral therapy in an OP setting is likely to be

understandably low. Our study revealed that nitrofurantoin had the highest sensitivity rate (approximately 70%) among oral antibiotics. Recent studies have also made similar observations.[1,3] We believe that nitrofurantoin could be started on an empirical basis for OP therapy and modified based on the antibiotic susceptibility reports. Again, it cannot be emphasized more that culture reports are essential in appropriate treatment. Nearly all the patients with a history of prior treatment were treated on an OP basis elsewhere before registration in our study. Failed treatment led to worsening of clinical status requiring hospitalization on presentation at our center. In our study, patients with prior empirical treatment had similar percentage of positive urine culture compared to naïve patients. Therefore, culture should always be done irrespective of the prior treatment status. Our study has shown that UC-UTI required a change of antibiotics to another class significantly more often when compared to C-UTI. The initial choice of antibiotics in our study (majority fluoroquinolones) was inappropriate. Based on our results, we feel that fluoroquinolones, cephalosporins, cefoperazone-sulbactam, amoxicillin-clavulanic acid, and co-trimoxazole should not be used for empiric therapy for community-acquired UTI in tertiary care setting. The relapse rate at <3% was negligible in our study. Antibiotic susceptibility reports were used to decide on prophylactic regimens in patients with a history of recurrent UTI.

CONCLUSIONS

The high prevalence of ESBL-producing organisms in community-acquired UTI makes the usage of carbapenems mandatory for empirical treatment. Once antibiotic susceptibility reports are available, it is possible to deescalate therapy in majority of patients and ensure successful treatment with low relapse rates.

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Conflicts of interest
There are no conflicts of interest.

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