

ROLE OF DE-ESCALATION OF ANTIBIOTIC THERAPY IN PATIENTS WITH URINARY TRACT INFECTIONS

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ABSTRACT

Introduction: The impact of de-escalation has not been studied in hospitalized patients with urinary tract infections (UTI). With the increasing use of empirical broad-spectrum antibiotics in patients with UTIs, there is a need to study the use of de-escalation in these patients. The aim of this study is to assess the frequency of de-escalation and outcomes in patients with urinary tract infections and to estimate the frequency of legitimate causes for the omission of de-escalation.

Methods: A descriptive study was conducted over a period of six months at a tertiary care teaching hospital in South India. Patients with urinary tract infections who were treated with empiric broad-spectrum antibiotics were included in this study. A urine culture was performed and the patients were followed up for any change in antibiotic therapy. The final outcomes of all the patients were noted.

Results: Of the 75 patients with UTIs who were treated empirically, de-escalation was done in only 31 (42%) patients. Legitimate causes for omission of de-escalation were observed in only 21.3% of patients with UTIs. In 37.3% of the patients with UTIs, de-escalation was omitted without any valid justifications. De-escalation was associated with a reduction in the mean duration of treatment and rate of re-infection. The mortality rate remained unaffected by de-escalation.

Conclusion: De-escalation is a feasible and safe strategy that is associated with a reduction in the duration of treatment, and hospital stays with no excess mortality and therefore should be routinely practiced.

Keywords: De-escalation, UTI, outcome.

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Introduction

Excessive and inappropriate use of antibiotics has led to the emergence of multi-drug-resistant organisms, which is a major public health challenge⁽¹⁾. It is therefore important to rationalize the use of antibiotics. De-escalation of antibiotic therapy refers to the replacement of an empirical broad-spectrum regimen by a narrow-spectrum agent when the identification and susceptibility testing results are known^(2,3). De-escalation is a key element in antibiotic stewardship programs as it avoids unnecessary use

of antibiotics that promote the emergence of drug resistance. It also has been reported to be clinically effective and appropriate^(2,4). Several studies have evaluated the use of de-escalation in the management of critically ill patients with sepsis and ventilator-associated pneumonia as empirical broad-spectrum antibiotic therapy is routinely advocated for the treatment of such critically ill patients⁽³⁻⁵⁾. Current guidelines do not provide specific recommendations for the de-escalation of antibiotic therapy in patients with UTIs⁽⁶⁾. The impact of de-escalation has been studied very sparsely in hospitalized patients with

UTIs^(3, 7). However, with the increasing use of empirical broad-spectrum antibiotics in patients with urinary tract infections (UTIs), especially in a hospital setting, there is a need to study the use of de-escalation in these patients. The aim of this study is to assess the frequency of de-escalation in patients with urinary tract infections, estimate the frequency of legitimate causes for omission of de-escalation and study the outcome of de-escalation in patients with urinary tract infections.

The present study will help us to determine how often de-escalation is being practiced in patients with urinary tract infections. It will also shed some light on the usefulness of de-escalation in the management of patients with urinary tract infections.

Methodology

This descriptive study was conducted over a period of six months (February - July 2017) at a tertiary care teaching hospital in South India. This study was approved by the Institute Ethics Committee and written informed consent was obtained from all the participants. All consecutive patients with urinary tract infections who were admitted as in-patients in the department of medicine and were treated with empiric broad-spectrum antibiotics were included in this study. Patients with any other bacterial infection besides UTI were excluded, as co-existing bacterial infection will affect the implementation of de-escalation in these patients. The basic demographic details of the patients were collected using a proforma. A urine culture was performed, and the isolates were identified based on the standard bacteriological techniques⁽⁸⁾.

Antibiotic susceptibility testing was done by the Kirby Bauer disc diffusion method according to CLSI guidelines⁽⁹⁾. *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *S. aureus* ATCC 25923 were used for quality control of the Kirby Bauer disc diffusion method. The urine culture report was made available to the treating physician. The patients were followed up for any change in antibiotic therapy until their discharge from the hospital. The final outcomes of all the patients such as duration of treatment, re-infection, and mortality rates were noted.

De-escalation was defined as either a switch to a narrow-spectrum antibiotic or a reduction in the number of antibiotics or early cessation of antibiotic treatment based on the urine culture report⁽¹⁰⁾. The following were noted as legitimate causes for

omission of de-escalation: Allergy or resistance to the narrow spectrum antibiotics, obstructive pyelonephritis, renal or perirenal abscess, and severe sepsis^(4, 11). We defined re-infection as the reappearance of an infection after the cessation of all antibiotic therapy. Data entry and analysis were done using SPSS for Windows Version SPSS 16.0 (SPSS Inc, Chicago, IL, USA). Means and standard deviations (SD) were calculated as required for numerical variables. Percentages were calculated for categorical variables. Chi square test or Fischer exact test were done to compare the re-infection rate in the two groups with and without de-escalation.

The mean duration of treatment in patients who had undergone de-escalation and those who were not de-escalated were compared using unpaired Student's t-test. All P values <0.05 were considered statistically significant.

Results

A total of 75 patients with UTI who were started on empirical antibiotics were studied. The mean age of the study cohort was 48.56 ± 17.87 years, and 58.6% (N=44) were female. The mean total duration of hospital stay of the study patients was 9.82 ± 8.87 days. Of the 75 patients, 48(64%) had some underlying condition, while the remaining 27 (36%) did not have any underlying condition or predisposing factor. The underlying condition of the 75 patients with UTI is shown in Table 1.

Characteristic	Value
Mean age \pm SD	48.56 \pm 17.87 years
Gender	
Male	31 (41.3%)
Female	44 (58.6%)
Co-morbidities	
Diabetes mellitus	15 (20%)
Antenatal	9 (12%)
Hypertension	6 (8%)
Gynecological condition	6 (8%)
Trauma	6 (8%)
Carcinoma penis	3 (4%)
Dengue fever	3 (4%)
No underlying co-morbidities	27 (36%)
Etiological agents of UTI	
<i>Escherichia coli</i>	56 (74.6%)
<i>Enterococcus spp.</i>	10 (13.3%)
<i>Klebsiella pneumoniae</i>	5 (6.6%)
<i>Candida spp.</i>	3 (4%)
<i>Pseudomonas aeruginosa</i>	1 (1.3%)

Table 1: Patient demographics and clinical characteristics.

Escherichia coli was the most common cause of UTI, while *Enterococcus* spp and *Klebsiella pneumoniae* were the other leading causes of UTI. The etiological agents of UTI in the 75 patients are shown in Table 1. Of the 75 isolates 47(62.6%) were multi-drug resistant (MDR) pathogens.

The antibiotic susceptibility of the 56 *Escherichia coli* isolated from patients with UTI are summarised in Table 2. About 53 of the 75 (70.6%) *Escherichia coli* were MDR. The initial empirical therapy given to the 75 patients included in this study is shown in Figure 1.

Antibiotic	No. of sensitive isolates (%)
Ampicillin	3 (8.1)
Cotrimoxazole	15 (40.5)
Nitrofurantoin	30 (81.1)
Ciprofloxacin	8 (21.6)
Norfloxacin	11 (29.7)
Gentamicin	13 (35.1)
Amikacin	35 (94.6)
Ceftriaxone	25 (67.6)
Imipenem	35 (94.6)

Table 2: Antibiotic susceptibility of the 37 *Escherichia coli* isolated from patients with UTI.

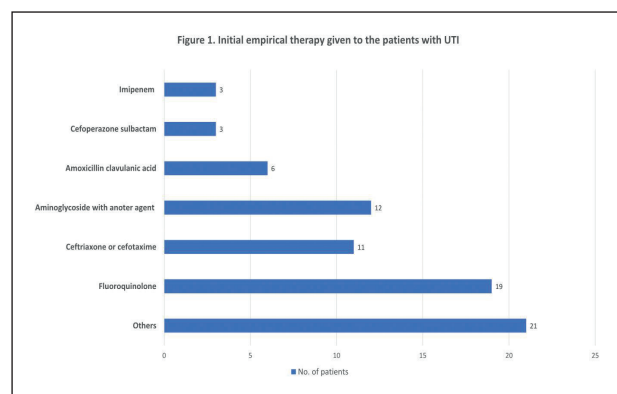


Figure 1: Initial empirical therapy given to the patients with UTI.

Of the 75 patients with UTI who were treated empirically, de-escalation was done in only 31 (41.3%) patients. A reduction in the number of antibiotics was found in 15 cases (20%), a reduction of the spectrum in 32 cases (42.6%), and both approaches were found in 28 cases (37.3%).

In 16 patients’ de-escalation could not be performed due to certain legitimate reasons, while in the remaining 28 patients’ de-escalation was missed without any valid reason. The status of de-escalation in the 75 patients with UTI is shown in Figure 2.

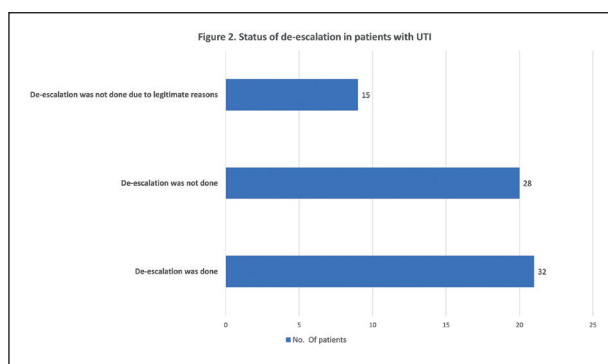


Figure 2: Status of de-escalation in patients with UTI.

Among the patients in whom de-escalation was not done due to legitimate reasons, 12 had infection with isolates which were not susceptible to lower class of antibiotics, and one patient had severe sepsis. In order to study the impact of de-escalation on patient outcome, we compared the patients in whom de-escalation was done with those who have not undergone de-escalation. In this comparison we have excluded the patients in whom de-escalation was not done due to legitimate reasons.

The mean duration of treatment in the de-escalation group was 7.14±1.77, while it was 9.25±4.05 in no de-escalation group (p value 0.042). Re-infections were observed in 25% (7/28) of the patients in whom de-escalation was not done, while it was seen in only 4.8% (3/31) of the patients who have undergone de-escalation (p value 0.168). The mortality rate was not different for the two groups as none of the patients died.

Discussion

Urinary tract infections are among the most common infections occurring in a healthcare setting. Uncomplicated UTIs frequently occur in healthy adult women, but complicated UTIs associated with either structural or functional abnormalities of the urinary tract can occur in both sexes and all age groups^(12, 13). In this study 44 female and 31 male patients with UTIs were studied. About 64% of the patients with UTIs included in this study had an underlying condition such as diabetes mellitus, hypertension, trauma, pregnancy, etc.

Escherichia coli is the most common organism causing urinary tract infections⁽⁷⁾. In the present study also *E. coli* was the commonest cause of UTI followed by *Enterococcus* spp and *Klebsiella pneumoniae*. Antibiotic resistance is increasing among the gram-negative bacterial isolates from patients with UTI due to various mechanisms such

as the production of extended spectrum β lactamases or AmpC β lactamases and plasmid co-expression of other resistance mechanisms⁽¹³⁻¹⁵⁾. In the current study about 62.6% of the isolates were multi-drug resistant. The increasing drug resistance diminishes the choice of agents to treat these infections. Antibiotic de-escalation is a strategy in which effective initial antibiotic treatment is ensured while avoiding unnecessary antibiotic use that would promote the development of resistance^(2,4).

In a recent study from France, it was observed that de-escalation was largely under-prescribed in patients with community-acquired UTIs⁽²⁾. In this study de-escalation was done in 31 patients out of 75 patients. Legitimate reasons for not de-escalating was found in only 21.3% of the patients who were not de-escalated⁽²⁾. The legitimate causes of omission of de-escalation observed in that study were shock, renal abscess, obstructive uropathy and bacterial resistance. Some of the valid justifications for omission of de-escalation are resistance or allergy to first line drugs such as β -lactams or cotrimoxazole, obstructive pyelonephritis, renal or perirenal abscess and severe sepsis with shock⁽²⁾. In the present study the de-escalation could not be done in 21.3% of patients with UTIs due to legitimate reasons such as severe sepsis and lack of susceptibility to lower antibiotics. However, in 37.3% of the patients with UTIs de-escalation was omitted without any valid justifications. It is therefore necessary to emphasize the importance of de-escalation to the clinicians to avoid the risk of promoting antibiotic resistance.

In this study fluoroquinolone and third-generation cephalosporins were observed to be the commonly used empirical therapy for treatment of UTIs. Fluoroquinolones and third-generation cephalosporins should not be routinely used for empirical therapy because they are prone to promote resistance to various classes of antibiotics and therefore should be used judiciously in clinical practice^(16,17). In the current study, the mean duration of treatment was shorter in the patients who were de-escalated. In the study by Morel et al, the mean duration of treatment was observed to be comparable in patients who were de-escalated and those were not de-escalated⁽¹⁾. In our study the rate of re-infections was noted to be less in patients who were de-escalated, but this was not statistically significant. In another similar study evaluating the importance of de-escalation, the recurrent infections were observed to be more common in those who were not de-escalated⁽⁵⁾. Treatment with broad

spectrum antibiotics is known to increase the risk of re-infection with multidrug resistant pathogens, which could probably explain the increased re-infection rate in the group where de-escalation was not done⁽⁵⁾. The mortality rate was not affected much by de-escalation. De-escalation therefore appears to be a safe strategy with a reduction in the treatment duration and rate of re-infection without any significant increase in the mortality. Further multi-centric studies involving a large sample size is needed to confirm the findings of this study.

Conclusion

De-escalation is omitted in many patients who were treated empirically for UTIs. The findings of this study make us realise the need to educate and persuade the clinicians to adopt this strategy while empirically treating the patients.

De-escalation is a feasible and safe strategy which is associated with reduction in duration of treatment, hospital stay with no excess mortality and therefore should be routinely practised.

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The research records will be available with the corresponding author and will be shared with the readers on request.

Competing interests:

"The authors declare that they have no competing interests relevant to this study and the publication thereof".

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