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A PROSPECTIVE STUDY OF THE PATTERN OF ANTIMICROBIAL USE IN COMPLICATED URINARY TRACT INFECTIONS IN INPATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Prescriptions of 100 inpatients with complicated urinary tract infections (cUTIs) were reviewed. The pattern of antimicrobial agent (AMA) use, criteria for selection either empirical or organism specific and any subsequent change in AMA therapy were analyzed. Mean age of patients at presentation was 50.6±11.4 years. There were 44% males and 56% females. Ofloxacin (n=26), ciprofloxacin (n=11), levofloxacin (n=9), ceftriaxone±sulbactam (n=29) and piperacillin+tazobactam (n=8) were the most common first choice AMAs. Aminoglycosides (n=6) and nitroimidazoles (n=12) were add on drugs in some selected cases. In majority of cases (85%), the choice of AMAs was empirical, predominantly as monotherapy (71%) by intravenous route (78%). All AMAs were used in their standard recommended doses and frequency. 78% showed clinical cure at the end of AMA therapy and 22% required change in AMA therapy due to inadequate clinical improvement (n=12) or isolation of drug resistant organism (n=10). Mean duration of AMA therapy was 9.2±2.2 days. Although empirical therapy has shown clinical improvement, evidence of bacteriological cure on urine culture ensures complete cure and prevents persistence or recurrence.

KEY WORDS: Complicated UTIs, AMAs, inpatients, Beta lactamase inhibitor (BLI)

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INTRODUCTION

Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and significantly contribute to morbidity and health care costs. cUTIs are associated with structural or functional abnormalities of the genitourinary tract or the presence of an underlying disease which increases the risks of acquiring an infection or of failing therapy.[1,2] Various predisposing factors for cUTIs include obstruction of urinary tract (e.g.: urolithiasis, strictures, prostate hypertrophy etc), instrumentation (e.g. urethral catheterization, stents, nephrostomy tube, urological procedures etc.), Impaired voiding (neurogenic bladder, cystocele), diabetes mellitus (DM), renal insufficiency, immunodeficiency states etc.[3,4] Common .causative organisms include E.coli, Klebsiella species (spp), Pseudomonas spp, Proteus spp, Enterobacter spp, Citrobacter spp, Serratia spp, Staphylococcus spp, Enterococcus spp etc. Since most of the uropathogens causing cUTI originate from patients at high risk profile, previous antimicrobial exposure and/from a hospital or nursing care environment, they tend to be more virulent, multidrug resistant than those associated with uncomplicated UTIs.[5,6] Effective management of cUTIs mainly involves AMA therapy along with treatment or control of predisposing factors. Appropriate AMA therapy is very crucial for the eradication of the infection, to prevent recurrence and to minimize antimicrobial resistance.[7] Although a wide range of AMAs like Flouroquinolones (FQs), penicillins, cephalosporins, aminoglycosides (AMGs) etc. have been used, selection of appropriate AMA therapy for cUTIs in inpatients can be challenging to the clinicians since these infections involve broader spectrum of drug resistant pathogens with unpredictable and changing susceptibility patterns, evolving antimicrobial resistance, the patient associated risk factors, high likelihood of persistence of infection, the need for longer duration of therapy and treatment failure.[3,5,8] Hence there is a need for periodic evaluation of the pattern of antimicrobial use in the management of cUTIs in inpatients and the present study is taken up to generate useful information which may aid to formulate appropriate hospital specific guidelines for effective therapy.

METHODS

This study was conducted in a tertiary care hospital, Bangalore. Institutional ethics committee approved study protocol. Data from medical records of 100 subjects, both males and females in the age group 18-65 years admitted with diagnosis of cUTI and receiving AMAs were evaluated. Patients with asymptomatic bacteriuria, subjects receiving AMAs for infections other than UTI (e.g. gastrointestinal, respiratory), pregnant and lactating women were excluded from the study. Clinical data like presenting symptoms and signs, complicating or risk factors were recorded. The laboratory data including urine microscopy and culture sensitivity/resistance pattern was recorded. The AMAs and AMA combinations, the criteria for selection of AMAs (empirical or on culture sensitivity reports), duration of therapy and any subsequent change in AMA therapy were recorded. The tolerability of AMA/AMA combinations was assessed by monitoring adverse events during the treatment. Clinical outcome was assessed based on relief of signs and symptoms of UTI at the end of AMA therapy. Clinical outcome was termed as cure if there was complete remission of signs and symptoms of infection without recurrence at the end of therapy, clinically improved if improvement in clinical signs and symptoms was observed but without complete resolution and failure if the symptoms and signs were persistent or worsened even after 72 hours of initiation of treatment.

Statistical analysis

The data collected in Microsoft Excel and used for analyzing descriptive statistics, mean and standard deviation, numbers and percentages.

RESULTS

The demographic, clinical characteristics and associated risk factors for cUTIs are shown in table-1. Mean age of presentation was 50.6±11.4years with 44% (n=44) males and 56% (n=56) females. 69% of the subjects were above 45 years of age (46-65 years). Dysuria (62%) and fever with or without chills (61%) were the most common presenting clinical symptoms. Most of the subjects had more than one presenting symptom and mean duration of symptoms was 9.3± 6.0 days. Predominant site of infection was the lower urinary tract (77%) in the form of urethritis with or without cystitis. Diabetes mellitus was the most common risk factor (43%) followed by urolithiasis (23%) and urethral catheterization (22%).

Table 1
Demographic and clinical characteristics of patients with complicated UTI

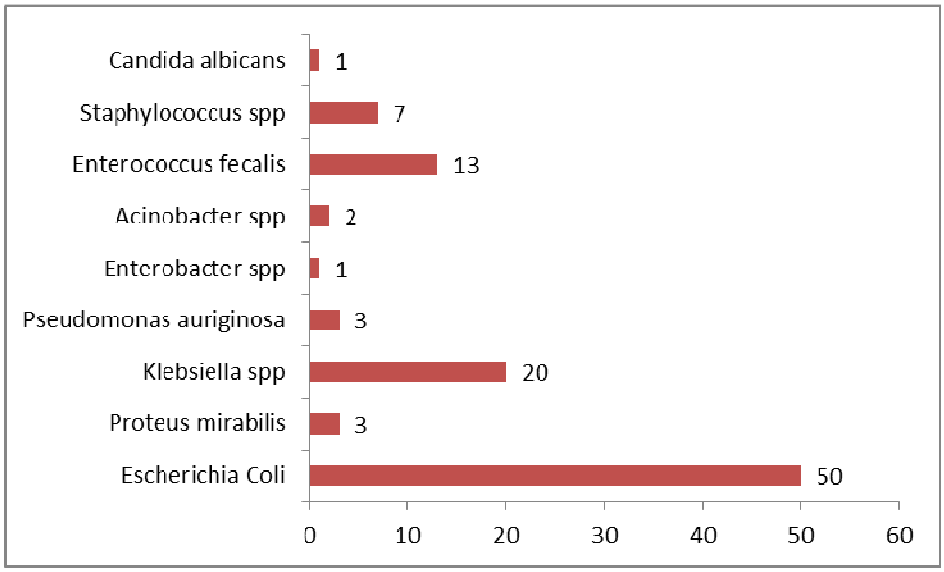
Age groups (years)	Males (n=44)	Females (n=56)	Total (n=100) N	%
18 – 25	1	4	5	5
26 – 35	3	6	9	9
36 – 45	7	10	17	17
46 – 55	11	17	28	28
56 – 65	22	19	41	41
Clinical symptoms*				
Dysuria	31	31	62	62
Frequency	7	6	13	13
Urgency	3	1	4	4
Hematuria	4	5	9	9
Fever	22	38	60	60
Others†	23	32	55	55
Predominant site of infection‡				
Lower urinary tract	33	44	77	77
Upper urinary tract	7	12	19	19
Risk Factors§				
Diabetes Mellitus	15	28	43	43
Calculi	12	11	23	23
BPH	24	-	24	24
Urethral catheterization	16	06	22	22
Postmenopausal age‖	-	31	31	31
Post-operative	3	4	07	07
Neurological disorders	2	2	04	04
Renal insufficiency	7	11	18	18
Ureteric stent	-	02	02	02
Stricture urethra	03	-	03	03
Others¶	01	02	03	03

All subjects presented with >1 presenting symptom; †others included symptoms due to complicating factors;‡4 subjects had generalized infection; §60 subjects had >1 risk factor; ‖post menopause: urinary incontinence (n=16), cystocele (n=15); ¶others: traumatic kidney injury (n=1); AIDS (n=2)

Benign prostate hyperplasia (BPH) in males (n=24) and postmenopausal age in females (n=31) were gender specific risk factors significantly contributing to cUTIs. About 55% of the subjects had additional symptoms due to underlying risk factors and included urine retention (n=7), urinary incontinence (n=9),renal /uretic colic (n=6), and vomiting (n= 23); urinary incontinence (n=4); incomplete voiding (n=5), generalized edema (n=1); bilateral lower limb edema (n=2); oliguria (n=1); nonspecific abdominal pain (n=3), renal colic (n=6) or systemic symptoms like nausea and vomiting (n=23), generalized weakness (n=3) owing to the severity of infections. Many subjects (60%) had more than one risk factor. All study subjects had significant bacteriuria (>10^5 cfu/ml of urine) at admission. Organisms isolated on baseline urine culture are shown in Figure 1, which includes gram negative organisms in 79% (n=79) cultures and gram positive in 20% (n=20) and one subject had *Candida spp*

isolated on urine culture. *E.coli* (n=50), *klebsiella spp* (n=20) were the commonest isolates among gram negative species. Gram positive isolates included *Enterococcus spp* (n=13) and *Staphylococcus spp* (n=7). Significant number of gram negative isolates (n=61) showed resistance to FQs (ciprofloxacin, norfloxacin), cotrimoxazole (n=69), co-amoxiclav (n=59), cephalosporins (cefipime, n=41, cefuroxime, n=45). Many isolates were susceptible to AMGs (gentamicin, n=76, amikacin, n=77), ceftriaxone+tazobactam (n=75) and piperacillin+tazobactam (n=79). Gram positive isolates, including enterococci and staphylococci showed significant resistance to erythromycin, moderate resistance to tetracyclines and most of them were susceptible to linezolid, vancomycin, cefoperazone and cloxacillin.

Figure 1
Number of isolates on urine culture



The choice of AMAs for initial therapy was empirical in the majority of cases (n=85, 85%).The AMAs were used by IV route in majority of the subjects (n=78, 78%), oral route in only 5% (n=5) of the subjects and both by oral and IV routes in 17% (n=17) of subjects. In most of the subjects (n=71, 71%) the AMAs were used as monotherapy. The most commonly used AMAs intravenously were flouroquinolones (FQs) (46%, n=46) which included ofloxacin (n=26), levofloxacin (n=9),ciprofloxacin (n=11) ceftriaxone ± sulbactam (29%, n=29) and piperacillin+tazobactam (8%, n=8).Other beta lactams included aminopenicillins (n= 6), 3rd generation cephalosporins like Cefotaxime (n=2), Ceftazidime (n=1), Cefoperazone (n=2), Cefuroxime+ sulbactam (n=3) and carbapenems like Meropenem (n=2), Doripenem(n=1) and Aztreonam (n=1). Other class of AMAs included AMGs (n=6, 6%) , nitroimidazoles (n=12,12%) and clindamycin (n=1).The AMAs used by oral route included the FQs (n=10), 3rd generation cephalosporins (n=9) (cefixime, cefpodoxime proxetil), nitrofurantoin (n=1) and the azole antifungal agent, fluconazole (n=1).Combination therapy was used in 29% (n=29) of the subjects and beta lactams with AMGs was most common combination (table -3).

Table 2
Pattern of antimicrobial use

Intravenous AMAs	N	%	Oral AMAs	N	%
Ofloxacin	26	21.4	Ofloxacin	4	18
Ciprofloxacin	11	9	Ciprofloxacin	4	18
Levofloxacin	9	7.4	Levofloxacin	1	4.5
Amoxicillin	1	0.8	Norfloxacin	1	4.5
Coamoxiclav	4	3.3	Cefipime	5	23
Ampicillin+sulbactam	1	0.8	Cefpodoxime proxetil	4	18
Piperacillin+tazobactam	8	6.6	Nitrofurantion	2	9
Cefuroxime+sulbactam	3	2.4	Fluconazole	1	4.5
Ceftriaxone	13	11			
Ceftriaxone+sulbactam	16	13			
Cefotaxime	2	1.6			
Ceftazidime	1	0.8			
Cefoperazone+ sulbactam	2	0.8			
Cefipime+sulbactam	1	0.8			
Meropenem	2	1.6			
Doripenem	1	0.8			
Aztreonam	1	0.8			
Amikacin	2	1.6			
Gentamicin	1	0.8			
Netilmicin	3	2.4			
Metronidazole	11	9			
Ornidazole	1	0.8			
Clindamycin	1	0.8			
AMA combinations†					
Beta lactam + aminoglycoside				13	45
Flouroquinolone+ nitroimidazole				3	10.3
Beta lactam + nitroimidazole				7	24
Flouroquinolone + beta lactam				3	10.3
Flouroquinolone + beta lactam + nitroimidazole				2	7
Beta lactam + aminoglycoside + nitroimidazole				1	3.4

N = number of patients; †Concurrent use of two or more AMAs of different classes

All AMAs were used in their standard recommended doses and frequency. Mean duration of AMA therapy was 9.2±2.2 days. Majority of the subjects (78%, n=78) showed clinical cure at the end of AMA therapy. 22 patients (22%) required change in initial AMA therapy, in 12 patients change in therapy was due to inadequate clinical improvement / persistence of symptoms even after 72 hours of initiation of treatment and in remaining 10 patients, change was based on isolation of drug resistant organism in urine culture. The AMAs substituted for initial therapy included piperacillin+tazobactam (n=11), ceftriaxone+sulbactam (n=7), cefoperazone+sulbactam (n=1), linezolid (n=1) and aztreonam (n=2). All AMAs were well tolerated with fewer gastrointestinal adverse effects like nausea (n=3), nonspecific abdominal pain (n=6).

DISCUSSION

In the present study, the pattern of antimicrobial use in subjects hospitalized with cUTIs was assessed. Majority of study subjects (69%) were above 45 years which may reflect the higher prevalence of various complicating factors like DM, BPH, cystocele, renal insufficiency etc. with advancing age (>45years).[1,9] There was no significant difference in gender distribution in the age group of >45 years, indicating that difference in incidence of UTI between the genders significantly declines with advanced age due to prostate hyperplasia in men and subsequent complications.[10] Duration of symptoms and severity of infection vary based on the risk factors or comorbid illness and also individual immune responses. The complicating factors encountered in our study predominantly

included DM, renal or ureteric calculi, BPH, postmenopausal age and urethral catheterization. Diabetes is an important and most common risk factor, and various factors like glycosuria, impaired immune responses, autonomic neuropathy leading to voiding dysfunction; diabetic nephropathy etc. predisposes to UTI.[11,12] Catheter associated UTIs (CA-UTIs) are the most common cause of hospital acquired/ nosocomial infections and are associated with substantial morbidity.[13] Other uncommon risk factors encountered in our study were a case of renal trauma following a road accident and Acquired immunodeficiency syndrome (AIDS). Baseline urine culture was done in all subjects before initiation of treatment. Majority of the isolates (79%) were gram negative indicating that gram negative bacteria belonging to Enterobacteriaciae are the most common causative organisms for UTIs including cUTIs.[3,14] The antimicrobial susceptibility pattern of uropathogens was similar to other studies done in south Asian countries.[15,16,17] Significant resistance of gram negative isolates to FQs and beta lactams is probably be attributed to the extensive use FQs and cephalosporins in the recent years as first line agents in the treatment of wide range of infections including UTIs.[1] Moreover history of AMA therapy in patients prior hospitalization was not available from the data, which may significantly contribute to emergence of drug resistance and clinical failure. The choice of AMAs was empirical in most of the subjects (85%).Although empirical selection of AMAs is usually based on prevalent uropathogens and their susceptibility patterns and majority of the subjects showed favorable clinical response (78%), definitive therapy initiated based on urine culture and susceptibility patterns individualized to patient specific risk factors would provide better overall clinical and bacteriological outcome with fewer chances of persistence and recurrence of infection.[17] The most commonly used FQ was ofloxacin (26%) and among the beta-lactams, ceftriaxone (29%). Other classes of AMAs used were aminoglycosides (6%), nitroimidazoles (12%) and clindamycin (1%).Aminoglycosides were mostly used in combination with beta lactams for their synergistic action, as a part of surgical prophylaxis or in case of inadequate response to monotherapy. Nitroimidazoles were used as part of surgical prophylaxis for anaerobic coverage in subjects who required surgical intervention to treat underlying cause. In one diabetic subject with renal abscess, clindamycin was used in combination with meropenem. IV route is generally preferred for inpatients to ensure quicker onset of action, rapid attainment of desired plasma concentration, higher antimicrobial efficacy, anticipated surgical interventions, in presence of poor oral tolerability and also feasibility for monitoring under hospital settings.[2,3] Oral AMAs were preferred as first-line agents because of their good oral bioavailability and tolerability, particularly in cases of mild to moderate cases with good oral tolerability, or as oral switch-over therapy following initial parenteral therapy with the respective AMAs of the same class. Both oral and IV routes were employed in 17 subjects because of concurrent administration of 2 or more AMAs effective by different routes. Combination therapy with concurrent use of two or more AMAs of different classes was employed in 29% of the subjects in severe forms of UTIs, infections with resistant strains or as part of surgical prophylaxis in subjects who required surgical interventions for correction of the complicating factors. The most common AMA combinations were beta lactams with aminoglycosides (n=11), beta lactam with nitroimidazoles (n=7).The combination of beta lactams and AMG or FQs can be considered as rational as these AMAs have different sites and mechanisms of action, and also have different antimicrobial spectrum to ensure adequate coverage of gram positive and gram negative organisms. The purpose of combining AMAs was to provide synergistic action, wider coverage and also to minimize antimicrobial resistance.[6,18,19] All AMAs were used in their standard adult recommended doses and frequency. In majority of the subjects (88%) the duration of therapy ranged from 6-10 days with the mean duration of 9.2 ± 2.2 days. In other studies the overall duration of therapy ranged from as short as 5 days to as long as 20 days.

Though there are no standardized guidelines for optimal duration of AMA therapy in UTIs, the duration of therapy is generally determined by the site and severity of infection, the likely pathogens and their susceptibility/resistance patterns and also on the management/ control of comorbid conditions and risk factors.[19, 20] Apart from AMAs, significant number of subjects received adjuvants which included probiotics (lactobacilli), urine alkalizing agents (sodium citrate, bicarbonate or potassium citrate) and urinary antispasmodics (flavoxate or dicyclomine). Urine alkalizing agents were used for their established role in control of distressing local irritative symptoms associated with UTIs, and also increasing the urinary concentration of certain AMAs and enhancing their antimicrobial effects. The urinary antispasmodics were used to relieve spasm or pain associated with renal calculi or other obstructive etiologies.[21, 22] The AMAs generally used for UTIs include the FQs, beta-lactams, AMGs and occasionally nitroimidazoles. All these AMAs have potent bactericidal action, low protein binding, no metabolic inactivation, high bactericidal concentration in the urine and renal parenchyma and potentially synergistic antimicrobial action, and hence considered most appropriate options for the therapy.[1, 21] Clinical outcome was assessed based on criteria of previous studies.[23, 24] Significant number of patients (n=78, 78%) showed clinical cure at the end of AMA therapy, 22% of the subjects required change in initial AMA therapy. Failure of therapy as evidenced by inadequate clinical improvement or persistence/worsening of symptoms after 72 hours of treatment could be attributed to inadequate control of comorbid conditions and other risk factors like catheterization (for neurological conditions/ long term immobility), ureteric stents, immunodeficiency states or infection with multidrug resistance organisms. Adequate measures were taken for control of comorbid illnesses with concomitant medications.11 patients required surgical interventions for correction of underlying risk factors. Limitations of the study: Data on repeat urine culture after completion of AMA therapy was not available in most of the subjects to assess bacteriological cure.

CONCLUSION

Complicated UTIs pose a therapeutic challenge due to associated risk factors and prevalence of drug resistant organisms in inpatients. Though empirical therapy showed clinical improvement, clinical response may not always imply bacteriological cure and appropriate definitive therapy based on urine culture and susceptibility is needed to ensure eradication of infection and prevent future recurrence. The choice and duration of AMA therapy should be individualized based on patient associated risk factors, along with effective measures for adequate control of the complicating factors. Combination of AMAs including 3rd cephalosporin+BLI with or without AMGs or piperacillin+tazobactam can be effective options. Others like vancomycin, linezolid, aztreonam and carbapenems may be reserved for specific situations.

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