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Antimicrobial Use and Susceptibility Pattern of Uropathogens Associated with Urinary Tract Infections at the Ghana Police Hospital

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Abstract: The changing pattern of urinary tract pathogens to antibiotics have been reported worldwide. To ensure appropriate treatment, knowledge of antibiotic susceptibility of pathogens is mandatory. The objective of this study was to determine the prevalence and antibiotic susceptibility pattern of microorganisms isolated from urine samples of UTI patients at the Ghana Police Hospital's Laboratory vis-à-vis the current UTI drug management pattern at the Hospital. The study involved analyzing urine samples of UTI patients who reported to the Ghana Police Hospital Laboratory from 1st July 2011 – 31st December 2011. Prevalence, uropathogen sensitivity pattern and drug management of UTI were assessed. Prevalence of UTI among 708 samples analyzed was 31.6%. The predominant bacterial isolates were *Coliforms* (44.2%) and *Escherichia coli* (36.2%). High susceptibility of bacteria was seen with Nitrofurantoin and Gentamicin. Out of the 120 drug managed cases, 83.2% had single drug therapy and drugs prescribed conformed to national standard treatment guidelines (STGs). In summary, pathogens showed resistance to a substantial number of antibiotics tested but susceptibility was observed with Nitrofurantion and Gentamicin. Most common drug used in the management of uncomplicated UTI was Ciprofloxacin.

Key words: Antibiotics · Resistance · Susceptibility · Urinary Tract Infection

INTRODUCTION

Urinary tract infection (UTI) is often caused by significant microbial growth in the urinary tract. It is a major health problem resulting in morbidity and high health care costs among all age groups and sexes [1, 2]. Generally, this infection can be distinguished as lower tract UTI (Cystitis) or upper UTI (Pyelonephritis) [3]. It may also be symptomatically characterized by fever, pain, frequent urination, urgency, dysuria, olysuria and tenderness or asymptomatic [4].

UTI accounts for 35% of nosocomial infections and more than 1 million hospitalizations in the United States at a cost of over 1 billion USD and is a leading cause of Gram-negative bacteremia [5, 6]. UTI related microbiological tests constitute a major portion of the workload in clinical microbiology laboratories [7].

Anatomical differences underpins higher incidence in women than in men [8, 9] and studies have showed that, 25% of all women with UTI would have a second re-infection within six months [10, 11]. Also, physiological changes such as hormonal changes during pregnancy increase its frequency of occurrence [12]. Pyelonephritis is the most common UTI observed in about 12% of all pregnancies [3]. Poor personal hygiene and some cultural practices among women have been cited as major predisposing factors to UTI [13].

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A number of microorganisms have been implicated in UTI. The most common pathogens cited in laboratory cultures of urine are *Escherichia coli* (*E. coli)* and other Enterobacteriace, accounting for approximately 75% of all isolates [14-18]. Other microbes such as *Klebsiella pneumonia, Proteus mirabilis, Staphylococcus aureus, Pseudomas aeruginosa* and *Enteroeaseus feacalis* have been cited in UTI studies in Ghana, Nigeria and other parts of the world [16, 19-22].

Antimicrobial drugs have played a significant role in reducing morbidity and mortality associated with infectious diseases in humans. In the management of UTI, antibiotics such as cefuroxime, amoxicillin/clavulanic acid, trimethoprim/ sulphmethoxazole and fluoroquinolones have been cited amongst others, as medications of choice [15, 21]. Unfortunately, recent management of UTI has become increasingly problematic as a result of emergence of resistance by causative uropathogens to first line antibiotics, especially *E. coli* strains [23]. The consequence includes treatment failure, spread of resistant strains and increased health care costs [24, 25]. This study sought to ascertain the prevalence and antibiotic susceptibility pattern of microorganisms isolated from urine samples of UTI patients reporting to the Ghana Police Hospital's Laboratory vis-à-vis the current UTI management pattern at the Hospital.

MATERIALS AND METHODS

Study Population: This was a descriptive study in which urine samples of patients were collected and analyzed. The patients, who on account of suspected UTI utilized the services of the Ghana Police Hospital Laboratory, Accra, Ghana. They presented their urine samples to the Laboratory between 1st July 2011 to 31st December 2011. The population included both in- and out-patients. Urine samples of 708 patients were conveniently captured within the study period. Drug therapy of 150 patients diagnosed with UTI was also assessed by reviewing medical records which showed drugs used in management between 1st July 2011 to 31st December 2011. The study protocol was approved by the Ghana Police Hospital Administration.

Urine Sample Collection by Patients: Midstream urine specimen were aseptically collected into sterile urine tubes (Labeled with procedure for urine collection) and transported to the Laboratory by patients. Samples of urine were analyzed within an hour after submission to the Laboratory. Those that could not be analyzed immediately were kept in the refrigerator at 4°C and analyzed not later than 4 hours after urine submission.

Culture of Urine Samples: Using a calibrated wire, a loop-full of urine specimen (0.01 ml) was inoculated onto a quarter-plate of Cysteine Lactose Electrolyte-Deficient agar [CLED] (Biotic Laboratories Ltd, U.K). This was then incubated at 37°C for 24 hours in Nodermann GMBH incubator (Germany). Colonies growing on the plates after incubation were enumerated. Plates with significant growth were examined, pathogen identified and then colonies selectively picked using inoculating loop. One colony, representing an isolate was emulsified in 2 ml sterile peptone water and then transferred into a plate of Sensitivity Agar (Biotec laboratories, UK).

Microbial Identification: Microbial colonies were identified on the basis of their colony morphology, colour (Due to fermentation of sugars), size and growth pattern. The standard procedure of Gram staining was done on isolates [Crystal violet, grams iodine, acetone-alcohol (v/v) and neutral red] (Sigma Chemical Company, USA). Slides were examined under x40 and x100 magnification of an Olympus CX 21 light microscope (England, UK). All isolates obtained from the urine samples were biochemically examined using Indole test and Kligler Iron Agar (KIA) techniques. Significant microbial growth was categorized by microbial count greater than $1x10^5$ cfu/ml.

Susceptibility Testing: Antimicrobial sensitivity test used in this study was the Kirby- Bauer disc diffusion method. Pure colonies of isolated organisms were picked into sterile peptone water and emulsified. This was compared with 0.5% barium chloride (McFarland Standard). Two to three loop-full of the emulsified organism was picked onto a sensitivity test agar. Then, with a cotton swab, the liquid was streaked to cover the entire surface of the plate. Standard urine antibiotic discs were then placed on the plate and this was incubated at 37°C for 24 hours. Antibiotics against which sensitivity was tested in the present study included Ampicillin, Cefuroxime, Co-trimoxazole, Gentamicin, Tetracycline, Nalidixic acid, Nitrofurantoin, Piperacillin, Cefixime, Dalacin C, Lincocin, Ofloxacin, Ceftriaxone, Flucloxacillin, Meropenem and Erythromycin. Antibiotic zones in diameter of inhibitions against microorganisms were measured with the aid of a rule. This was then compared with standard interpretation charts [26] and scored as sensitive or resistant.

Data Analysis: Data generated were entered into Excel Spreadsheet (2007), after manual verification and cleaning. Descriptive statistics (percentages) was used to present results.

RESULTS

Of 708 urine samples examined within the period, 52% were from males and 48% from females. Significant microbial growth ($\geq 1x10^5$ cfu/ml) was observed among 224 (31.6%) of the urine samples, of which 67.4% and 32.6% were observed in females and males respectively. Table 1 shows the sex distribution of cases with and without significant microbial growth.

Eight different microorganisms were identified among the 224 urine cultures that showed significant growth: *Coliforms*, *Escherichia coli, Pseudomonas*, *Staphylococcus aureus, Proteus*, *Klebsiella, Candida* species *and Providencia*. The predominant bacterial isolates were *Coliforms* (44.2%) and *Escherichia coli* (36.2%). The other isolates were in the following percentages; *Pseudomonas* (5.4%), *Staphylococcus aureus* (4.5%), *Proteus* (1.3%), *Klebsiella* (1.3%) and *Providencia* (1.8%). Mixed infection isolates identified were: *Candida* species with *Escherichia coli* (1.3%) and *Candida sp*. with *coliform* (4.0%). Table 2 shows the summary of microorganisms isolated from urine cultures.

A greater percent of bacteria isolated (n = 224) were observed to be susceptible to Gentamicin (66.5%) and Nitrofurantion (76.3%). High microbial resistance was observed with Ampicillin (95.5%), Co-trimoxazole (89.3%), Tetracycline (77.2%), Nalidixic acid (77.7%), Piperacillin (79.5%), Cefixime (70.1%) and Cefuroxime (55.4%). Meropenem and Ofloxacin discs were also tested on a few isolates (5 each). Isolates showed high sensitivity to the Meropenem and Ofloxacin (100% and 80% respectively). A summary of antimicrobial sensitivity and resistance patterns of urinary bacteria isolates is shown in Table 3.

Of the 150 cases of UTI in which drug management was assessed, the reviewed records showed 51 (34%) male patients and 89 (66%) female patients. The patients' ages ranged between 6 months to 80 years and mean age was 27.4 ± 1.3 years. Single drug therapy management of UTI cases constituted 83.2% and combination drug therapy was 16.8%. The duration of treatment for either single or combination drug therapy ranged between 5 - 10 days. Of the records reviewed, 132 (88%) had antibiotics in oral tablet or capsule formulations. Antibiotic suspensions and injectables were present on 18 (12%) and 1 (0.7%) assessed records respectively (Table 4).

Reviewed records also showed that Ciprofloxacin (46%), Cefuroxime (20.6%) and Co-amoxiclav (4.7%) were the highest single drug therapeutic agents used in the treatment of UTI's at the Hospital. Other drugs included Azithromycin (2.4%), Cefixime (2.6%), Cotrimoxazole (2.6%), Nitrofurantion (2.0%), Flucloxacillin (2.6 %) and Erythromycin (0.7%). Ciprofloxacin with Tinidazole (9.3%) and Ciprofloxacin with Metronidazole (2.7%) were the highest used combination drugs for UTIs. Other combination drugs included: Co-amoxiclav (Amoxicillin plus Clavunalic acid) with Metronidazole (1.3%); Azithromycin with Tinidazole and Ciprofloxacin (0.7%);

Table 1: Sex distribution of urine culture samples with and without significant growth (n = 708)

Sex	Significant Growth (%)	No Significant Growth (%)	Total (%)
Male	73 (32.6%)	295 (60.9%)	368 (52%)
Female	151 (67.4%)	189 (39.1%)	340 (48%)
Total	224 (31.6%)	484 (68.4%)	708 (100%)

Table 2: Frequency of microbial isolates among sexes and isolate per total obtained (n = 224)

Microbial Isolates	Male	Female	Isolate per Total
Coliforms (Cf)	36 (49.3%)	63 (41.7%)	99 (44.2%)
Escherichia coli (EC)	24 (32.9%)	57 (37.8%)	81 (36.2%)
Pseudomonas	5 (7%)	7 (4.6%)	12 (5.4%)
Staphylococcus aureus	4 (5.5%)	6 (4.0%)	10 (4.5%)
Proteus spp.	1 (1.4%)	2 (1.3%)	3 (1.3%)
Klebsiella spp.	1 (1.4%)	2 (1.3%)	3 (1.3%)
Providencia spp.	2 (2.7%)	2 (1.3%)	4 (1.8%)
Candida spp. + EC	-	3 (2.0%)	3 (1.3%)
Candida spp. + Cf	-	9 (6.0%)	9 (4.0%)
Total	73 (32.6%)	151 (67.4%)	224 (100%)

Table 3: Overall sensitivity patterns of microbial isolates

Drugs	Total Isolates	Resistant	Sensitive
Ampicillin (AMP)	224	214 (95.5%)	10 (4.5%)
Cefuroxime (CEF)	224	124 (55.4%)	100 (44.6%)
Co-trimoxazole (COT)	224	200 (89.3%)	24 (10.7%)
Gentamicin (GEN)	224	75 (33.5%)	149 (66.5%)
Tetracycline (TET)	224	173 (77.2%)	51 (22.8%)
Nalidixic Acid (NAL)	224	174 (77.8%)	50 (22.3%)
Nitrofurantoin (NIT)	224	53 (23.7%)	171 (76.3%)
Piperacillin (PIP)	224	178 (79.5%)	46 (20.5%)
Cefixime (CEFI)	224	197 (87.9%)	27 (12.1%)
Dalacin c (DAL C)	54	39 (72.2%)	15 (27.8%)
Lincocin (LIN)	18	18 (100%)	-
Ofloxacin (OFL)	5	1 (20%)	4 (80%)
Ceftriaxone (CEFT)	1	1 (100%)	-
Flucloxacillin (FLU)	3	2 (66. 7%)	1 (33.3%)
Meropenem (MER)	5	-	5 (100%)
Erythromycin (ERY)	2	-	2 (100%)

Table 4: Reviewed records of drug management (n = 150)

	Parameter on record form	Result
1.	Age range (years)	6 – 80
2.	Mean age (years)	27.4 ± 1.3
3.	Number of days for drug therapy (range)	5 – 10
4.	Single drug therapy (%)	83.2
5.	Combination drug therapy (%)	16.8
6.	Antibiotics in tablet/ capsule formulation (number; percent)	131 (87.3%)
7.	Antibiotics in suspension formulation (number; percent)	18 (12%)
8.	Antibiotics in injectable formulation	1 (0.7%)

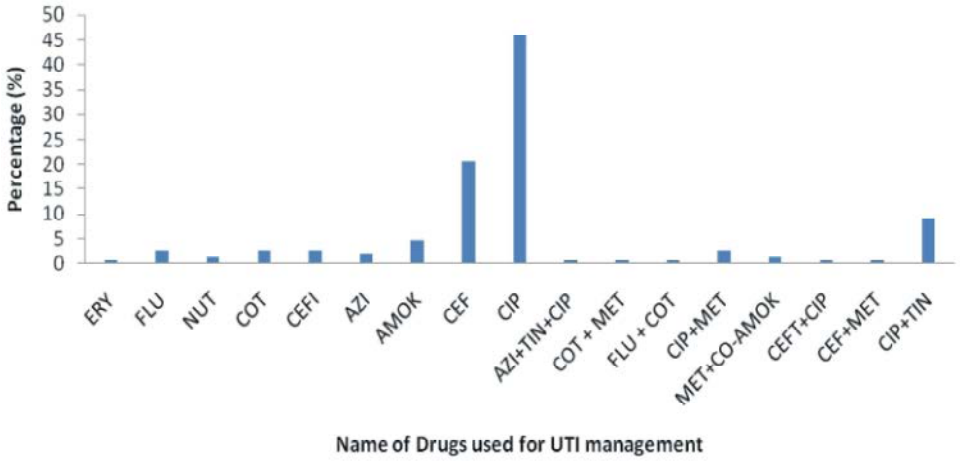

Fig. 1: Histogram showing single and combination drug therapies for UTI management at the Ghana Police hospital from 1st July 2011 – 31st December, 2011

ERY- Erythromycin; FLU – Flucloxacillin; NUT – Nitrofurantoin; COT – Co-trimoxazole; CEFI – Cefixime; AZI – Azithromycin; AMOK/ CO-AMOK – Co-amoxiclav; CEF – Cefuroxime; CIP – Ciprofloxacin; TIN – Tinidazole; MET – Metronidazole; CEFT – Ceftriazone

Cotrimoxazole with Metronidazole (0.7%); Flucloxacillin with Cotrimoxazole (0.7%); Ceftriaxone with Ciprofloxacin (0.7%); and Cefuroxime with Metronidazole (0.7%). The summary of drugs used in the management of UTI is presented in Figure 1:

DISCUSSION

Urine culture analysis has been used over decades for diagnosing patients who have urinary tract infections (UTIs). However, antibiotic use by patients prior to

presentation of urine samples could significantly alter microbial yield and consequently prediction of prevalence rates [27]. Prevalence rate of UTI at Ghana Police Hospital Laboratory within the study period was 31.6%. Although the rate from this study was appreciably high, it was lower compared with findings obtained in other studies from Cape Coast - Ghana (50.4%) and Benin City – Nigeria (86.6%) [22, 28]. Poor personal hygiene, pregnancy, self medication, re-infection as a result poor antibiotic compliance and cross infections from spouses are underlying causes of UTI identified from similar studies in the West African sub-region [13]. Although the proportion of males in this study was higher than females, the significant microbial presence in urine samples of females than males (67.4 and 32.6% respectively) affirmed other studies that reported prevalence being generally higher in women than in men [8, 9, 29, 30]. Anatomical differences between the male and female urethra, proximity of the female urethra to the anal opening as cited by Ebie *et al*. [10], coupled with poor personal hygiene may be underlining factors for the moderately high UTI incidence observed among females in this study.

Identification of UTI causing microorganisms and their antibiotic susceptibility pattern enables practitioners choose the right antibiotics for management. The most common pathogens in laboratory cultures of urine are *E. coli* and other Enterobacteriaceae. These account for approximately 75% of all isolates from urine samples of UTI patients [7, 14, 16]. Several studies done in regional hospitals in Ghana: Koforidua, Kumasi and Cape Coast, revealed that *E. coli* and *Klebsiella spp.* are the most dominant bacterial isolates responsible for UTIs [20, 31]. This study revealed that Enterobacteriaceae family, *E. coli* and other *coliform* isolates constitute 80.4% of the total microbial isolates, with *Proteus spp., Providencia spp., Klebsiella spp.* and *Staphlococcus aureus* identified among significant microbial isolates. This observation is similar to findings by Kahlmeter [32] and other UTI studies in Ghana and Nigeria [31, 33]. Also a study by Turpin *et al*., [34] among pregnant Ghanaian women identified a similar bacteria spectrum, with *Enterococcus faecalis* also being present among isolates. On the contrary, other studies done with pregnant women in Nigeria showed that, *Staphylococcus aureus* was the predominant isolate [28, 35].

Gram-negative bacteria have been found to be the dominant etiologic agents accounting for more than 85% of all UTI cases and are the normal flora of the intestinal tract especially the rectum which is in close proximity to the urethral orifice [36, 37]. This compares favorably with findings of this study, as the only gram-positive organism identified among the microbial isolates was *Staphylococcus aureus* which constituted only 4.5% of significant microbial isolates.

When yeast-like microbes which are often Candida species, are found in urine, it is important to establish whether this signifies infection of either the upper or lower urinary tracts, colonization of the bladder, or contamination of the urine sample [38, 39]. Candiduria in a patient with or without symptoms should be neither dismissed nor hastily treated, but requires a careful evaluation before therapeutic intervention [40]. UTI studies in Israel and Italy showed the proportion of candiduria among isolates ranged between 0.14 – 0.77% [41, 42]. This study however revealed the occurrence of mixed fungal and bacterial infections such as *Candida spp*. with *Escherichia coli* and *Candida spp*. with *coliform* in 5.3% of urine samples analyzed. Hence, in the absence of possible contamination of the urine sample, medical practitioners should consider treatment of possible underlying fungal infections in cases of frequent recurrent UTI infections after completion of recommended antibiotic course.

Knowledge of antimicrobial resistance pattern among bacteria responsible for UTI is not only vital in guiding clinicians to prescribe appropriate antibiotics, but also provides evidence based recommendations in empirical antibiotic treatment of UTI [43]. In this present study, a high level of bacterial resistance was seen with Ampicillin, Co-trimoxazole, Tetracycline, Nalidixic acid, Piperacillin, Cefixime and Cefuroxime. This could make these agents somewhat ineffective against most uropathogens. Also, some level of resistance was seen against Lincocin, Ceftriaxone and Flucloxacillin when discs with these antibiotics were tested with a few isolates. Resistance of *E. coli* to cotrimoxazole (95.1%) in this study was much higher than findings from other studies which ranged from 17 - 66.7% [44, 45]. Coliforms isolated in this study also showed similar but much higher resistance patterns to the antibiotics used. Due to the varied microbial resistance rates observed from different parts of the world [46-50], it is essential that attention be given to local susceptibility patterns to help in the effective management of UTI.

On the contrary, there was generally high susceptibility of microbes to Nitrofurantion and Gentamicin, which corroborates similar studies in Ghana [35] and Nigeria [51, 52, 53]. Nitrofurantoin, unlike beta-lactam containing antibiotics (e.g. Ampicillin) is not inactivated by beta-lactamases so remains largely active against most urinary tract bacteria. Consequently, it is

being suggested that Nitrofurantion be considered as first line therapy for uncomplicated UTI, based on efficacy, cost and impact on bacterial isolates [54, 55, 56]. Unfortunately, the possible side effects of nitrofurantoin such as; nausea, diarrhea, haemolytic anaemia in glucose-6-phosphate dehydrogenase infants, teratogenic risks among others, has limited its use [57]. Furthermore, since most of the microbial isolates in this study were gram negative, the generally high sensitivity of the majority of isolates to gentamicin (an aminoglycoside) was similar to other studies that found gentamicin to be effective in treating gram negative bacteria [58, 59]. However, because of the nephrotoxic potentials of gentamicin, it should be used for UTI when absolutely necessary [60]. This study also revealed uropathogens showing substantial multi-drug resistance to antibiotics *in vitro*, which has also been reported by Mandal *et al.* [61].

Timely treatment of UTI caused by bacteria, yeast or viruses may be necessary to avert possible complications. Some studies have reported that treatment of bacteriuria with a 3 - 7 day course of antimicrobials reduces risk of symptomatic UTI by 80 – 90% [3, 62]. Drug therapy as a treatment measure for UTI patients at the Ghana Police Hospital revealed that, 83.2% of the cases were treated with single oral drug therapy whilst 16.8% had combination therapy. In drug management of UTI at the Ghana Police Hospital, Ciprofloxacin (46%), cefuroxime (20.6%) and Co-amoxiclav (4.7%) were the most prescribed, according to medical records. This observation suggests high adherence by medical practitioners to recommendations of the Standard Treatment Guidelines (STGs) [63]. Despite the fact that there was high level of adherence to STGs, antimicrobial resistance to these three commonly used medications; Ciprofloxacin, Cefuroxime and Co-amoxiclav, needs to be monitored over time. For instance, in China, from 1998 to 2002 the incidence of Ciprofloxacin resistance among uropathogens increased steadily from 46.6% to 59.4% [64]. Resistance rates were 56% to Ampicillin, 24% to Ampicillin/Sulbactam, 15% to Ciprofloxacin, 36% to Trimethoprim-Sulfamethoxazole and 75% to Cefuroxime according to a study from Turkey [65]. However, other recent international studies on susceptibility has demonstrated that Zinnat, the original brand of Cefuroxime, has a high inhibitory activity (82% - 98%) against *E. coli* [66, 67].

With 55.4% of overall isolated uropathogens and specifically 69.1% of *E. coli* in this study exhibiting resistance to most standard treatment drugs, e.g. cefuroxime, should be of great concern. Substantial microbial resistance was also observed for Co-trimoxazole (83.9%). This observation corroborates with findings of Yilmaz *et al.* [68], who reported that treatment of choice for UTI has changed from Co-trimoxazole to Quinolones due to high rate of therapeutic failure over the last decade.

In patients with severe (complicated) UTIs, the national STG recommends use of injectable antibiotics, Ciprofloxacin, Gentamicin and Ceftriaxone for adults and Amoxicillin plus Gentamicin or Cefuroxime for children [63]. With 0.7% (1) of the 150 medical records reviewed indicating Ceftriaxone was prescribed affirms our earlier view that, majority of the UTI cases seen and/ or managed at the hospital were mild or moderate (Uncomplicated). Although none of the combination antibiotic therapies in this study conformed to the STGs, it is worth mentioning that, 92% of these cases included at least one of the national STG recommended antibiotics for management of mild or moderate UTI. This study also revealed that, in all the cases of single drug management of UTI, doses and dosage regimen prescribed were within the national STG recommendations.

The high risk of UTI recurrence among women after initial treatment with single-dose antibiotics, one-time drug administration, has been associated with failure to eradicate gram-negative bacteria from the rectum, the source or reservoir for ascending uropathogens [2]. Hence, the absence of single-dose antibiotic therapy in any of the UTI drug managed cases suggests prudent management of uncomplicated UTIs at the hospital and likely minimal recurrence, as reported by other studies [69, 70, 71]. Also, with 5.3% of microbial isolates being a combination of Candida plus *E. coli* or coliforms, medical practitioners may have to treat empirically possible underlying fungi in some recurrent UTI cases.

CONCLUSION

Nitrofurantoin and Gentamicin were found to be active against most of the isolated bacteria. High resistance was observed for Ampicillin and Co-trimoxazole. Ciprofloxacin was the most prescribed drug for UTI at the Ghana Police Hospital. Overall, a high antibiotic resistance pattern of uropathogens was observed in this study. Regular monitoring of local UTI-causing microorganisms, their respective antimicrobial sensitivity and resistance patterns and adherence to the national STG is vital to achieve optimal empiric treatment of patients.

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