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A Review of Empirical Treatment of Urinary Tract Infections Based on National Antimicrobial Sensitivity Data

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Abstract

Background

The Namibia Standard Treatment Guidelines (STGs) recommends empirical antibiotic treatment in patients with signs and symptoms of Urinary tract infections (UTIs). The goal of UTI treatment is to eliminate the bacteria from the urinary tract. Efficacy of empirical antimicrobial treatment of UTI depends on the sensitivity of common microorganisms, the level of the antimicrobial load in the urine and the duration of treatment. The objective of this study was to identify the common uropathogens that cause UTI, describe the sensitivity pattern of common isolates to antibiotics that are used in the treatment of UTI and recommend appropriate antibiotics for the empirical treatment of UTI in Namibia.

Methods

This was a cross-sectional descriptive analysis of antibiotic susceptibility of isolates from urine using routinely collected data from the Namibia Institute of Pathology (NIP) database. Urine culture and sensitivity results from health facilities throughout Namibia from January 1, 2009 to June 30, 2013 were analysed. A total of 94, 682 urine samples were tested during the study period.

Results

The most common pathogens isolated were *Escherichia coli* (n = 18668, 34.1 %), *Proteus mirabilis* (n = 3520, 6.8%), and *Klebsiella pneumoniae* (n = 3266, 6.4%). *E. coli* showed very high resistance rate to amoxicillin and co-trimoxazol (79.6%, 78.64%) respectively. About one third (28%) of *E. coli* were resistant to Cephalothin and Nalidixic Acid. However, *E. coli* remained highly sensitive to ceftriaxone, amikacin, cefuroxime, gentamycin, nitrofurantoin, ofloxacin, norfloxacin, ciprofloxacin, and amoxicillin/ clavulanic acid its resistance ranging from 2.2% -16.82%. *Proteus* was found to be highly resistant to amoxicillin (55.91%), co-trimoxazole (57.85%) and nitrofurantoin (77.37%). However, it is less resistant to cephalothin (15.51%) and nalidixic acid (11.14%). *Klebsiella*, on the other hand, was found to be more resistant to Amoxicillin (96.72%) but less resistant to nitrofurantoin (23.87). It also demonstrated resistance to co-trimoxazole (56.52%) and cephalothin (35.79%).

Conclusions

E. coli isolated from urine showed high resistance to nalidixic acid which is the first line treatment for community acquired UTI. In addition, the second common isolate *Proteus* spp is naturally resistant to nitrofurantoin but highly sensitive to nalidixic acid. *Klebsiella* showed moderate resistance to nitrofurantoin but less resistance to nalidixic acid. We therefore recommend the substitution of nalidixic acid with fosfomycin as first line treatment of community acquired UTI.

Keywords Mid stream urine; Antimicrobial resistance; Culture and sensitivity; Empiric therapy; UTI; Namibia

Introduction

Urinary tract infection (UTI) is an extremely common bacterial infection that occurs in both males and females of all ages. According to a US survey conducted in 1997, UTI accounts for nearly 7 million office visits and 1 million emergency department visits, resulting in 100,000 hospitalizations. It has been estimated that 1 in 5 women will develop UTIs in their lifetime and 34% of adults over 20 self-reported having at least one urinary tract infection in the US [1-3].

Women are more likely to experience UTI than men. Almost half of all women experience a UTI during their lifetime [2,3]. 10.8% of women aged 18 and older reported at least one presumed UTI during the past 12 months, with the majority of cases occurring among women with a history of two or more UTI episodes in their life. Nearly 1 in 3 women will have had at least 1 episode of UTI requiring antimicrobial therapy by the age of 24 years [2,3]. Infants, pregnant women, the elderly, patients with spinal cord injuries and/or catheters, patients with diabetes or multiple sclerosis, patients with acquired immunodeficiency disease syndrome/human immunodeficiency virus, and patients with underlying urologic abnormalities have increased risk of UTI [2,4].

UTI is believed to be a benign illness with no long-term medical consequences. However, UTI elevates the risk of pyelonephritis, premature delivery, and fetal mortality among pregnant women, and is associated with impaired renal function and end-stage renal disease among paediatric patients.

Physicians distinguish UTIs from other diseases by clinical presentations and lab tests. Among the diagnostic tests, urine analysis is useful mainly for excluding bacteriuria. None of these tests have adequate sensitivity and specificity. Urine culture is not necessary for the diagnosis of uncomplicated UTIs [5]. It is, however, indicated for patients who have recurrent UTIs, treatment failures, or have complicated UTIs [5,6].

E. coli is the most frequent cause of UTIs accounting for 85% of community acquired infections. Other pathogens include *Enterobacteriaceae (Proteus, Klebsiella)* and *Gram positive (Enterococcus faecalis* and *Staphylococcus saprophyticus), Enterobacteriaceae* are the most common organisms isolated from uncomplicated UTI in children [5-9].

The antibiotic treatment for UTIs is usually empirical and it has important medical and economic implications. The goal of UTI treatment is to eliminate the bacteria from the urinary tract. Antibiotic agents such as beta-lactams, trimethoprim, and cotrimoxazole have been used for the treatment of UTIs [6,10,11]. Efficacy of antimicrobial used in the treatment of UTI depends on the sensitivity of the organism, the level of the antimicrobial in the urine, and the duration of treatment [8,13]. If appropriate antibiotics are used, the bacteria can be eliminated within hours. The initial choice of antibacterial therapy should therefore be based on the knowledge of the predominant pathogens in the patient's age group, antibacterial sensitivity patterns in the area, the clinical status of the patient, and the opportunity for close follow-up [11].

The frequency and pattern of resistant UTI pathogen have changed over time. There is also remarkable increase of antibiotic resistance in uncomplicated UTI, notably increased resistance seen in *E.coli* to some commonly used antimicrobial agents, particularly to trimethoprim-sulfamethoxazole [8,10,11]. The emergence of *extended-spectrum beta-lactamases* (*ESBLs*) producing *E.coli* exhibiting high rates of resistance has also been noted [8-12]. Following these changes in resistance, the prescribing pattern and use of certain antibiotics such as fluoroquinolones and cephalosporins as first-line UTI therapy have increased with possible emergence of resistance to fluoroquinolones [13,19].

The Namibia Standard Treatment Guidelines (STGs) recommends empirical antibiotic treatment of patients with UTI. According to the STG, uncomplicated UTIs are managed at the primary health care level. Only resistant and complicated cases are referred to physicians at the secondary care level. The medicines recommended for the treatment of community acquired UTI includes nitrofurantoin for adults and nalidixic acid for children. cefuroxime is recommended as second line to be used only after culture and sensitivity result. cefuroxime and gentamicin IV are recommended for the treatment of upper UTI and prostatitis. Health practitioners, however, raised concerns about lack of efficacy of 1st line medicines frequently used as empirical treatment of UTI and requested the inclusion of Fosfomycin as first line antibiotic for the treatment of uncomplicated UTI.

This study was therefore conducted to produce a local evidence on antimicrobial sensitivity of common uropathogen to inform the Namibian Essential Medicine List (NEMIST)/STGs committee's review of the empiric antibiotics treatment of uncomplicated UTI.

Objectives

- To identify the common uropathogens that cause UTI
- To describe the sensitivity pattern of common isolates to antibiotics that are used in the treatment of UTI
- To recommend an appropriate antibiotic for empirical treatment of UTI in Namibia

Methods

This was a cross-sectional descriptive study using routinely collected antibiotic susceptibility data from the Namibia Institute of Pathology (NIP) database. Results of mid-stream urine culture and sensitivity tests from January 1, 2009 to June 30, 2013, carried out in health facilities throughout Namibia were stored in Meditech®, which is a commercial laboratory management software that capture routinely collected antibiotic susceptibility test results and other laboratory data from health facilities throughout the country. Culture and sensitivity data were entered into Meditech® by NIP regional and central laboratories as part of their routine diagnostic testing. Mid-stream urine samples were collected at the sites and transported to NIP's regional or central laboratory. The NIP immediately conducts standard bacterial culture and sensitivity test using horse blood agar (5%) or chocolate agar.

Pathogen identification and antibacterial susceptibility tests were performed using appropriate Wellcogen® Bacterial Antigen Kit, Gram stain, and methylene blue stain. Standard antibiogram profile tests were done for specific microorganism isolates with some variations according to the doctors' request. Culture results were read after 24 hours of incubation. Plates were re-incubated for a further 24 hours and re-examined for additional organisms. The results were recorded on a worksheet and entered into Meditech®. Printed results were sent back to the clinicians, who could also obtain the results by logging into the tool's web-based reporting module.

Urine culture and antibacterial sensitivity results were extracted from Meditech® using WHONET 5.6. The extracted data was cleaned thorough visual checks and preliminary frequency counts on the raw data set and identified errors were corrected by the lead author. Cleaned data was analysed using Statistical Package for the Social Sciences SPSS® version 12.0.1 (Statistical Package for the Social Sciences).

The main outcome variable was the proportion of samples with positive cultures of suspected microorganisms and the sensitivity patterns of isolates from urine. Descriptive statistics were used to summarize the frequencies and distributions of microbial isolates and their sensitivity to various antimicrobials. Since the analysis was conducted on de-identified electronic records of samples tested by the NIP, individual patient consent was not required. Authorization to conduct the analysis was granted by the Permanent Secretary of Ministry of Health and Social Services of Namibia (MoHSS) and the NIP management.

Results

A total of 94, 682 urine samples were collected for culture and sensitivity tests during the study period. On average, 19677 urine C/S tests were per year. Out of the total urine samples submitted, (n = 54,796; 57.9 %) pathogenic microorganisms were isolated. The remaining (n = 39,886; 42.1%) showed no growth of uropathogen. The mean age of the patients was 33.3 years and (n = 36280; 66.2%) and (n = 18516; 33.8 %) of isolates were obtained from women and men, respectively. (Table 1) A majority (n = 65,773; 69.5%) of the patients with urine culture and sensitivity tests were adult patients and (n = 18315; 19.4%) were children and neonates. (Table 2) Of the samples from outpatient and inpatient departments, (n = 34,103; 61.9%) and (n = 15, 011; 26.7%) showed growth of pathogenic organisms, respectively (Table 3).

Pathogen isolated	Female	Male	Total
Yes	36280 (66.2%)	18516 (33.8)	54796 (57.9%)
No	20656 (51.8%)	19230 (48.2)	39886 (42.1%)
Total	56936 (60.1%)	37746 (39.9%)	94 682 (100%)

Table1: C/S tests by gender. The majority (66.2%) of the isolates were from female.

Age category	Culture Positive	Culture Negative	Total
Adult	36 482 (66.58%)	29 291 (73.44%)	65 773 (69.47%)
Children	10 851 (19.80%)	6 378 (15.99%)	17 229 (18.20%)
New born	606 (1.11%)	480 (1.20%)	1 086 (1.15%)
Age unknown	6 857 (12.51%)	3 737 (9.37%)	10 594 (11.19%)
Total	54 796 (100%)	39 886 (100 %)	94 682 (100 %)

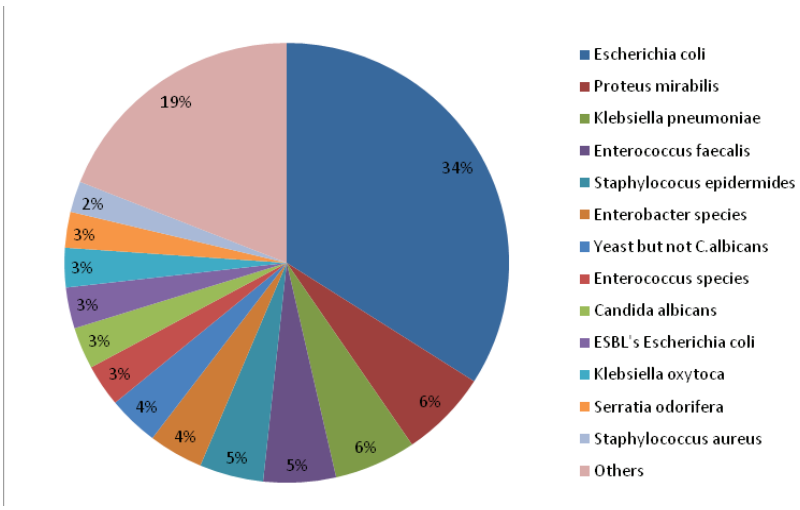
Table 2: C/S tests by age category. Nearly 20 % of urinary pathogens were isolated from children However, UTI seem to be less common among neonates.

Department	Culture Positive	Culture Negative	Total
out patient	34 103 (61.9%)	24 516 (61.47%)	58 619 (62.24%)
Inpatient	15 011 (26.7%)	10 223 (25.63%)	25 234 (27.399%)
ICU	1 204 (2.9%)	1 560 (3.91%)	2 764 (2.20%)
Emergency	580 (1.15%)	509 (1.28%)	1 089 (1.06%)
Not known	3 898(7.4%)	3 078(7.72%)	6 976 (7.11%)
Total	54 796 (100%)	39 886 (100%)	94 682 (100%)

Table 3: C/S tests by Department. Most of the urine culture and sensitivity tests were from outpatient department hence community acquired infection.

The top three common *gram negative* organisms isolated were:- *E.coli* (n = 18,668; 34.1%), *Proteus mirabilis* (n = 3,520; 6.8%), and *Klebsiella pneumoniae* (n = 3,266; 6.4%).

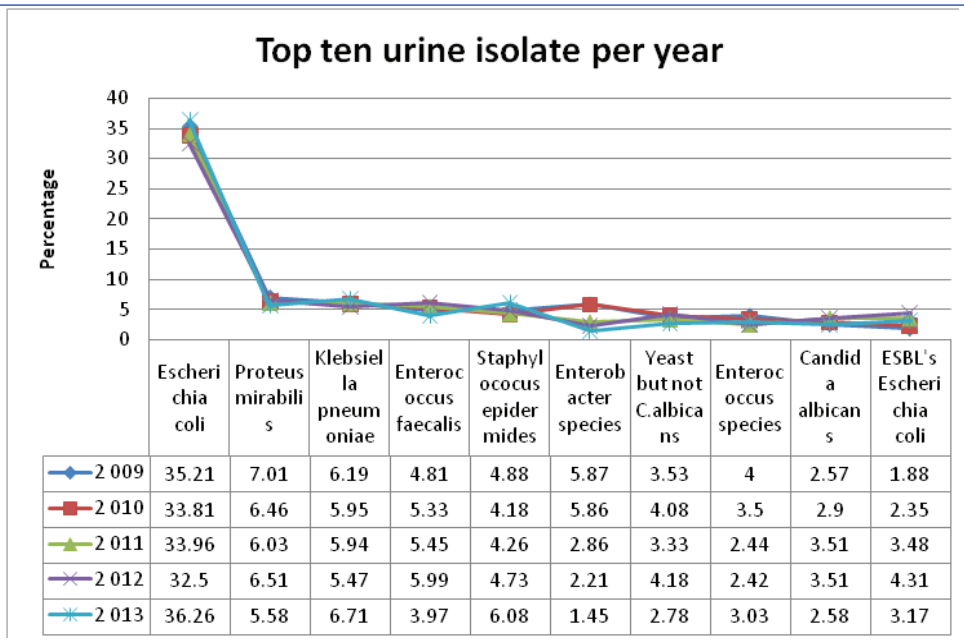
The most common *gram positive* organisms isolated were: *Enterococcus faecalis* (n = 2,888; 5.3%), and *Staphylococcus epidermidis* (n = 2,551; 4.7 %), (Graph 1). There was no change of uropathogens over time during the study period. The percentage of common microorganism isolated remained same throughout the study period. (Graph2)



Graph 1: Common isolates from urine culture during 2009-13. *E. coli* is the most common isolate accounting for 34%.

E.coli showed very high resistance rate to amoxicillin and co-trimoxazol (79.6%, 78.64%) respectively. Over one third (28%) of *E.coli* were resistance to Cephalothin and Nalidixic acid. *E.coli* remained highly sensitive to ceftriaxone, amikacin, cefuroxime, gentamycin, nitrofurantoin, ofloxacin, norfloxacin, ciprofloxacin and amoxicillin/ clavulanic acid with only 2.2 -16.82% resistance.

The second most common isolate was *Proteus mirabilis. Proteus mirabilis* was found to be highly resistant to amoxicillin (n = 1 863, 55.91%), co-trimoxazol (n = 2, 533; 77.37%) and nitrofurantoin (n = 2, 533;77.37%). However, *Proteus mirabilis* was found to be highly sensitive to ceftriaxone, cefuroxime, cephalothin, gentamycin, ofloxacin, nalidixic acid, norfloxacin, ciprofloxacin, and amoxicillin/ clavulanic acid as only 3.9% -16.67 % were resistant (Table 4).



Graph 2: Top ten uropathogens isolate per year during 2009-13. The common uropathogenes isolated remained similar throughout the study period.

	E. Coli (n=18 668)	*Proteus mirabilis* (n=3 520)	*Klebsiella pneumonia* (n=3 266)	*Enterococcus faecalis* (n=2 888)	*Staphylococcus epidermidis(n=2 551)*	*Enterobacter Species (n=2 178)*	*Enterococcus Species*(n=1 695)	*ESBL's E. coli* (n= 1 653)	*Klebsiella oxytoca*(n=1 590)	*Serratia odorifera*(n=1 442)
CRO	12.42	7.43	16.35	22.22	75.00 *	67.49*	72.00*	88.99 *	23.20	24.61*
AMK	2.02	1.9	3.6			5.4				5.4%
AMX	79.65 *	55.91*	96.72*	6.56	65.89 *	89.05*	25.19*	98.73*	90.45*	85.42 *
CXM	9.69	6.57	16.79	21.88	12.52	26.62*	11.11	95.57 *	23.83	22.26
CEP	28.10 *	15.51	35.79*	21.84	9.93	44.72*	11.34	63.64*	36.15*	38.27*
GEN	14.27	9.55	18.32	30.43*	23.73*	26.61*	40.00*	58.05 *	22.25	21.00
NAL	28.06 *	11.14	17.28	50.00*	47.37*	28.87*	37.50*	91.95*	26.55*	33.74*
NIT	6.52	77.37*	23.87	2.42	8.26	21.48	4.86	13.83	18.97	17.55
OFX	13.46	3.90	9.78	16.84	24.83 *	14.78	24.73*	49.03 *	12.80	17.49
NOR	7.26	16.67	0.00	0.00	50.00*	0.00	14.29	0.00	0.00	0.00
CIP	16.82	4.13	10.49	9.73	31.85*	45.18*	22.06	83.79*	17.78	25.37*
AMC	13.70	7.19	12.76	18.75	1.72	17.73	1.43	92.47*	23.52	30.83*
SXT	78.64 *	57.85*	56.52*	90.63*	69.49*	76.31*	79.31*	94.22*	72.47*	80.61 *
VAN				2.32	7.91		15.56			

Table 4: Percentage of top ten urine isolates resistant to the antibiotics used in UTI treatment. E coli showed resistance against amoxicillin, co-trimoxazol, cephalothin and nalidixic acid Other uropathogens such as Enterococcus faecalis, Staphylococcus epidermidis, Enterobacter Species, Enterococcus species, Klebsiella oxytoca, Staphylococcus aureus and Serratia odorifera also showed resistance to nalidixic acid.

CRO, ceftriaxone; AMK, amikacin ; AMX, amoxicillin; CXM, cefuroxime; CEP, cephalothin; GEN, gentamycin; NAL, nalidixic acid; NIT, nitrofurantoin?; OFX, ofloxacin; NOR, norfloxacin; CIP, ciprofloxacin; AMC, amoxicillin/ clavulanic acid; SXT, co-trimoxazole; VAN, vancomycin

* percentage of resistance greater than 24.5%

Discussion

The majority of pathogens isolated were from adult patients 36482 (66.58%). Females accounted for (n=36,280, 66.2%) of all patients. Women are known to have a higher prevalence of UTI than men, due to anatomic factors [2, 3]. *E.coli* (n=18, 668; 34 %) was the predominant pathogen isolated from patients with UTIs followed by *Proteus mirabilis* (n = 3,520; 6.4%), and *Klebsiella pneumoniae* (n = 3,266; 6.8%). The most common *gram positive* organisms isolated were: *Enterococcus faecalis* (n = 2,888; 5.3%), and *Staphylococcus epidermidis* (n = 2,551; 4.7 %). This is consistent with the findings of other studies in which *E.coli* was the predominant pathogen isolated from patients with community acquired UTIs [7–9,12,15,16,19].

E.coli showed a very high level of resistance against amoxicillin (79.65%) and co-trimoxazol (78.64%) while (28.10%) and (28.06%) of *E. coli* isolates were found to be resistant to cephalothin and nalidixic acid respectively. The resistance level in our study found to be comparable with the findings in Senegal where *E. coli* was found to be resistant to amoxicillin (73.1%), co-trimoxazole (68.1%), cephalothin (55.8%), and nalidixic acid (23.9%). A similar study from India demonstrated that 76% *E.coli* isolates to be resistant to ampicillin while 75% were resistant to co-trimoxazole [20]. *E. coli* was found to have very low resistance (6.52%) to nitrofurantoin compared to the findings from India where resistance against nitrofurantoin was reported to be 80% [7]. In Sudan, *E.coli* was found to be highly resistant to ciprofloxacin (62%), amoxicillin/ clavulanic acid (64%), ceftriaxone (42%), co-trimoxazole (66%) and norfloxacin (56%) [7]. Whereas in Turkey, all isolates tested were found to be susceptible to fosfomycin and nitrofurantoin. [11,21]

Proteus, on the other hand, was the second most common isolate and found to be highly resistant to amoxicillin (55.91%), co-trimoxazole (57.85%), and nitrofurantoin (77.37%). However it is less resistant to cephalothin (15.51%) and nalidixic acid (11.14%). Several other studies demonstrated that *Proteus* was among the most common organisms isolated and percentage of resistant to nitrofurantoin is very high [8,9].

Klebsiella (n = 3,266; 6.8%) was the third most common isolates. *Klebsiella* was found to be more resistant to Amoxicillin (96.72%) but less resistant to nitrofurantoin (23.87%). It also demonstrated resistance to co-trimoxazole (56.52%) and cephalothin (35.79%). The findings were comparable with that of India where (75%) *Klebsiella* isolates demonstrated resistance to ampicillin while (53%) were resistant to co-trimoxazole. *Klebsiella* isolate was found to have low resistance (23.87%) to nitrofurantoin compared to the findings from India where resistance against nitrofurantoin was reported to be 76% [7].

There were (n=1 653, 3%) *ESBL's E. coli* isolated. The *ESBL's E. coli* were highly resistant to all antibiotic except nitrofurantoin. *ESBL's E. coli* was found to be ceftriaxone (88.99%), amoxicillin (98.73%), cefuroxime(95.57%), cephalothin (63.64%), gentamycin (58.05%), nalidixic acid (91.95%), ofloxacin (49.03%), ciprofloxacin (83.79%), amoxicillin/ clavulanic acid (92.47%) and co-trimoxazole (94.22%) resistant.

The other common isolates which showed more than 25% resistance to nalidixic acid were *Enterococcus faecalis, Staphylococcus epidermidis Enterobacter species, Enterococcus species, Klebsiella oxytoca, Staphylococcus aureus and Serratia odorifera.* Their rate of resistance to nalidixic acid were (50.00%), (47.37%), (28.87%), (37.50%), (26.55%), (25.00%) and (33.74%) respectively.

These antibiotics have been widely used for the treatment of UTIs for quite some time. There is an emergence of resistant uropathogens such as *E. coli, Enterococcus faecalis, Staphylococcus epidermidis, Enterobacter species, Enterococcus species, Klebsiella oxytoca, Staphylococcus aureus, and Serratia odorifera* to nalidixic acid which is an empiric treatment recommended by the STG. In addition, there is emergence of *E.coli*, with high rates of resistance due to the production of *extended-spectrum beta-lactamases (ESBLs)*. On the other hand, fosfomycin has not been used in the public sector in Namibia so far and seems to be an alternative for empirical treatment of urinary tract infections as it has a good level of activity against common uropathogens [11,20,22].

Strengths and Implications

The strength of this epidemiologic analysis is that it provided the national picture of microorganisms causing UTI and their resistance pattern. We analysed 4 years and 6 months period retrospective data. There is no selection bias as we analysed all the data in the database. It also showed the common isolates among different age groups and their resistance pattern. These findings can be used to guide empirical treatment of patients with UTI. It can also inform the essential medicine list (NEMLIST)/ STG committee in the review of empiric treatment guidelines for UTI. This exercise demonstrated the importance of analysing routinely collected clinical laboratory data in the monitoring of the emergence of antimicrobial resistance. This activity was time efficient and inexpensive and can be replicated on other clinical conditions to see trends in antimicrobial resistance patterns.

Limitations

The main limitation of this analysis was the use of secondary data. The data was not primarily collected to answer a specific research question. It was collected as part of NIP's routine testing clinical samples. The results of the laboratory tests were recorded mainly for reporting back to clinicians as well for administrative and billing purposes. As a result of this set up, not all species of microbes were identified or tested against the antibiotics of interest such as Fosfomycin. There were also some important variables that were not captured in the system, including the possible alternative diagnoses and a patient's history of prior treatment with antibiotics before collection the mid-stream urine samples.

Conclusions and Recommendations

E.coli remained the most frequent cause of UTI. *E.coli* isolated from urine samples showed high resistance to nalidixic acid which is the first line treatment for community acquired UTI. In addition the second common isolate *Proteus* is naturally resistant to nitrofurantoin. Both *E. coli* and *Proteus* are sensitive to cefuroxime. We therefore recommend the substitution of naldixic acid with fosfomycin as a first line treatment of community acquired UTI and continue the use of cefuroxime as second line as in the Namibia Standard Treatment Guidelines.

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