Health-point survey of bacteria urinary tract infections among suspected diabetic patients attending clinics in Bushenyi, Uganda

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Abstract

Background: Although Urinary tract infections (UTI) and diabetes are individual public health pandemic, their comorbidities remain a global health dilemma. Regional surveillance holds the key to effective intervention.

Objectives: To evaluate the prevalence and antibacterial resistance pattern of bacteria etiological agents of UTI among diabetic patients in the Bushenyi district of Uganda.

Methods: In this cross-sectional study, 418 midstream urine from consenting 331 diabetics (230 females and 101 males) and 87 non-diabetic (60 females and 27 males) individuals were collected aseptically and processed using standard microbiological methods. Data generated were tested for statistical significance and scientific relevance.

Results: Bacteria UTI was 31.1% prevalent in diabetic and 11.4% in non-diabetics. Diabetic patients yielded: 13.6%, *Staphylococcus* species, 8.8% *E.coli*, and 8.6% *Klebsiella* species. *Klebsiella* species showed 100% resistance to Erythromycin, 71.4% to Cotrimoxazole, and 92.9% to Ampicillin. Bacteria from diabetic patients remained sensitive to Nitrofurantoin, Ciprofloxacin, Ceftazidime, and Ceftriaxone. Extended Spectrum β-Lactamases were detected in 3.5% of *Klebsiella* species. Age and sex significantly ($p<0.05$) influenced diabetic UTI prevalence.

Conclusion: Diabetes significantly ($p<0.05$) influenced the observed (27%) UTI distribution. Resistance to Ampicillin and Cotrimoxazole may affect their use in UTI management. Antibacterial misuse is highly discouraged and Nitrofurantoin remains urinary antiseptic.

Keywords: Diabetic patients, Bacteria UTI, Bushenyi, Uganda

Introduction

Urinary tract infection [UTI] is an infection of the urinary tract leading to inflammation of the entire tract or the upper or lower section of the track causing asymptomatic, acute, chronic, and complicated/non-complicated infection and depends on the portion of the urinary tract involved, the etiologic organisms, the severity of the infection, and the patient's ability to mount an immune response (1). UTI remains

one of the most common causes of hospitalization and symptoms depends on the age of the patient and the location of the urinary tract infected (2, 3). The influence of diabetes mellitus on the induction and progression of UTI has been documented and asymptomatic bacteriuria, low socioeconomic status, and sickle cell trait are predisposing factors for UTI (4, 5).

The leading bacteria causes of acute and uncomplicated UTI include *Escherichia coli, Staphylococcus aureus, Proteus* species*, Klebsiella* species, and *Pseudomonas aeruginosa* (6-8). In Nigeria, *E. coli, Proteus* species, and *Klebsiella* species have been isolated in 90% of UTI reported cases (9, 10). Complications of UTI, such as emphysematous cystitis, pyelonephritis, occur more commonly in diabetic patients (11). The diabetics are more likely to develop asymptomatic and symptomatic bacteriuria often leading to UTI, emphysematous cystitis, abscess formation, and renal papillary necrosis (11-13).

The sensitivity of bacteria to antibiotics shows a great geographical and historical variability (14). The variation is even more complicated in settings with poor resources and with no defined surveillance system and where information storage and retrieval remain difficult. Sporadic UTI data may exist in African sub-regional, the exact UTI situation in underlying co-morbidities like diabetes and HIV are lacking or highly limited. The pattern of bacteria UTI in diabetes and the detailed susceptibility status of etiology are needed for effective intervention in HIV and diabetes pandemics.

Altered immunity, the impaired anti-oxidant system involved in the bactericidal activity and neuropathic complications, predisposes the diabetics to UTI more than the nondiabetics (15, 16). Unfortunately in Uganda diabetic patients have limited access to the national diabetic clinic and there is no surveillance on UTI in diabetic patients especially at the grassroots level. In this study, we therefore isolated, characterized, and determined the susceptibility status of bacterial etiological agents of UTI among diabetic patients in the Bushenyi district of Uganda with the ultimate goal of providing a database for effective intervention and a baseline for a future surveillance system.

Materials and methods
Isolation and characterization of isolates:

In this cross-sectional prospective health-point survey, microbiological evaluation of 418 clean-catch mid-stream urine samples was aseptically collected and analyzed using standard microbiological methods, for bacteria UTI among diabetic patients attending: Kampala International University-Teaching Hospital (KIU-TH), Ishaka Adventist Hospital, Comboni Hospital, Bushenyi Health Center IV, Kitagata Hospital and Kabwohe Health Center IV. Those included: were clinically diagnosed with UTI in diabetes living in Bushenyi, Uganda. Isolation and identification of the bacteria were done at the Microbiology Laboratory of KIU-TH and Mbarara University Teaching Hospital. Significant UTI was defined as the presence of

100,000 CFU/milliliter in the culture of a clinical urine sample (17). CHROMagar orientation was introduced to boost the discriminatory power of routine phenotypic identification protocols [18, 19],

Four hundred and eighteen patients sampled was guided by the upper limit required to give 95% level of confidence at an expected prevalence of about 36.15% (20) using the precise prevalence formula: Sample size (N) = Z^2P (100-P)/D2 (Epi-info version 3.2 database; 1995), where Z is a constant given as (1.96), P is expected prevalence (36.2%), and D is an acceptable error (5%). Ethical approval was obtained from KIU-WC Research and Ethics Committee and informed consent was sought and obtained from the patients. The consent letter was written in English and translated into local languages and participants who could not read or write gave a thumbprint to indicate approval. The patient's Diabetic status was confirmed using calibrated Abbot Precision-Xceed-Pro Glucometer and test strips dosed with 2.5 microliters of whole blood and then result read in 20 seconds as directed by the manufacturers. After analysis bacteria and media were decontaminated by autoclaving (at 121^0C at 15psi for 15minutes), incinerated and ashes buried accordingly.

Antibiotic susceptibility testing:
The antibiotic susceptibility was performed by Clinical Laboratory Standards Institute (CLSI) modified Kirby Bauer method (21) on Muller Hinton agar. The prepared media was inoculated with bacterial suspension equivalent to 0.5 McFarland turbidity standards and allowed to stand for 30 minutes. The commercially available discs used contained the following antibiotics: Ceftazidime (30ug), Erythromycin (15ug), Ciprofloxacin (5ug), Ceftriaxone (30ug), Cotrimoxazole (25ug), Nitrofurantoin (300ug), Ampicillin (10ug), and Chloramphenicol (5ug) (BIOLAB Inc., Budapest Hungary). They were aseptically inoculated on the sensitivity agar plates and were incubated for 18 - 24hrs at 37°C. Zones of inhibition were measured and interpreted using standard methods.

Detection of Extended-spectrum beta-lactamase [ESBL] producing isolates:
Gram-negative bacteria which showed resistance to either ceftazidime or ceftriaxone were screened for ESBL-production using double-disc synergy tests (DDST) (22). Confirmation of ESBL production was done by combined disc diffusion (23). Each of the Petri dishes containing Mueller-Hinton agar was seeded with bacterial suspension matched to 0.5 Mac Farland turbidity for 30 minutes. In this test, a disk of ceftazidime (30µg) alone and a disk of ceftazidime in combination with clavulanic acid (30/10µg) was used. Both disks were placed 25mm apart, center to center, on a lawn culture of the test isolate on Muller Hinton agar plate and incubated overnight at 37° C. Difference in zone diameter with and without clavulanic acid was measured. The positive result was defined as a ≥5mm increase in inhibition zone diameter around combination disks with clavulanic acid versus its standard zone when tested alone (23). Data generated from this research was analyzed statistically using SPSS.

Results
We report a 27% overall prevalence of bacteria (*Staphylococcus aureus, Escherichia coli, Klebsiella* species, *Enterococcus* species) from 418 participants (290 females and 128 males). Out of 418 samples analyzed, 103 (31.1%) samples were positive for UTI among the diabetic patients and 10 (11.4 %) of the non-diabetic patients (Table 1). The overall prevalence of UTI was 78 (33.9%) of diabetic females and 25 (24.8%) of diabetic males. The highest (10%) and the lowest (0.9%) UTI prevalence occurred among female participants aged 41-50 years and 11-20years respectively. The highest (14.9%) and lowest (2%) UTI prevalence were among the males aged >60years and 21-30years. The prevalence of bacterial UTI was significantly ($p<0.05$) dependent on age and the sex of the diabetic patients. Out of 87 (60 females and 27 males), non-diabetic patients, 10.3% females and 1.1% males had UTI with the highest prevalence (5%) recorded in the age group 21-30 years and the lowest UTI (1.7%) prevalence recorded in the age group 11-20

years and >60 years respectively (Table 1). The prevalence of bacterial UTI had no significant (p>0.05) association with age and sex of the non-diabetic participants.

Among diabetic patients, (Table 1) 13.6% *Staphylococcus aureus* was the most prevalent bacteria followed by 8.8% *E. coli*, 8.6% *Klebsiella* species` and 0.3% *Enterococcus* species prevalences respectively. Among non-diabetic patients, 5.7% *E. coli* was the most prevalent followed by 4.6% *Staphylococcus aureus* and 1.1% *Klebsiella* species. The sex of patients had no significant (p>0.05) influence on bacteria distribution in both diabetic and non-diabetic patients. From Table 2, all the isolated bacteria were highly resistant to Ampicillin. *Klebsiella* species was the most resistant among diabetic patients. The resistance of *Klebsiella* species to selected antibiotics included: 100% to Erythromycin; 71.4% to Cotrimoxazole and 92.9% to Ampicillin respectively. *Enterococcus* species isolated did not respond to any of the tested antibiotics. Table 2 also shows that all the isolated bacterial from the non-diabetic patients were highly resistant to Ampicillin with *Escherichia coli* as the highest showing 100% resistance to Erythromycin, Cotrimoxazole, and Ampicillin respectively. Among resistant Gram-negative bacteria, tested for ESBLs, 3.5% *Klebsiella* species strains were positive for ESBLs. The prevalence of ESBLs was not significantly (p>0.05) dependent on the sex of the diabetic patients (Table 2).

Discussion

Human development characterized by the availability of basic life amenities continues to define the relationship between regional disease endemicity and the health status of people living in a particular community. In communities with limited resources, it is common to see preventable diseases like urinary tract infections (UTI) ravage the lives of ordinary citizens. The situation becomes even complicated if the infected individual harbors underlying chronic debilitating disease like

diabetes (24) and the tendency of the involved microorganism to develop resistance to routine treatment regimen and also cause invasive diseases becomes very likely (25).

The observed 27% overall prevalence of bacteria (*Staphylococcus aureus, Escherichia coli, Klebsiella* species*, Enterococcus* species) among 418 participants (290 females and 128 males) clinically diagnosed with UTI, re-emphasizes the fact that regular survey (depending on resources availability) holds the key to effective intervention especially in patients with the debilitating disease living in disease endemic low-income countries. To confirm the significant (p<0.05) influence of diabetes on UTI prevalence as suggested by Pozzilli and Lesli, (26), we discovered a relative prevalence of 31.1% of UTI among the 331 diabetic patients compared to 11.4% of UTI among 87 non-diabetic patients.

Generally, our result is comparable with reports from elsewhere, because we found that our 31.1% prevalence of UTI among the diabetics is: lower than the newer Nigerian report of 36.2% prevalence (20), among similar cohorts. However, the 31.1% prevalence report is higher than older Nigerian reports of 26% and 23.3% respectively (27, 10); 21% in Karachi (4), 19% in Bahrain (28), 11.1% in Kenya (29), and 9.3% in Ethiopia (30) respectively.

While it may be difficult to explain the upward trend in UTI prevalence noted in the reported Nigerian studies from 26% and 23% in 2004/2003 to 36.2% in 2010, limited resources to enhance information storage and retrieval, underlying conditions such as HIV, sickle cell disease, immunological impairments, neutropenic disorders, pregnancy poor hygiene, use of contraceptive pills and menstruation in females are known factors which predispose people to UTI and may have played a role in this report. The trend noted from 21% in Karachi to 9.3% in Ethiopia may have clinical, socio-economic

Table 1
Age and distribution of bacterial agents of UTI among 331 diabetics and 87 non=diabetic patients

Age range	No (%) UTI prevalence in diabetics		No (%) UTI prevalence in non-diabetics	
	Females n=230	Males n=101	Females n=60	Males n=27
<10	00(0.0)	00(0.0)	00(0.0)	00(0.0)
11 − 20	02(0.9)	00(0.0)	01(1.7)	00(0.0)
21 − 30	05(2.2)	02(2.0)	03(5.0)	01(3.7)
31 − 40	15(6.5)	02(2.0)	02(3.3)	00(0.0)
41 − 50	23(10.0)	04(4.0)	02(3.3)	00(0.0)
51 − 60	14(6.1)	02(2.0)	00(0.0)	00(0.0)
>60	19(8.3)	15(14.9)	01(1.7)	00(0.0)
Total	78 (33.9)	25(24.8)	09 (15.0)	01(3.7)

Bacterial strains	No (%)prevalence in diabetics		No (%) prevalence in non-diabetics	
S.aureus	31(13.4)	14(13.9)	03(5.0)	01(3.7)
E.coli	24(10.4)	05(5.0)	05(8.3)	00(0.0)
Klebsiella spp	22(9.6)	06(5.9)	01(1.7)	00(0.0)
Enterococcus spp	01(0.4)	00(0.0)	00(0.0)	00(0.0)

Foot note; *S. aureus = Staphylococcus aureus, E.coli = Escherichia coli, Klebsiella* spp *= Klebsiella* species, *Enterococcus* spp *= Enterococcus* species. n=number, %=percentage. p=probability. (p>0.05)

TABLE 2 Resistant profile of bacterial isolates from 331 diabetics and 87 non-diabetic patients against commonly used antibiotics

Uropathogens	Number (%) resistance of bacteria isolates from 331 diabetic patients							
	CIP	CRO	CAZ	E	NF	SXT	C	AM
S.aureus (n=45)	14(31.1)	25(55.5)	27(60.0)	23(51.1)	04(8.9)	34(75.5)	17(37.8)	35(77.8)
E. coli (n=29)	10(34.5)	02(6.9)	01(3.4)	28(96.6)	09(31.0)	25(86.2)	08(27.6)	29(100)
Klebsiella spp (n=28)	11(39.3)	07(25.0)	05(17.9)	28(100)	12(42.9)	20(71.4)	13(46.4)	26(92.9)
Enterococcus spp n=1)	01(100)	01(100)	01(100)	01(100)	00(0.0)	00(0.0)	00(0.0)	00(0.0)
	Number (%) resistance of bacteria isolates from 87 non-diabetic patients							
S.aureus (n=4)	01(25.0)	02(50.0)	00(0.0)	02(50.0)	00(0.0)	02(50.0)	01(25.0)	03(75.0)
E.coli (n=5)	02(40.0)	01(20.0)	00(0.0)	05(100)	00(0.0)	05(100)	02(40.0)	05(100)
Klebsiella spp (n=1)	00(0.0)	00(0.0)	00(0.0)	01(100)	00(0.0)	01(100)	01(100)	01(100)

Foot note; *S.aureus = Staphylococcus aureus, E.coli = Escherichia coli, Klebsiella* spp *= Klebsiella* species, *Enterococcus* spp *= Enterococcus* species. *CIP = Ciprofloxacin, CRO = Ceftriaxone, CAZ= Ceftazidime, E= Erythromycin, NF = Nitrofurantoin, SXT = Cotrimoxazole, C= Chloramphenicol, AM = Ampicillin.* n=number, %=percentage.

and religious undertone because Karachi and Bahrain have Muslim majority populations while Kenya and Ethiopia have mixed religious populations respectively.

UTI prevalence was higher in both the diabetic (33.9%) and nondiabetic (15.0%) females when compared to their corresponding male counterparts with 24.8% and 3.7% prevalence respectively (Table 1). Sex and age significantly (p<0.05) influenced the prevalence of UTI among the surveyed participants, especially among the diabetic population.

The anatomy of the female genitourinary system and waning immunity in the elderly

remains outstanding among factors that predisposes people to UTI especially in this setting with limited resources, poor hygiene, and low socioeconomic status. This also explains why females are more prone to UTI than their male counterparts (31, 32). One unique observation in this study is that the underlying medical condition determines the etiology of UTI. This was clear in table 1 where there was a difference in etiology of the diabetic and non-diabetic population. Thus the diabetic population was predominated by 43.7% *Staphylococcus aureus* whereas the non-diabetic population was predominated by 50% *Escherichia coli*. This observation is far lower than 46.3% *Staphylococcus* species and 39% *Escherichia coli* prevalence in UTI reported in Northern Uganda City of Gulu (33). Patients with diabetes mellitus have a two to three-fold increased risk of bacteremia and sepsis originating from the urinary tract compared with those without diabetes [34]. This places the surveyed population at great risk of *Staphylococcus aureus* and *Escherichia coli* bacteremia. The sex of patients had no significant (p>0.05) influence on bacteria distribution in both diabetic and non-diabetic patients. Thus, although the anatomy of the female genitourinary system played a role in determining UTI prevalence, it had no influence (p>0.05) on the bacteria etiology.

Treatment of infection with *Staphylococcus* species remains a challenge due to the high tendency of the bacteria to develop resistance to conventional antibiotics. *Staphylococcus* resistance to the penicillins, cotrimoxazole, and the cephalosporin (77.8% resistance to Ampicilin, 75.5% resistance to cotrimoxazole, 60% to ceftazidime, and 55% to ceftriazone) is not surprising given the elaborate virulence factors produced by this bacterium. Resistance to penicillin is a consequence of beta-lactamase production and is common in developing country settings where uptake of hospital services is low and the tendency for self-medication is high leading to antibiotic abuse. Administration of cotrimoxazole to HIV-infected individuals as life prophylaxis and the use of cotrimoxazole as a broad-spectrum antibiotic in febrile illness including

indiscriminate use of antibiotics (due to lack of prescription policies) to treat symptomatic/asymptomatic UTI may explain the observed bacteria resistance to these antibiotics.

The overall resistance profile of *Staphylococcus aureus, Escherichia coli, Klebsiella* species, and *Enterococcus* species which we report in this study done in the western Uganda district of Bushenyi (Table 2) is in line with other reports from North and central Uganda (35-37, 33). The overall high bacterial resistance to Ampicillin and Cotrimoxazole (Table 2) is similar to a study carried out by Mwaka et *al,* (36) in Kampala, Uganda and few isolates were sensitive to Ampicillin and Erythromycin similar to the one reported in Western Nigeria (20, 38) and Northern Nigeria in West Africa (39). Also, the low level of resistance of uropathogens to third-generation cephalosporins and ciprofloxacin used in this study conforms with the report of Randrianirina *et al.,* (40) from the Southern African city of Madagascar. It is therefore clear that our result is in line with East, South, and West African reports about African literature regarding the chemotherapy of bacteria etiological agents of UTI. Our report is slightly different from the resistance report from apparently healthy females genital tract isolates in West Africa-Nigeria city of Ekpoma (41) were *Escherichia coli* and *Staphylococcus* species were: 44% and 37% resistant to oxacilline; 6% and 55% resistant to ceftriazone; and 34% and 31% resistant to ciprofloxacin respectively (Table 2).

The factors that may help explain the observed pattern of resistance to uro-pathogens remain relatively similar irrespective of the locality. Prominent is antibiotic abuse due to a lack of effective and implementable policies, enabling sick people to purchase small amounts of antibiotics from drug shops manned by unqualified health workers. This may give room for the emergence of resistant strains due to low dose misuse of such antibiotics and poor adherence occasioned by the tendencies of the patients to back out from completing the dose when they get a little relief from the symptoms of the infection. Fecal contamination of UTI

due to poor hygiene, genital manipulation due to use of douches, insertion of intrauterine devices, contraceptive pills, and use of poor quality contaminated condoms during sexual intercourse are all factors that predispose to UTI (41, 33).

We tested gram-negative bacteria for the presence of Extended Spectrum Beta-lactamase production (ESBLs). We were surprised to discover that 3.5% of the antibiotic-resistant *Klebsiella* species were also positive for ESBLS. The prevalence of ESBLs among the gram-negative bacterial uropathogens was not significantly (p>0.05) dependent on the sex of the diabetic patients (Table 2). Multiple-antibiotic resistant, UTI-associated enterobacteria show their pathogenicity by expressing gene (SHV) encoded ESBLs enzymes (42). The occurrence of ESBLs-producing *Klebsiella* species in this study is similar to an old report by Hadziyannis *et al.*, (43). Although we could not confirm if the isolated ESBLs-producing *Klebsiella* species is from pneumonia or the oxytoca substrain, further studies are needed to adequately characterize the strains of *Klebsiella* strains in this region. Our report of the regional emergence of ESBLs producing enterobacteria confirms the earlier Tanzania report by Sabrina *et al.,* (44).

In conclusion, bacteria UTI is highly (31.1%) prevalent among diabetic patients attending hospitals/clinics in Bushenyi. Diabetes significantly (p <0.05) impacted participants' acquisition of UTI. Diabetes and other underlying conditions appear to determine the distribution of bacteria etiological agents of UTI. Nitrofurantoin, Ciprofloxacin, and Ceftriaxone, Ceftazidime were the most effective antibiotics. Underlying medical condition influenced bacteria etiology of UTI and the observed resistance to Ampicillin and Septrine, may influence their use in UTI treatment. Antibacterial misuse is highly discouraged and Nitrofurantoin remains an effective urinary antiseptic.

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