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Research article

Microbial sensitivity of the common pathogens for UTIs are declining in diabetic patients compared to non-diabetic patients in Bangladesh: An institution-based retrospective study

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A R T I C L E I N F O

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A B S T R A C T

Background: Urinary tract infection (UTI) is one of the most recurrent infections in the community and healthcare settings. Although many studies related with microbial sensitivity (MS) of uropathogens (UPs) to antibiotics have been done in Bangladesh, no conclusive study has compared antibiotic sensitivity (AS) to UPs in diabetic and non-diabetic patients. The aim of the study is to find out whether there is a difference in AS in common UPs between diabetic and non-diabetic UTI patients.
Methods: A retrospective review was conducted on 833 patients. The data was collected from different diagnostic centers located within Dhaka city in Bangladesh, and the data was analyzed using convenient statistical tools.
Results: We have studied a total of 833 UTI patients. Out of 833 patients, 664 were diabetic and 169 were non-diabetic patients respectively. Among the studied population, females were found to be more inclined to have UTIs as compared to males. *E. coli* was found to be the leading UPs in our study. Patients within the age of 20–34 were more vulnerable to UTI in both groups. Imipenem and meropenem showed 100% sensitivity against *E. coli*, *Staphylococcus* and *Klebsiella* in non-diabetic patients, while both antibiotics showed lower sensitivity to the same organisms in diabetic patients. Antibiotics like nitrofurantoin ($p \leq 0.0002$), ceftazidime ($p \leq 0.0124$) and ceftriaxone ($p \leq 0.0168$) showed less sensitivity to *E. coli* in diabetic UTI patients as compared to non-diabetic UTI patients. Overall sensitivity patterns elucidated that all the studied antibiotics, except ciprofloxacin and levofloxacin, showed lower sensitivity against UPs in diabetic while compared to non-diabetic UTI patients (p= <0.05 to 0.0001).
Conclusion: We found significant difference in microbial sensitivity in patients with diabetes compared to non-diabetic UTI patients. Diabetes changes the pathophysiological state of the uropathogens leading to the declining sensitivity of the antibiotics in diabetic patients with UTIs.

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1. Introduction

Uropathogens (UPs) are frequently considered as a risk factor in patients for urinary tract infection (UTI). UTI is one of the most prevalent infections in the community and healthcare settings that accounts for substantial antibiotic consumption [1-4]. People with diabetes are usually more prone to infections, of which urinary tract infection (UTI) is the most prevalent, compared to non-diabetic patients because of degenerative effects of diabetes on the genitourinary system [5,6]. Direct medical costs for mitigating UTIs in 2012 exceeded $2.3 billion in the United States alone [7,8]. The occurrence of UTI is more likely in women than compared to men due to difference in anatomical metamorphoses and sexual behavior [9,10]. UTI is one of the major culprits for morbidity and mortality in developing countries like Bangladesh owing to the lack of noble research, erroneous diagnostic procedures, irrational use of chemotherapy in UTI and overall lack of awareness [11]. The predominant microbiota in UTI is *E. coli*, followed by a number of gram-positive cocci and other Enterobacteriaceae [12].

In recent times, antibiotic resistance (AR) has become a global health challenge as a consequence of inappropriate use of antibiotics in the animal and plant kingdom which not only affects this generation but also threatens to severely affect the next [13]. AR's present impact in Bangladesh is massive due to poor healthcare standards along with the irrational and overuse of antibiotics [14]. Antibiotic sensitivity to UTI pathogens may decline over time thus, growing resistance to commonly prescribed antibiotics ultimately leading to a global problem [15-17]. Therefore, clinicians and pharmacists need to be informed about the trends of microbial susceptibility for the proper selection of antibiotics in the fight against target pathogens.

Although there are comparative studies of antibiotic resistance against UPs in diabetic and nondiabetic patients that have been conducted in different countries [18-21], to the best of our knowledge, no comparative study of antibiotic resistance among diabetic and non-diabetic UTI patients has been conducted in Bangladesh. Therefore, the purpose of our study was to determine the difference in antibiotic sensitivity to the common microorganisms in both diabetic and non-diabetic UTI patients in Bangladesh for the selection of appropriate antibiotics in the treatment of UTIs.

2. Methodology

2.1. Data collection and study guideline

This was a retrospective study conducted on a total of 833 UTIs patients (including 664 non-diabetic and 169 diabetic, UTIs patients) where the urine culture sensitivity data was obtained and studied for a period of one year (from January 2019 till December 2019). Data was collected from the diagnostic centers situated within Dhaka; Bangladesh similar to our previous study [10]. Culture sensitivity assay was performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines [22]. Mueller-Histon agar disk diffusion test method was used for the bacterial sensitivity test. We used standard concentration of the studied antibiotics according to CLSI guideline [22]. Shortly, ceftazidime (30 μg), cefixime (30 μg) ceftriaxone (30 μg), imipenem (10 μg), meropenem (10 μg), ciprofloxacin (5 μg), levofloxacin (5 μg), nitrofurantoin (300 μg), gentamycin (10 μg) and amikacin (30 μg) were used. We took permission from institutional review board (IRB), North South University, Bangladesh (OR-NSU/IRB/0804) to conduct this study.

2.2. Inclusion criteria of the patients for the study

For the selection of diabetic UTIs patients, we considered blood sugar level greater than 7.8 mmol/l (random) and 11.1 mmol/l (2 h after oral glucose intake) and/or revealed one of the following: glycosouria, pyelonephritis, urethritis, cystitis or any other complications; while non-diabetic UTIs patients showed either pyelonephritis, urethritis, cystitis, or other genital complications with negative diabetic tests. In both cases, bacterial count greater than 105 cfu/ml in their urine culture were taken into consideration for inclusion in this study. We did not differentiate Type 2 or Type 1 diabetes in the studied population. Rather, we considered blood glucose level (random and OGTT) and either of the complication including glycosuria, pyelonephritis, urethritis, cystitis etc. as the inclusion criteria of the diabetic UTI patients in this study.

2.3. Statistical analysis

For statistical analysis, we entered all the data into Statistical Package for Social Sciences (IBM SPSS Statistic, IBM Corporation, USA) version 23 and calculated frequencies with percentages for categorical variables. We determined the p-value by using Fisher's exact test through two-tailed contingency table (2*2) and a value less than 0.05 was considered as significant. We have chosen Fisher's exact test in our study instead of chi-squared test because of the nature of our samples [23].

3. Results

3.1. Distribution of studied population and pathogens for UTIs

A total of 833 non-diabetic and diabetic patients were distributed according to the age and sex category. Out of the 833 patients (664 in non-diabetic and 169 in diabetic), there were 238 (35.84%) male and 426 (64.16%) female in the non-diabetic group, and 59 (34.91%) male and 110 (64.09%) female in the diabetic group. The occurrence of having UTIs were higher among females than to male patients in both diabetic and non-diabetic groups. In the study, the highest number of patients with UTIs were in the 20–35 years age group, followed by 35–49 years in both groups of patients. The details are provided in Table 1.

The prevalence of the UPs responsible for UTIs in non-diabetic and diabetic patient groups is shown in Figs. 1A and B respectively. Among all of the patients, the most common and prevalent organism found was *E. coli*, at 64.91% in non-diabetic and at 46.75% in the diabetic group.

Similarly, *Staphylococcus*, *Klebsiella*, and *Pseudomonas* were common in two groups at 2.41%, 11.90%, and 2.86% in non-diabetic and at 21.89%, 8.28% and 3.55% in diabetic patients respectively. Pathogen like *Citrobacter* (17.47%) was isolated only in non-diabetic patients, while *Enterococcus* (11.83%), and *Acinobaceria* (7.10%) were found only in diabetic patients.

3.2. Results of the antibiotic sensitivity of the common pathogens among non-diabetic and diabetic UTIs patients

The sensitivity pattern for the most common UPs for non-diabetic and diabetic patients are summarized in Figs. 2 and 3 respectively. Meropenem and imipenem showed 100% sensitivity against *E. coli* while *Staphylococcus, Klebsiella* and *Citrobacter* showed 94.1% sensitivity against *Pseudomonas* in non-diabetic patients. Moreover, amikacin and gentamycin showed 100% sensitivity against *Staphylococcus,* and showed remarkable sensitivity against *E. coli* (99.7% and 91.0%), and *Klebsiella* (100% and 92.4%) respectively. Fluoroquinolones and cephalosporins showed moderate to low activity against *E. coli*; briefly, levofloxacin, ciprofloxacin, ceftriaxone, cefixime, and ceftazidime exhibited 58.0%, 40.5%, 62.8%, 44.6% and 70.2% sensitivity in non-diabetic patients respectively. Nitrofurantoin showed 88.0% sensitivity against *E. coli* in non-diabetic patients' group. Details are provided in Fig. 2.

On the other hand, in diabetic patients' group, we found that *E. coli* exhibited its high sensitivity to imipenem (87.3%), while it revealed moderate sensitivity to gentamycin (71.2%), meropenem (68.8%), levofloxacin (63.2%), nitrofurantoin (67.7%) and amikacin (58.7%), and lowest sensitivity to cephalosporins. Levofloxacin and gentamycin showed 100% sensitivity to *Klebsiella* and *Pseudomonas* respectively. Meanwhile, antibiotics like cefixime and nitrofurantoin showed no sensitivity to *Pseudomonas*. Further details are shown in Fig. 3.

3.3. Comparative results of the overall sensitivity of the studied antibiotics among diabetic and non-diabetic patients

The overall sensitivity of antibiotics among studied patients elucidated that all antibiotics except fluoroquinolones (ciprofloxacin and levofloxacin) showed significant (p-value, $\leq$0.05 to $\leq$0.0001) decrease in its sensitivity to the common pathogens in diabetic patients compared to non-diabetic patients. Ceftazidime, imipenem, meropenem, gentamycin, and amikacin showed the most significant (p-value, $\leq$0.0001) decline in sensitivity. More details are provided in Fig. 4.

3.4. Pathogen wise comparative results of the antibiotic sensitivity among diabetic and non-diabetic UTIs patients

Among the studied population, imipenem, meropenem and amikacin showed extreme decrease in sensitivity against *E. coli* in the diabetic compared to non-diabetic patients (p-value, $\leq$0.0001) Similarly, nitrofurantoin, gentamycin, ceftriaxone and ceftazidime also showed significant declined in its sensitivity to *E. coli* in diabetic compared to non-diabetic patients (p-value, $\leq$0.02 to $\leq$0.0002). Activity of meropenem and gentamycin is also found to have declined profoundly against *Staphylococcus* among diabetic compared to non-diabetic UTI patients (p-value, $\leq$0.008 and $\leq$0.0008 respectively). Moreover, cefixime, ceftazidime, levofloxacin and meropenem also significantly showed its reduced sensitivity against *Klebsiella* in diabetic patients (p-value, $\leq$0.05). Details are given in Table 2.

4. Discussion

The aim of the study is to find out whether diabetic condition play a role in antibiotic sensitivity among UTI patients or not. Our study also aims to figure out the difference in antibiotic sensitivity to common uropathogens found in diabetic and non-diabetic patients in Bangladesh. The present study confirmed that the occurrence of UTIs is more frequent in females than in males which matches with the previous studies in both non-diabetic and diabetic patients [10,24,25]. The maximum number of female patients were in the age group of 20–34 years of which 20.03% is in the non-diabetic and 23.07% is in the diabetic group. The incidence of UTIs

Table 1
Age-wise distribution of patients among the studied population.

Age (Years)	Non-Diabetic UTIs patients			Diabetic UTIs patients		
	Total N (%)	Male N (%)	Female N (%)	Total N (%)	Male N (%)	Female N (%)
<1	17 (2.56)	8 (1.20)	9 (1.36)	2 (1.18)	2 (1.18)	0 (0.0)
1–4	49 (7.38)	18 (2.71)	31 (4.67)	4 (2.37)	4 (2.37)	0 (0.0)
5–11	29 (4.37)	11 (1.66)	18 (2.71)	3 (1.78)	2 (1.18)	1 (0.60)
12–19	47 (7.08)	18 (2.71)	29 (4.37)	6 (3.55)	0 (0.0)	6 (3.55)
20–34	202 (30.42)	69 (10.39)	133 (20.03)	55 (32.54)	16 (9.47)	39 (23.07)
35–49	139 (20.93)	44 (6.63)	95 (14.30)	39 (23.08)	13 (7.69)	26 (15.39)
50–65	117 (17.62)	36 (5.42)	81 (12.20)	37 (21.89)	16 (9.47)	21 (12.42)
>65	64 (9.64)	34 (5.12)	30 (4.52)	23 (13.61)	6 (3.55)	17 (10.06)
Total (N)	**664**	**238**	**426**	**169**	**59**	**110**

Abbreviation: UTIs, Urinary Tract Infections; N, number; %, percentile.

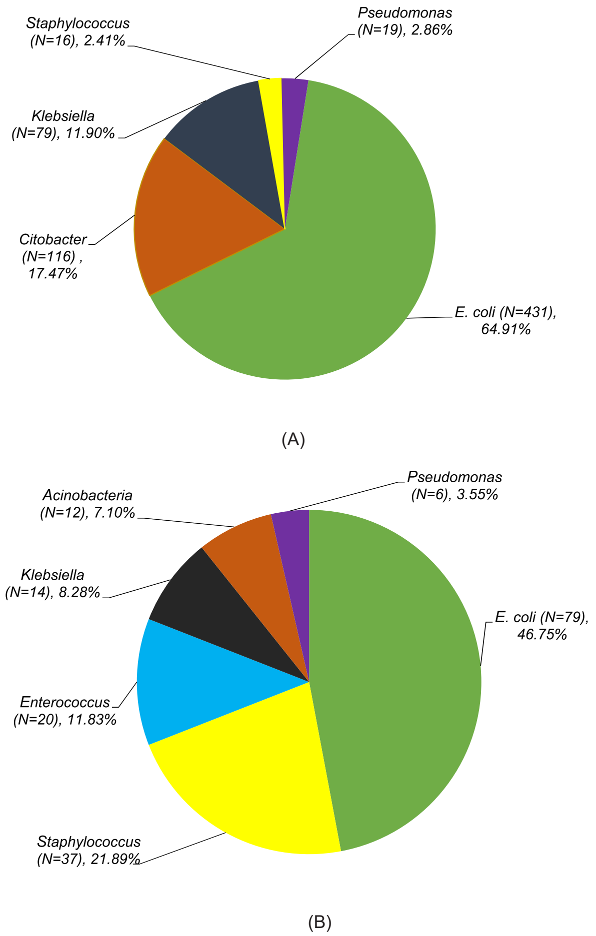

Fig. 1A. Distribution of different uropathogens found among non-diabetic patients with UTIs. Data is expressed in number (N) and percentile (%). Fig. 1B Distribution of different uropathogens found among diabetic patients with UTIs. Data is expressed in number (N) and percentile (%).

is more common in young and adult females who are physically fit and have anatomically normal urinary tracts with having some risk factors including shorter urethra that facilitate colonization, high intercourse frequency, having close proximity of the urethral meatus to the anus, being on oral contraceptive, voiding dysfunction, use of diaphragm or spermicide and bad toilets [9,26,27]. Furthermore, prostatic fluid which contains antimicrobial properties makes male less susceptible than female to UTISs [28]. In this study, majority of the patients were in the age group of 20–34 years for both the non-diabetic (30.42%) and the diabetic (32.54%) cases which is similar with reports showed by Ahmed et al. [29] and Yasmeen et al. [30]. Sexually active young individuals are more susceptible to UTIs due to initial sex period, lack of related personal hygienic practices, and child bearing age for females [31].

Among all the isolated UPs, *E. coli* was the most prevalent gram-negative micro-organism in both groups (diabetic and non-diabetic) which is analogous to previous reports in Bangladesh and other countries [10,22,24,32,33]. Thus, it can be said that, *E. coli* is the most prevalent and leading UPs responsible for UTIs. Other common isolated pathogens found in the present study were *Staphylococcus*, *Klebsiella* and *Pseudomonas* along with *Citrobacter* only in non-diabetic; while *Enterococcus,* and *Acinobacteria* found in diabetic patients. The identified UPs of the present study showed similar results of the study by Akhtar et al. [34].

Our results showed that among non-diabetic patients, *E. coli* was found to be the most sensitive to imipenem (100%), meropenem (100%), amikacin (99.67%), gentamycin (91.03%) and nitrofurantoin (88%) respectively, while it was less sensitive to cefixime (44.5%), ciprofloxacin (40.5%) and levofloxacin (57.95%) respectively. The sensitivity pattern of *E. coli* showed in our study is similar to other relevant studies [30,34–36].

Our study showed profound changes in the degree of sensitivity of the studied antibiotics to the uropathogens due to the influence of diabetic condition (Fig. 4). These results are similar to the recent meta-analysis where a positive correlation with antibiotic resistance and diabetic condition in UTI patients was demonstrated [37]. Another study also showed declining of bacterial sensitivity in diabetic condition [38].

Studies conducted in Europe and Bangladesh [33,39], reported that the choice of the first line antibiotics for UTIs were nitrofurantoin followed by cephalosporins (ceftazidime, cefixime, ceftriaxone) and fluroquinolones (ciprofloxacin, levofloxacin) [28]. Unfortunately, those first-line treatments were found to have an alarmingly low sensitivity pattern to the UPs in developing countries

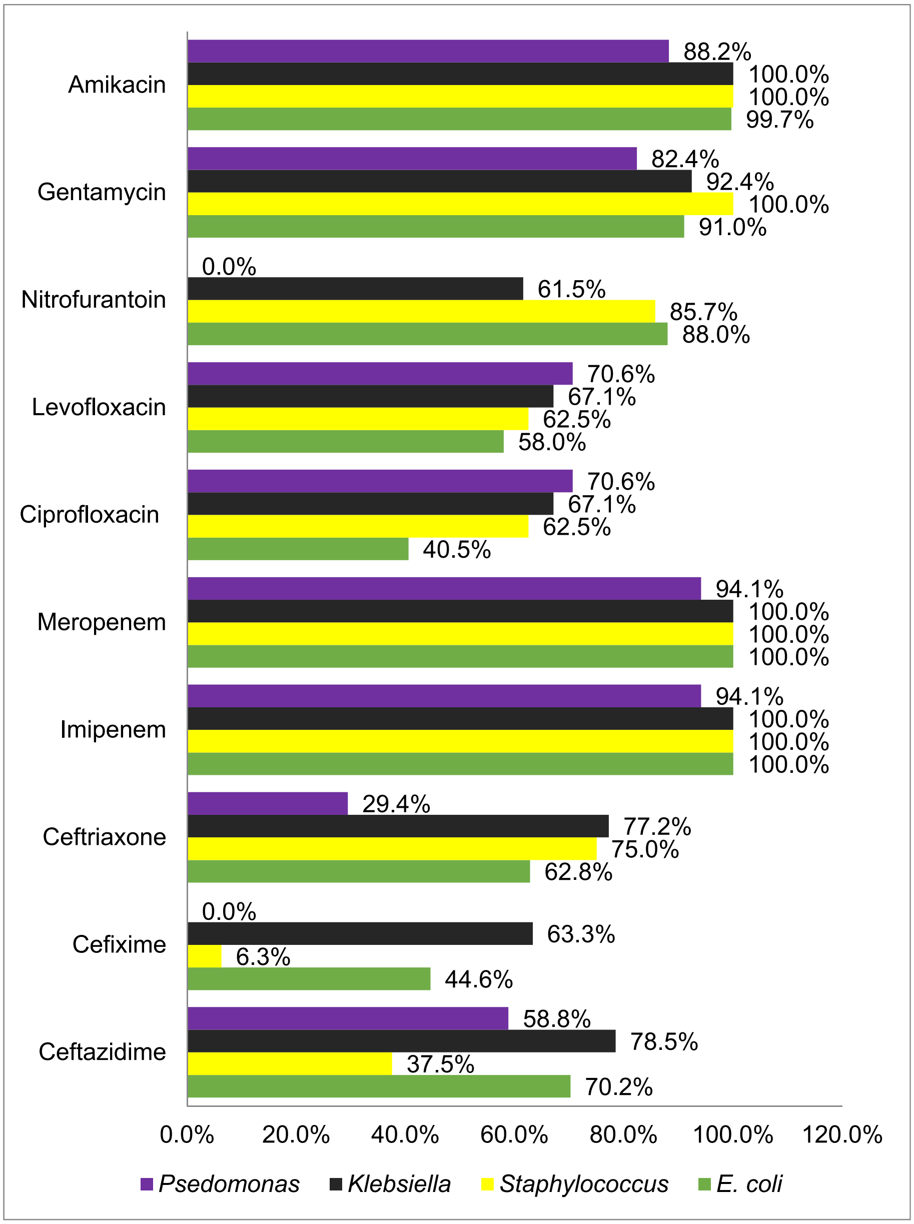

Fig. 2. Antibiotic sensitivity pattern of studied antibiotics against common UPs found among non-diabetic patients with UTIs. Data is expressed in percentile (%).

like Bangladesh. It may be due to antibiotic abuse, lack of patient's adherence, inadequate dose, physician's irrational prescribing habit and widespread antibiotics are used/sold as an OTC drug in Bangladesh [31,34]. The current prescription pattern of antibiotics for outpatients with UTI in Bangladesh reveals that antibiotics are given inappropriately without having culture sensitivity tests [33]. To treat UTIs (both uncomplicated and complicated), once ciprofloxacin (broad-spectrum molecule) was considered to be the most appropriate antibiotics of choice in Bangladesh which has already lost its effectiveness due to lack of rational selection of antibiotics. Similar pattern was perceived for cephalosporins (1st to 3rd generation) [31–33,40]. In this study, nitrofurantoin exhibited moderate sensitivity against *E. coli*, and was totally useless against *Pseudomonas* which however, does not correlate with Haque et al. [32], but displays similarity with other such studies [36,40].

We found indiscriminate use of antibiotics in primary healthcare systems in Bangladesh in our previous report [41]. We also reported lack of knowledge and awareness, non-adherence and self-prescription of antibiotics among Bangladeshi patients [42]. Our previous study not only elucidated unsafe and unnecessary use of injection medications (including antibiotics) but also showed many underlying factors including patients' demand, doctors' unethical practice, pursuance of drug companies and healthcare institutions are associated with indiscriminate use of medications [43]. All these provoke unsafe and irrational use of antibiotics, and contribute to

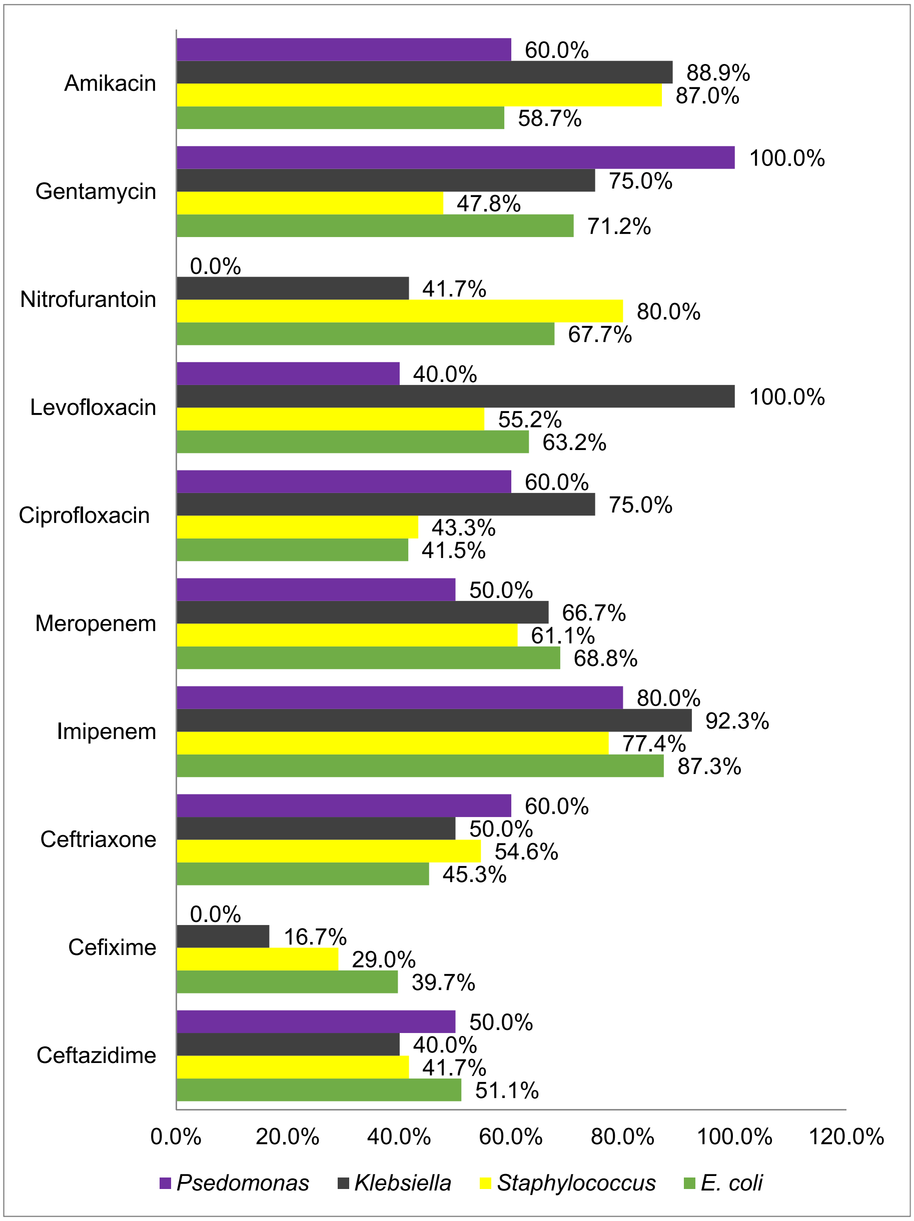

Fig. 3. Antibiotic sensitivity pattern of studied antibiotics against common UPs found among diabetic patients with UTIs. Data is expressed in percentile (%).

antibiotic resistance.

The influence of diabetic condition for the declining antibiotic sensitivity among UTIs patients remains unclear. Several studies provided possible mechanisms of the relationship of the declining antibiotic sensitivity and hyperglycemia in diabetic condition.

In diabetic patients, high level of sugar in urine makes favorable environment for bacterial colonization leading to lazy bladder which further promotes bacterial growth [44]. Diabetic medications including sodium glucose co-transporter 2 (SGLT2) inhibitors increase the risk of glycosuria and genital infections [45,46]. Glycosuria alters virulence in *Streptococcus agalactiae* resulting in increased bacterial confluence in the epithelium of the bladder, and increased desensitization to peptides LL37 which acts like orthodox antibiotics in human body. Besides, glycosuria causes profound biofilm growth and changes in virulence of *E. coli* in urogenital patients [47-49]. All of these factors contribute to bacterial resistance.

Hyperglycemia alters neutrophilic chemotaxis resulting in the weakened bacterial phagocytosis, and increased bacterial resistance in diabetic patients. Besides, in diabetes, persistence of defensive antibodies is diminished due to changes in humoral immune response [50]. Thus, diabetic patients are prone to infections and are certainly required to take more antibiotics leading to high chance of bacterial resistance [51].

Antibiotics	p-value (diabetic vs. non-diabetic patients)
Ceftazidime	0.0001
Cefixime	0.0202
Ceftriaxone	0.0073
Imipenem	0.0001
Meropenem	0.0001
Ciprofloxacin	0.8317
Levofloxacin	0.5001
Nitrofurantoin	0.0034
Gentamycin	0.0001
Amikacin	0.0001

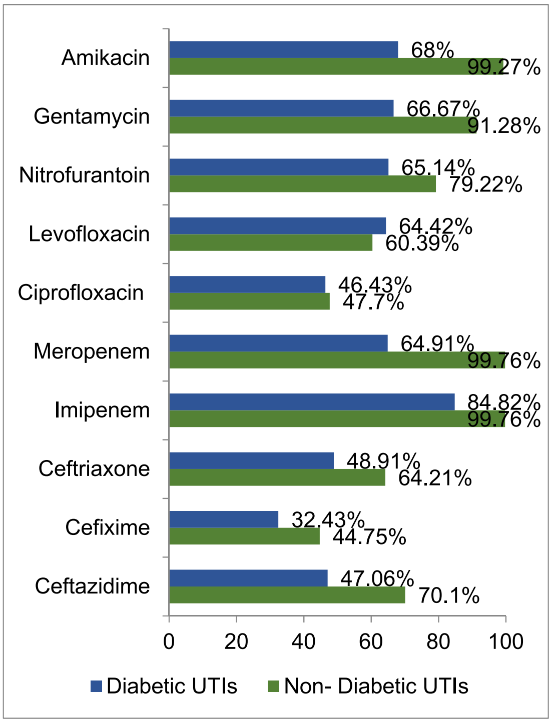

Fig. 4. A comparative antibiotic sensitivity pattern of studied antibiotics against common UPs found among diabetic and non-diabetic patients with UTIs. Data is expressed in percentile (%). p-value ≤ 0.05 is considered as statistically significant.

Moreover, current studies demonstrated pivotal role of insulin signaling in bacterial resistance. Usually, epithelium of the healthy urinary system release AMPs (antimicrobial proteins and peptides) which restrict the prevalence of uro-pathogen in kidney. In the diabetic condition (T2DM), antimicrobial defense system is interrupted due to compromised insulin-dependent AMPs [52,53]. Besides, antibiotics also showed low tissue permeability leading to the high chance of resistance in patients with diabetes and vascular diseases [54].

This report also unfolds some issues like irrational use of antibiotics, lack of continuously updated antibiogram and antibiotic use guideline, influence of marketing people, selling of antibiotics without prescription, patients' noncompliance to medicines, lack of graduate pharmacist for the prescription review and medicine dispensing and counselling [31,33,34,40–43,55], which are all linked to the antibiotic's resistance in Bangladesh. To resolve the issue, diagnosis-based (culture sensitivity test) definitive treatment should be encouraged rather than symptomatic treatment especially in diabetic patients with UTIs. Physicians should take proper training according to the WHO (world health organization) guideline for the rational use of medication. Antibiotic stewardship program should be implemented in the hospital. Besides, graduate pharmacist should be included in the healthcare management system for better medicine management especially for the drugs like antibiotics. Drug regulatory authority must take the lead role to stop selling of antibiotics without prescription in Bangladesh.

5. Conclusion

Our study demonstrated that antibiotics, including cephalosporin and fluroquinolone have shown decreased sensitivity to the UTI patients. Moreover, most effective antibiotics (such as imipenem and meropenem) also showed alarmingly less sensitivity to uro-pathogens found in diabetic patients with UTIs. We found statistically significant lower in sensitivity of the studied antibiotics in the diabetic patients with UTIs compared to non-diabetic patients.

This is the first ever report regarding the relationship of antibiotic sensitivity and diabetic condition in Bangladesh. We strongly believe that the results of the study will help medical practitioners for the formulation of new antibiotic treatment guideline and also will encourage rational use of antibiotics.

We must keep in mind that antibiotic resistance is not the issue for Bangladesh only but rather it's a global dilemma. So, we need to build an international outline, collaborate globally and enact a comprehensive antibiotic use monitoring system to win the battle.

5.1. Limitations

We did not measure the bioavailability of antibiotics in the studied population. We could not take medication histories and also could not document patients' histories like menstrual cycle (female patients) or type of bacterial flora in diabetic and nondiabetic

Table 2
Comparison of antibiotic sensitivity pattern of the common uro-pathogens found in non-diabetic and diabetic patients. Data expressed in number of isolates and p-value ≤0.05 is considered as statistically significant. *(≤0.05), **(≤0.001), ***(≤0.0001).

Antibiotics Studied		*E. coli*		*Staphylococcus*		*Klebsiella*		*Pseudomonas*	
		ND-UTIs	D-UTIs	ND-UTIs	D-UTIs	ND-UTIs	D-UTIs	ND-UTIs	D-UTIs
Ceftazidime	S	301	24	6	10	62	4	10	2
	R	128	23	10	14	17	6	7	2
p-value		**0.0124***		1.0000		**0.0167***		1.0000	
Cefixime	S	192	25	1	9	50	2	0	0
	R	239	38	15	22	29	10	17	5
p-value		0.4992		0.1307		**0.0036***		1.0000	
Ceftriaxone	S	270	24	12	12	61	6	5	3
	R	160	29	4	10	18	6	12	2
p-value		**0.0168***		0.3087		0.0742		0.3089	
Imipenem	S	301	55	16	24	79	12	16	4
	R	0	8	0	7	0	1	1	1
p-value		**0.0001*****		0.0782		0.1413		0.4113	
Meropenem	S	301	22	16	11	79	2	16	2
	R	0	10	0	7	0	1	1	2
p-value		**0.0001*****		**0.0080***		**0.0366***		0.0797	
Ciprofloxacin	S	122	27	10	13	53	9	12	3
	R	179	38	6	17	26	3	5	2
p-value		0.8901		0.3534		0.7455		1.000	
Levofloxacin	S	175	36	10	16	53	13	12	2
	R	127	21	6	13	26	0	5	3
p-value		0.5577		0.7565		**0.0165***		0.3089	
Nitrofurantoin	S	264	42	12	24	48	5	0	0
	R	36	20	2	6	30	7	17	5
p-value		**0.0002****		1.0000		0.2204		1.0000	
Gentamycin	S	274	37	16	11	73	9	14	3
	R	27	15	0	12	6	3	3	0
p-value		**0.0002****		**0.0004****		0.0939		1.0000	
Amikacin	S	300	37	16	20	79	8	15	3
	R	1	26	0	3	0	1	2	2
p-value		**0.0001*****		0.2551		0.1023		0.2098	

Abbreviations: ND-UTIs, uropathogens in non-diabetic patients; D-UTIs, uropathogens in diabetic patients; S, antibiotic sensitivity; R, antibiotic resistance.

patients.

Author contribution statement

Manik Chandra Shill, Hasan Mahmud Reza: Conceived and designed the experiments.
Md. Nurul Absar Bin Mohsin, Usha Showdagor, Sharif Nahid Hasan: Performed the experiments.
Md. Zahidul Islam Zahid, Sabrin Islam Khan: Analyzed and interpreted the data; Wrote the paper.
Murad Hossain: Analyzed and interpreted the data.
Ghazi Mohammad Sayedur Rahman: Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

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