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Original Article

Emergence of multidrug resistant and extensively drug resistant community acquired uropathogens in Dhaka city, Bangladesh.

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Abstract

Because of indiscriminate, inadequate and irrational usage of antimicriobials, the sensitivity pattern of community acquired uropathogens is changing drastically, specifically in developing countries, such as Bangladesh. This study was undertaken to investigate the profile of common uropathogens in community settings and to evaluate their antimicrobial resistance profile in order to categorize them into multidrug resistant (MDR), extensively drug resistant (XDR) and pandrug resistant (PDR) organisms.Total 800 urine samples were collected from symptomatic UTI cases and processed in the Department of Microbiology of DMC following standard microbiological methods. Antimicrobial susceptibility pattern was determined by Kirby Bauer Disc diffusion method following Clinical and Laboratory Standards Institute (CLSI) guidelines.Simultaneously, the percentage prevalence of MDR, XDR, and PDR isolates were alsodetermined. Out of the 800 urine samples screened, 150 (18.75%) samples yielded significant growth. The most common bacterial isolate was *Esch. coli* (60%), followed by Klebsiella species (13.33%). A significantly high resistance was noted to the beta-lactam group of antimicrobials, fluoroquinolones and cotrimoxazole, both by the gram-negative bacilli (GNB) as well as gram-positive cocci (GPC). However nitrofurantoinwas found to be most effective oral drug against both GNB and GPC. Out of total 150 bacterial strains studied, 106 (70.67%) bacterial strains were MDR, 21 (14%) strains were XDR, and no PDR was detected.So, close monitoring of MDR, XDR, or even PDR must be done by all clinical microbiology laboratories to implement effective measures to reduce the menace of antimicrobial resistance.

Key words: Antimicrobial resistance, Bangladesh, Extensively drug resistant, Multi drug resistant, Pan drug resistant, Uropathogens.

Introduction

In developing countries, UTI is a common experience in clinical practice. Each year up to 150 million individuals are affected by UTIs[1]. Colonization of normal and opportunistic microflora is main causal agent for UTIs. In the third world, causes behind high UTI patients are due to poor hygiene, long time catheterization, uncontrolled sexual intercourse, pregnancy and spermicidal contraception etc[2]. However, the causal organisms are easily predictable and UTI can be classified by different criteria. The most predominant uropathogens for UTIs are gram negative bacteria; particularly *Escherichia coli* are responsible for the high prevalence[3]. In those with frequent infections, low dose antibiotics may be taken as a preventative measure. For recurrent and complicated infections, intravenous daily antibiotics or prolonged antibiotics course may be effective. Unfortunately, several studies reported that many uropathogens became resistant to a wide range of antibiotics due to abuse, over dosage use, non-prescribed use, uncompleted dosages, and ease of access of antimicrobial-drugs[4]. The extensive and inappropriate use of antimicrobial agents has invariably resulted in the emergence of multidrug resistant (MDR), extensively drug resistant (XDR), and pan drug resistant (PDR) isolates that leaves few therapeutic options5. As per standardized international terminology created by European Centre for Disease Control (ECDC) and Centre for Disease Control & Prevention (CDC), Atlanta, the multidrugresistant (MDR), extensively drug resistant (XDR), and pan drugresistant (PDR) bacteria have been well defined[6]. Under such circumstances of extreme resistance towards

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antibiotics, the pathogens remain susceptible only to colistin and tigecyclineorcombination therapy[7]. However, with its increased use, we may actually trigger the resistant mechanisms against theseantibioticsin future leading to the end of the current era of pharmacopoeia[8]. Due to the continuous evolution of antibiotic resistance, regular monitoring of antibiotic resistance has become extremely necessary. In order to improve the antibiotic therapy, priorinformation about the most probable microorganisms and their susceptibilities according to the characteristics of the population must be known[9]. Given this background, this study was carried out to determine the prevalent uropathogens in community settings and to evaluate their antimicrobial resistance profile in order to categorize them into MDR, XDR and PDR organisms.

Materials and Methods

This prospective cross sectional study was carried out over a period of one year from January 2014 to December 2014 in the Department of Microbiology of Dhaka Medical College (DMC), Dhaka.Approval was obtained from institutional ethical committee according to the Declaration of Helsinki and national and institutional standards. Urine samples of clinically suspected UTI patients who attended to outpatient departments were processed in the Department of Microbiology of DMC for culture irrespective of age, sex and antibiotic intake were included in this study.Informed written consent was taken from each participant prior to collecting sample.With all aseptic measures clean catch mid-stream urine collection technique was applied to collect 12 ml of urine sample from each patient. Urine samples were processed within 2 hours of collection and, in case of delay, the samples were refrigerated at 2-8°C for up to 6 hours. Two ml of urine was transferred aseptically from each sample in a sterile test tube for culture. A 10 ml aliquot of urine was centrifuged at 3000 rpm for five minutes. The supernatant was discarded. Then the sediment was remixed by tapping the bottom of the tube. One drop of the well mixed sediment was placed on a clean glass slide, covered with a cover slip and examined under light microscope. Cut off values for positive result was ≥5 pus cells/HPF. Urine samples with pus cells ≥5/HPF were inoculated onto the blood agar and MacConkey agar media by the semi-quantitative plating method using the calibrated loop technique (0.001 ml).Plates were incubated aerobically overnight at 37°C. Pure growth of an isolate in a count of $\geq 10^5$ colony forming units (CFU) per milliliter of urine was considered as significant bacteriuria. All the organisms were identified by colony morphology, hemolytic criteria, staining character, pigment production and biochemical tests as per standard techniques[10]. Mueller-Hinton agar was used for antimicrobial susceptibility testing (AST) following Kirby-Bauer disc diffusion methodas per Clinical and Laboratory Standard Institute Guidelines[11].Antibiotics used for gram positive cocci (GPC)were oxacillin, levofloxacin, vancomycin, linezolid, amoxiclav, ceftriaxone, azithromycin, gentamicin, ciprofloxacin, nitrofurantoin and for gram negative bacilli (GNB) were ceftazidime, ceftriaxone, cefuroxime, imipenem,amoxiclav, ciprofloxacin, gentamicin, co-triamoxazole, azithromycin, nitrofurantoin, and colistin respectively. *Escherichiacoli* ATCC 25922 and Staphylococcus aureusATCC 25923 wereused as control strains to assess the performance of the method.The antibiotic resistance pattern of individual isolates was evaluated and then the isolates were categorized as MDR, XDR and PDR.

MDR, XDR and PDR isolates were identified according to the guidelines recommended by joint initiative of the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC)[6]. According to the guidelines,Multidrug resistant (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories (such as, aminoglycosides, tetracycline, carbapenem, cephalosporine, fluoroquinolones, phosphonic acids, glycylcycline, monobactams, polymyxins).Extensively drug resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories and pandrugresistant (PDR) was defined as non-susceptibility to all agents in all above mentioned antimicrobial categories[6].

Data were analyzed by using Microsoft Excel (2007) software (Microsoft, Redmond, WA, USA).

Results:

A total of 800 patients were enrolled and provided a urine sample. Of these, 150 (18.75%) were culture positive, 100 (67%) were female and 50 (33%) were male and the ratio between female and male was 2:1. Frequency of UTI in case of female was found highest (45%) in age group of 16-30 years followed by 38% in age group of 31-45 years. In case of male, the peak of UTI was found (32%) in age group of >60 years. Out of 150 culture positives, we isolated 92% (n=138) gram negative bacilli (GNB) and 8% (n=12) gram positive cocci (GPC). *Esch. coli* was the most predominant (60%) isolate followed by *Klebsiella spp*. (13.33%) and *Citrobacter spp.* (6.67%) (Table 1).

Table 1. Bacteria isolated from urine culture.

Bacteria	Number (%)
Esch. coli	90 (60)
Klebsiella spp.	20 (13.33)
Citrobacter spp.	10 (6.67)
Pseudomonas spp.	8 (5.33)
Proteus spp.	5 (3.33)
Esch. fergusonii	2 (1.33)
Acinetobacter spp.	1 (0.67)
Enterobacter spp.	2 (1.33)
Staphylococcus aureus	8 (5.33)
CONS*	4 (2.67)
Total	150 (1000)

* CONS= Coagulase negative Staphylococcus

Very high frequency of resistance ranging from 75.56% to 90% to cotrimoxazole, ciprofloxacin, cefuroxime, azithromycin, amoxiclav, ceftriaxone, ceftazidime, moderately high resistance to gentamicin (40 to 50%) and low resistance to imipenem (10% to 25%) and nitrofurantoin (10% to 25.56%) were shown by gram negative bacilli (Table 2).

Table 3. Antibiotic resistance pattern of isolated gram-positive cocci (n=12)

Antibiotic	*Staphylococcus aureus* (n=8) (%)	CONS (n=4) (%)
Amoxiclav	4 (50)	2 (50)
Ceftriaxone	4 (50)	2 (50)
Azithromycin	6 (75)	2 (50)
Nitrofurantoin	2 (25)	0 (0)
Oxacillin	3 (37.5)	0 (0)
Levofloxacin	5 (62.5)	2 (50)
Vancomycin	0 (0)	0 (0)
Linezolid	0 (0)	0 (0)
Ciprofloxacin	6 (75)	2 (50)
Gentamicin	3 (37.5)	0 (0)

Out of total 150 bacterial strains studied, 106 (70.67%) bacterial strains were MDR and 21 (14%) strains were XDR.

Table 2. Antibiotic resistance pattern of isolated gram negative bacilli (n=138).

Antimicrobial drugs	*Esch. coli* (n=90) (%)	*Klebsiella* spp (n=20) (%)	*Citrobacter* spp (n=10) (%)	*Pseudomonas* spp (n=8) (%)	*Proteus* spp (n=5) (%)	*Esch. fergusonii* (n=2) (%)	*Acinetobacter* spp. (n=1) (%)	*Enterobacter* spp. (n=2) (%)
Amoxiclav	68 (75.56)	14 (70.00)	6 (60.00)	6 (75.00)	3 (60.00)	0 (0.00)	1 (100.00)	0 (0.00)
Ceftriaxone	68 (75.56)	14 (70.00)	7 (70.00)	6 (75.00)	3 (60.00)	0 (0.00)	1 (100.00)	1 (50.00)
Ceftazidime	63 (70.00)	14 (70.00)	6 (60.00)	5 (62.50)	2 (40.00)	0 (0.00)	0 (0.00)	0 (0.00)
Cefuroxime	63 (70.00)	14 (70.00)	7 (70.00)	6 (75.00)	2 (40.00)	0 (0.00)	0 (0.00)	1 (50.00)
Azithromycin	68 (75.56)	15(75.00)	7 (70.00)	6 (75.00)	3 (60.00)	0 (0.00)	-	1 (50.00)
Ciprofloxacin	72 (80.00)	15 (75.00)	6 (70.00)	4 (50.00)	3 (60.00)	0 (0.00)	0 (0.00)	0 (0.00)
Cotrimoxazole	81 (90.00)	19 (95.00)	9 (90.00)	7 (87.50)	4 (80.00)	0 (0.00)	1 (100.00)	1 (50.00)
Gentamicin	36 (40.00)	10 (50.00)	3 (30.00)	4 (50.00)	2 (40.00)	0 (0.00)	0 (0.00)	0 (0.00)
Nitrofurantoin	23 (25.56)	5 (25.00)	1 (10.00)	2 (25.00)	1 (20.00)	0 (0.00)	-	0 (0.00)
Imipenem	13 (14.44)	5 (25.00)	1 (10.00)	1 (12.50)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Colistin	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Note: '-' = not used

Among gram positive cocci commonly isolated Staphylococcus aureusshowed maximum resistance to ciprofloxacin and azithromycin (75%,) levofloxacin (62.5%), ceftriaxone and amoxiclav(50%), oxacillin and gentamicin (37.5%), with no resistance to vancomycin, and linezolid (Table 3).

Amongst 138 GNB isolates, 98 (71%) and 20 (14.5%) were MDR and XDR, respectively. Out of 12 GPC isolates, 8 (66.67%) were MDR and 1 (8.33%) wasXDR. No PDR strain was detected (Figure 1).

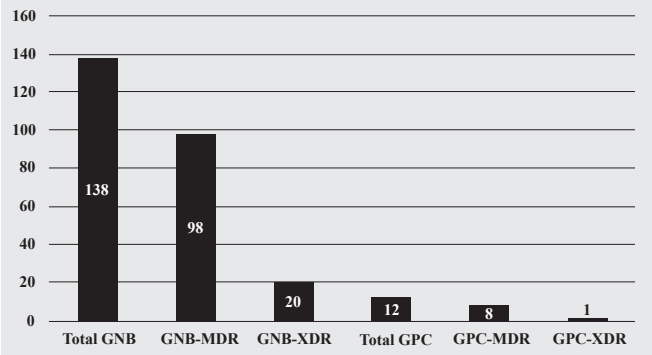

Figure 1: Incidence of MDR and XDR among total bacterial strains studied (n=150)

Discussion:

Antibiotic resistance is a worldwide problem that can cross international boundaries and spread between continents very easily and speedily. World health readers have described antibiotic resistant organisms as "nightmare bacteria" that pose a "catastrophic threat" to people inevery country in the world. The use of antibiotic is the single most important factor leading to antibiotic resistance around the world[12].The emergence of antibiotic resistance in the management of UTI is a serious public health issue, particularly in the developing countries where apart from high level of poverty, ignorance and poor hygienic practices, there is also high prevalence of fake and spurious drugs of questionable quality in circulation[13]. Besides, antibiotics are available over the counter in all over Bangladesh which contributes to the misuse and overuse of antibiotics by the common people[14] resulting treatment failure, increased length of hospital stay, increase in term and magnitude of morbidity, high rates of mortality, high treatment costs and above all the emergence of drug resistance[15]. Hence to avoid the emergence of bacterial resistance knowledge about common uropathogens and their regional susceptibility pattern is crucial to optimize the therapeutic strategy.

The culture-positive rate was 18.75% (150/800) in the present study, and a similar culture-positive rate has been observed inother studies16,17.Majority of uropathogens were GNB (92%) followed by GPC (8%) and *Esch. coli* remain the leading uropathogen being responsible for 60% of community acquired UTIs in our area which are in accordance with other studies[18,19,20,21]. It is documented that UTI is more common in females than in males and findings of our investigation are also in agreement with this generalization[22]. The reasons for women to be more susceptible to UTI are due to shortness of urethrae, close proximity of urethrae with vagina and anus which makes them more prone to get infection from perineal colonization and after sexual intercourse[23]. Frequency of UTI in female was found highest (38%-45%) in age group of 16-45 years. It has been reported that women of ages between 20-40 years, 25%-35% have had a UTI [24] which merges with the results of our study. In case of male, the peak of UTI was found (32%) in age group of >60 years. Prostatic gland enlargement and decrease of bacteriostatic prostatic secretions might account for such infections[25].

Increasing drug resistance is a great concern to common bacterial infections including UTI. Still antimicrobial agents like amoxicillin-clavulanate, cotrimoxazole, ciprofloxacin, azithromycin are in place to treat many gram-positive and gram-negative bacterial infections including UTI in many underdeveloped and developing countries including Bangladesh. Unfortunately all these agents were found to have unacceptable range of antimicrobial activity to uropathogens isolated in our setting. This finding is alarming in regards to the choice of effective therapeutic options in the treatment of community acquired UTI and obviously a great concern to treating physicians.

Ciprofloxacin was once considered to be the drug of choice for uncomplicated and complicated UTI but due to lack of rational use, this broad spectrum molecule has entirely lost its efficacy not only in UTI but to other common infections too. Similar picture is also noted in case of β-lactam antibiotics. Our study confirms the global trend towards increased resistance to β-lactam antibiotics. Nitrofurantoin was found to be reasonably high efficacious agent among all antimicrobials used to almost all uropathogens in the current setting and similar results were also reported from other studies[26,27]. This is good news indeed especially for uncomplicated UTI and prophylaxis in the context of gradually decreasing susceptibility of most of the comparatively cheaper oral anti-UTI drugs. Low antimicrobial resistance for nitrofurantoin can be attributed to its localized action on urinary tract and not being exposed outside urinary tract[28]. Though moderate to high susceptibility was also noted for gentamicin and imipenem for most of the uropathogens which is comparable to nitrofurantoin but one has to remember that their uses are limited due to parenteral route and patient's noncompliance. Gram positive cocci were found to be highly resistant to ciprofloxacin, azithromycin, and levofloxacin. Vancomycin, linezolid showed to be highly effective drug followed by nitrofurantoin, also showed by other studies[17,29].

Another important finding of the study is that a very high percentage of MDR uropathogens (70.67%) are existing in our setting with a considerable number of extensively drug resistant pathogens (14%). Such high level of multidrug resistance among uropathogens have also been reported from

other studies[5,30]. Hence, detection and prevention of transmission of MDR organisms by following infectioncontrol practices, antimicrobial surveillance, and stewardship are need of the hour. Research should be done for the development ofsafe antibiotics for the treatment of these kinds of infections. Legislative changes should be made if necessary to prevent irrational use of antibiotics. At the same time clinicians should be trained about the rational use of antibiotics[31].

Conclusion:

Our study had given an overview of the common uropathogens in community settings. Most useful antibiotic wasnitrofurantoin effective against both gram negative and gram positive organisms can be given orally highlighting the main advantage in UTI patients. As imipenem was the most promising drug among gram negative and vancomycin among gram positives, can be considered as the alternative option in the empirical treatment of UTI. Moreover high level of MDR and emergence of XDR strains were observed. Hence it is our responsibility to prevent the development of MDR, XDR and potential PDR organisms, which will be impossible to handle with the low availability of new and broader spectrum antibiotics in the development pipeline. Closemonitoring of MDR, XDR, or even PDR must be done by all clinical microbiology laboratories to implement effective measures toreduce the menace of antimicrobial resistance.

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