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Antibiotic resistance pattern in pregnant women with urinary tract infections in a tertiary care Indian teaching hospital

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Abstract

Back ground: Urinary tract infections (UTIs) are one of the most common bacterial infections in women. During pregnancy physiological changes, like frequency, mimic UTI symptoms and therefore bacteriological cultures are needed to confirm the diagnosis. However, in developing countries antibiotic therapy is commonly initiated without culture confirmation.

Methods: We have screened bacteriuria among pregnant women with and without UTI symptoms in a tertiary care teaching hospital. A total of 1000 urine samples were evaluated with nitrite and leukocyte esterase tests, using urine culture and/or dipslide with species identification as reference.

Results: The prevalence of culture-proven UTI among pregnant women with UTI symptoms was 4%. Since treatment is initiated based only on the presence of symptoms, 96% were erroneously given antibiotics. Further, there is a high prevalence of resistance to commonly used antibiotics, with 18% ESBL and 36% multidrug resistant *Escherichia coli* strains. With culture morphology and biochemical tests were mostly able to identify *E. coli* and negative cultures. Mixed Gram-negative flora, suggesting fecal contamination was, however, in the majority of cases interpreted as a single pathogenic bacterium and would have resulted in antibiotic treatment.

Conclusions: To prevent excessive use of antibiotics, dipslide possibly supported by a combination of nitrite and leukocyte esterase tests can be used. Trained frontline health care professionals correctly diagnosed *E. coli* UTI and negative urine cultures, which would help preventing antibiotic misuse. In addition, regular screening for antibiotic resistance would improve correct treatment.

Keywords: Urinary tract infections; *E. coli*; antibiotics; pregnant women, India

Introduction

Urinary tract infections (UTIs) belong to the most common bacterial infections worldwide, primarily affecting women and are a frequent indication for antibiotic therapy [1]. In contrast, asymptomatic bacteriuria (ABU), is often benign and does not require antibiotic therapy in nonpregnant and otherwise healthy women [2]. However, during pregnancy, 25–30% of pregnant women with ABU are at risk of developing acute pyelonephritis [3], associated with complications such as preterm birth [4]. Although screening for and antibiotic treatment of ABU in pregnant women to reduce the risk of acute pyelonephritis is common in developed countries [5], the beneficial effects of such an intervention have recently been questioned [6]. In nonpregnant women, management of uncomplicated UTI relies on clinical diagnosis and empiric antibiotic therapy [7]. During pregnancy, physiological changes, such as micturation frequency, and during the later part of the pregnancy, also nocturia and suprapubic pain [8], may mimic UTI. Therefore, bacteriological diagnosis is particularly important during pregnancy, especially because antibiotic exposure in utero may have deleterious effects on the fetus [9]. However, in countries like Bhubaneswar, with limited diagnostic resources, diagnosis of UTI is based on clinical symptoms. Moreover, midwives hand out antibiotics free of charge to pregnant women with suspect UTI. The extensive and widespread use of antibiotics, dispensed without prescription, is a leading cause of resistance among pathogenic bacteria, thus complicating management of infections in the long run [10]. *Escherichia coli* and other Enterobacteriaceae account for the majority of UTI [11]. We recently reported high antibiotic resistance among *E. coli* isolates from Bhubaneswar compared to those from Sweden [11], further demonstrating this relation. The increasing antibiotic resistance calls for deliberate actions to change the current treatment policy.

We speculate that a high proportion of pregnant women with lower UTI symptoms receive antibiotics without having an infection. The limited diagnostic services available in Bhubaneswar and other low-income countries, leading to overconsumption of antibiotics, is likely an important reason promoting the high prevalence of antibiotic resistance. We here investigate the prevalence of bacteriuria in pregnant women with and without symptoms consistent with lower UTI and the antibiotic susceptibility of *E. coli* isolates in relation to the empirically prescribed antibiotics in Bhubaneswar. Further, the reliability of nitrate and leukocyte esterase tests, as well as microscopy for identification of bacteriuria in pregnant women, and lastly, the possibility to use point of care dipstick for urine culture in areas without clinical laboratories were investigated.

Materials and methods

A total of 395 urine samples from pregnant women with or without having symptoms of UTI were collected during October 2012 to January 2014. The age of people included in the study ranged from 25-40 years. Verbal informed consent from target population and approval from institutional research ethical committee were obtained before starting the experiment.

Female patients aged between 25-40 years with uncomplicated UTI symptoms like frequency, urgency and dysuria were included in the study. Pregnant women on antibiotics within the last 2 weeks and those who could not give consent to participate in the study were excluded. Clean catch midstream urine samples were collected into a sterile screw capped universal container by standard method. The samples were labeled and 0.2 mg of boric acid was added to prevent the bacterial growth in urine samples. The samples were cultured on cysteine-lactose electrolyte deficient agar and blood agar using a sterile 4 mm platinum wired calibrated loop for the isolation of microorganisms. The plates were incubated for overnight at 37 °C and the samples were considered positive when an organism was cultured at a concentration of 10⁴ CFU/mL which was estimated through multiplying the isolated colonies by 1 000. The isolates were identified up to the species level by standard biochemical tests [15].

Antibiotic sensitivity testing was performed by the modified disc diffusion method as per the recommendations [16]. Inoculums adjusted to 0.5 McFarland standard was swabbed on Mueller Hinton agar plates for antibiotic sensitivity assay. Eight groups of antimicrobials such as penicillins, cephalosporins, fluoroquinolones, aminoglycosides, macrolides, lincosamides, glycopeptides and sulfonamides were selected based on frequent prescription and used in this study. Among the group, the antibiotics tested were amoxicillin (10 µg), oxacillin (10 µg), cloxacillin (5 µg), cefotaxime (10 µg), ceftriaxone (30 µg), nalidixic acid (30 µg), ciprofloxacin (5 µg), norfloxacin (10 µg), amikacin (30 µg), gentamycin (10 µg), erythromycin (10 µg), clindamycin (2 µg), vancomycin (30 µg) and co-trimoxazole (30 µg). Statistical analysis was done using Chi-square test and student's t-test.

Results

Among the 1000 samples collected, 180 were laboratory confirmed cases of UTI with a positive culture percentage of 46.6% (Table 1). The age of the pregnant women ranged from 25-40 years. Majority (50.6%) of the study participants

were in the age group of 30-34 years. The highest UTI were observed at third trimester gestational age (n=103; 57.2%). From the 180 isolates, 154 were Gram negative while 26 were Gram positive bacteria (Figure 1). *Escherichia coli* (*E. coli*) was the most common organism isolated accounting for 79 (43.9%) and the second highest organism was *Klebsiella oxytoca* (*K. oxytoca*) (n=35; 19.4%) followed by *Klebsiella pneumoniae* (*K. pneumoniae*) (n=24; 13.3%). The other bacterial isolates obtained in the study were *Enterococcus faecalis* (*E. faecalis*), *Staphylococcus saprophyticus* (*S. saprophyticus*), *Staphylococcus aureus* (*S. aureus*), *Proteus mirabilis* (*P. mirabilis*), *Proteus vulgaris* (*P. vulgaris*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Citrobacter koseri* (*C. koseri*) and *Citrobacter amalonaticus* (*C. amalonaticus*).

The frequency of occurrence of other bacterial isolates were *E. faecalis* (n=12; 6.7%), *S. saprophyticus* (n=10; 5.5%), *P. mirabilis* (n=9; 5.0%), *S. aureus* (n=4; 2.2%), *P. aeruginosa* (n=3; 1.7%), *P. vulgaris* (n=2; 1.1%), *C. koseri* (n=1; 0.6%) and *C. amalonaticus* (n=1; 0.6%). Antibiotic sensitivity pattern of the bacterial isolates revealed that *E. coli* with 89.9% sensitivity to amikacin, 83.5% to co-trimoxazole, 79.7% to clindamycin and 77.2% to ciprofloxacin (Table 2). The antibiotics which had poor activity against *E. coli* were cloxacillin (13.9%), gentamycin (12.6%), vancomycin (8.9%), erythromycin (7.6%), amoxicillin (5.1%) and oxacillin (2.5%). *K. oxytoca* showed 88.5% sensitivity to ciprofloxacin and 62.8% to nalidixic acid while sensitivity to erythromycin was 0%. Most of the antibiotics were effective against *K. pneumoniae* with co-trimoxazole has significant activity (91.6%) followed by cefotaxime (83.3%). Gross 100% sensitivity was noted on nalidixic acid against *E. faecalis* and *P. mirabilis*. *S. saprophyticus* was 90% sensitive to co-trimoxazole and 80% to nalidixic acid, clindamycin and vancomycin. A complete 100% sensitivity to cefotaxime and clindamycin was observed with *P. aeruginosa*, *P. vulgaris*, *C. koseri* and *C. amalonaticus*. The isolated uropathogens revealed the presence of high levels of single and multiple antimicrobial resistances against commonly prescribed drugs as shown in Table 3. Amikacin had the highest overall sensitivity (n=138; 76.7%) against the 180 isolates tested. This was followed by ciprofloxacin (n=132; 73.3%) and clindamycin (n=124; 68.9%). Cefotaxime and nalidixic acid were exhibited 65.0% and 63.9% sensitivity against the isolates. Ceftriaxone had the overall sensitivity of 52.8%. The other antibiotics were recorded lesser than 50% of the sensitivity as follows: co-trimoxazole 45.0%, cloxacillin 31.6%, oxacillin 31.1%, norfloxacin 29.4%, vancomycin 28.9%, amoxicillin.

Table 1: Characteristics of UTI in pregnant women.

Variables		Numbers (n=180)	
		Percentage	
Age	25-29 years	87	48.3
	30-34 years	91	50.6
	≥	2	1.1
Gestational period	35 years		
	First trimester	21	11.7
	Second trimester	56	31.1
	Third trimester	103	57.2

Table 2: Antibiotic sensitivity pattern of urinary isolates. n(%).

Antibiotic	<i>E. coli</i>	<i>K. oxytoca</i>	<i>K. pneumoniae</i>	<i>E. faecalis</i>	<i>S. saprophyticus</i>	<i>P. mirabilis</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>P. vulgaris</i>	<i>C. koseri</i>	<i>C. amalonaticus</i>
Amoxicillin (10 µg)	4 (5.1)	11 (31.4)	8 (33.3)	9 (75.0)	7 (70.0)	7 (77.7)	2 (50.0)	2 (66.6)	0 (0.0)	0 (0.0)	1 (100.0)
Oxacillin (10 µg)	2 (2.5)	12 (34.2)	16 (66.7)	9 (75.0)	7 (70.0)	6 (66.6)	1 (25.0)	2 (66.6)	0 (0.0)	0 (0.0)	1 (100.0)
Cloxacillin (5 µg)	11 (13.9)	8 (23.0)	10 (41.6)	11 (91.6)	3 (30.0)	8 (88.9)	3 (75.0)	1 (33.3)	1 (50.0)	0 (0.0)	1 (100.0)
Cefotaxime (10 µg)	53 (67.0)	17 (48.5)	20 (83.3)	7 (58.3)	4 (40.0)	8 (88.9)	1 (25.0)	3 (100.0)	2 (100.0)	1 (100.0)	1 (100.0)
Ceftriaxone (30 µg)	47 (59.5)	8 (22.8)	15 (62.5)	7 (58.3)	6 (60.0)	8 (88.9)	0 (0.0)	2 (66.6)	1 (50.0)	1 (100.0)	0 (0.0)
Nalidixic acid (30 µg)	38 (48.1)	22 (62.8)	17 (70.8)	12 (100.0)	8 (80.0)	9 (100.0)	3 (75.0)	2 (66.6)	2 (100.0)	1 (100.0)	1 (100.0)
Ciprofloxacin (5 µg)	61 (77.2)	31 (88.5)	11 (45.8)	8 (66.6)	6 (60.0)	8 (88.9)	2 (50.0)	3 (100.0)	1 (50.0)	1 (100.0)	0 (0.0)
Norfloxacin (10 µg)	45 (56.9)	10 (28.6)	14 (58.3)	9 (75.0)	4 (40.0)	6 (66.6)	1 (25.0)	2 (66.6)	1 (50.0)	1 (100.0)	1 (100.0)
Amikacin (30 µg)	71 (89.9)	18 (51.4)	19 (79.1)	9 (75.0)	5 (50.0)	8 (88.9)	3 (75.0)	2 (66.6)	2 (100.0)	0 (0.0)	1 (100.0)
Gentamycin (10 µg)	10 (12.6)	5 (14.2)	17 (70.8)	4 (33.3)	5 (50.0)	3 (33.3)	2 (50.0)	2 (66.6)	1 (50.0)	0 (0.0)	0 (0.0)
Erythromycin (10 µg)	6 (7.6)	0 (0.0)	7 (29.1)	5 (41.6)	7 (70.0)	4 (44.4)	3 (75.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
Clindamycin (2 µg)	63 (79.7)	18 (51.4)	10 (41.6)	9 (75.0)	8 (80.0)	6 (66.6)	3 (75.0)	3 (100.0)	2 (100.0)	1 (100.0)	1 (100.0)
Vancomycin (30 µg)	7 (8.9)	3 (56.0)	18 (75.0)	8 (66.6)	8 (80.0)	2 (22.2)	4 (100.0)	1 (33.3)	1 (50.0)	0 (0.0)	0 (0.0)
Co-trimoxazole (30 µg)	66 (83.5)	20 (57.1)	22 (91.6)	10 (83.3)	9 (90.0)	6 (66.6)	3 (75.0)	3 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)

Table 3: Antibiotic sensitivity pattern of the isolates.

Antibiotics		Frequency	Percentages	
			Sensitive	Resistance
Penicillin	Amoxicillin	51	28.3	71.7
	Oxacillin	56	31.1	68.9
	Cloxacillin	57	31.6	68.4
Cephalosporin	Cefotaxime	117	.	.
	Ceftriaxone	95	52.8	47.2
Fluoroquinolones	Nalidixic acid	115	63.9	36.1
	Ciprofloxacin	132	73.3	26.7
	Norfloxacin	53	29.4	70.6
Aminoglycosides	Amikacin	138	76.7	23.3
	Gentamycin	49	27.2	72.8
Macrolide	Erythromycin	33	18.3	81.7
	Clindamycin	124	68.9	31.1
Lincosamides	Vancomycin	52	28.9	71.1
Glycopeptide	Co-trimoxazole	81	45.0	55.0

Discussion

Clinical diagnosis and empiric antibiotic therapy of UTI among pregnant women lead to massive antibiotic misuse, inadvertently rendering the first line of drugs ineffective. Diagnostic tests, easy to carry out and evaluate also by inexperienced staff, are therefore necessary. In this study, we investigated a total of 2 562 patients for bacteriuria. Of these 1 621 were urine samples from pregnant women in IMS and SUM Hospital, Bhubaneswar with and without UTI symptoms, in order to verify the prevalence of cystitis and ABU. Because physiological changes during pregnancy might cause symptoms similar to cystitis, a low frequency of bacteriologically confirmed UTI among patients with symptoms was anticipated. Although the prevalence of UTI among pregnant women in our study is close to those reported regionally [17, 18], it is particularly alarming that our observations show that as many as 96% of patients are routinely treated with antibiotic therapy that they do not require. The positive correlation between antibiotic misuse

and development of drug resistance [19] may in part explain the high antibiotic resistance seen in developing countries as we and others have demonstrated [11, 20]. To improve the diagnosis, we evaluated nitrite and leukocyte esterase tests and a simplified culture method, dipslide. In line with previous reports, nitrite and leukocyte esterase tests alone demonstrated insufficient diagnostic value in this study. The combined results of these 2 tests demonstrated acceptable specificity and low sensitivity but were still of limited value. Although the nitrite test had high specificity, the sensitivity was low, especially among pregnant women, which is line with other studies [21] and may relate to frequent urination leading to reduced bacterial concentration. Further, presence of vitamin C in urine is another confounding factor [22], which cannot be ruled out among our patients. During pregnancy, the specificity of urinary leukocytes as an indicator for bacteriuria per se might be questionable because of elevated urine specific gravity that may give false negative results [22]. Similarly, low sensitivity was

obtained in urine samples collected from nonpregnant women. Moreover, false negative results have been reported with common antibiotics like cephalosporins^[23]. Also, the poor correlation between enzymatic activity and microscopic detection of leukocytes in urine is a major concern. Even though microscopy is regarded as the golden standard for this analysis, high variability between replicate leukocyte counts suggest that the analysis suffers substantial drawbacks, when performed in the clinical setting. Moreover, false negative results might be due to cell lyses if analysis is delayed. In addition, microscopic analyses of leukocyturia are time consuming if carried out with care. Taken together, detection of leukocytes especially using microscopy but also leukocyte esterase test are poor markers for the detection of UTI particularly among pregnant women and is in line with previous studies^[24, 25]. The use of dipslide culture was, on the other hand, particularly rewarding in urine samples with no bacterial growth. These samples constitute the majority and were correctly diagnosed. Therefore, even in the hands of inexperienced healthcare providers this would substantially decrease the antibiotic use. The identification of *E. coli* and other Enterobacteriaceae was also satisfactorily evaluated with the dipslide test even with inexperienced medical doctors and nurses. This can in part be attributed to the *E. coli*-specific agar containing β glucuronidase, resulting in a color change. However, false negative results can occur in rare cases if the strain lacks the enzyme^[13]. Also, false positive results may occur among *Citrobacter* spp.^[26]. Interestingly, we demonstrated that nurses with very limited training, and with no access to a professional microbiological laboratory or expert personnel, correctly diagnosed *E. coli* UTI in almost 80% of cases. To accurately define mixed fecal flora using dipslide^[27] was problematic, and the nurses prescribed antibiotics in 91% of such cases. In the current study, contamination was observed in 5%, whereas others have demonstrated up to 10%^[28], which would implicate risk of overinterpretation. Another drawback for dipslide culture especially among pregnant women is the failure to detect GBS, which is in line with observations made employing 2-medium dipslides^[29]. Treatment recommendations differ between countries. In IMS and SUM Hospital, Bhubaneswar, pregnant women with UTI receive amoxicillin, amoxicillin/clavulanic acid, or cephalexin without laboratory verification and susceptibility testing, whereas nitrofurantoin or amoxicillin are recommended in Kenya, Tanzania, and Rwanda^[30-32]. The use of nitrofurantoin and pivmecillinam are also recommended by international guidelines^[33]. In our study, *E. coli* was highly resistant to many of the drugs used for treatment of pregnant women like 66% resistant to ampicillin (amoxicillin), 38% to amoxicillin/clavulanic acid, and 18% to cephalexin, which decreases the treatment options. In addition, we report a high ESBL prevalence (18%), even higher than the general ESBL prevalence in Africa^[34]. As a consequence, almost all pregnant women presenting with UTI symptoms will receive antibiotics either not indicated at all or with high risk of being ineffective. International and East African regional guidelines recommend nitrofurantoin and during the last 2 trimesters also pivmecillinam. An appropriate alternative would therefore be nitrofurantoin or pivmecillinam, where low resistance is observed^[30-33].

The high antibiotic consumption proves the importance of continuously reviewing the susceptibility pattern of uropathogens. It also calls for diagnostic methods possible to use in clinics with no access to laboratory service. To the best of our knowledge, this is the first study investigating the practicability of the dipslide culture test under clinically relevant conditions in a low-resource country. To introduce dipslide in clinical routine, possibly supported with nitrite and leukocyte esterase tests would substantially reduce the misuse of antibiotics. Healthcare professionals can learn to correctly evaluate samples with no bacterial growth. Compared to clinical diagnosis alone, the use of dipslide would imply substantially decreased antibiotic consumption and as a consequence decreased risk for development of resistance among bacterial pathogens. The massive amount of saved antibiotics might furthermore outweigh, at least in part, the costs associated with the increased diagnostic efforts.

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