Journal of Infection and Public Health (2016) 9, 308—314

http://www.elsevier.com/locate/jiph

Prevalence of multidrug resistant uropathogenic bacteria in pediatric patients of a tertiary care hospital in eastern India

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Received 25 June 2015; received in revised form 12 September 2015; accepted 7 October 2015

KEYWORDS
Urinary tract infection;
Multidrug resistance;
Community;
Pediatric UTI

Summary Today, because systemic infections such as urinary tract infection (UTI) affect even pediatric patients, antibiotic resistant bacteria have become a constant clinical challenge. In the present study, a total of 1054 urine samples were collected from pediatric patients over 18 months. From these samples, 510 isolates of pathogenic bacteria were collected using HiCrome UTI agar. Antibiotic sensitivity tests of isolates were performed using the Kirby—Bauer method. Two Gram-positive bacteria (*Enterococcus faecalis* and *Staphylococcus aureus*) and 7 Gram-negative bacteria (*Citrobacter freundii*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus vulgaris* and *Pseudomonas aeruginosa*) were isolated. Antibiograms of isolated bacteria were ascertained using antibiotics of 4 classes: aminoglycosides, β-lactams, fluoroquinolones and 2 stand-alones (co-trimoxazole and nitrofurantoin). Based on percent values of antibiotic resistance, isolated bacteria were (in decreasing order of number of isolated isolates): *E. coli* (109) > *S. aureus* (65) > *E. faecalis* (82) > *E. aerogenes* (64) > *C. freundii* (41) > *P. aeruginosa* (32) > *K. pneumoniae* (45) > *K. oxytoca* (50) > *P. vulgaris* (22). Surveillance results show that MDR isolates of 9 pathogenic bacteria were prevalent in

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http://dx.doi.org/10.1016/j.jiph.2015.10.002

the environment around the hospital. Thus, revisions to the antimicrobial stewardship program in this area of the country are required to increase clinician confidence in empiric therapy, which is often used for UTI cases.

Introduction

Urinary tract infection (UTI) is defined by the presence of a threshold number of pathogenic bacteria (10^5 CFU/mL) in urine. Invasive/progressive infections of the tract with a higher bacterial population cause cystitis, urethritis and pyelonephritis. Symptoms of UTI in children include hematuria, dysuria, cloudy urine and nocturnal enuresis, sometimes associated with nausea and vomiting along with fever [1,2]. Febrile young female children without proper toilet training, infants with vesicoureteral reflux and tight phimosis are at risk for UTI. The resultant blood stream infection can lead to fatal bacteremia, with symptoms ranging from skin reactions, subcutaneous nodules, metastatic abscesses, and meningitis, etc., which may lead to terminal illness [3—5]. UTI is often associated with other ailments such as acute respiratory infection and acute diarrhea. Due to the vague clinical manifestation in children and infants, basic first level diagnostic tests of urine are not advised regularly in developing countries, thus, UTI is not reported as a cause of childhood morbidity.

Antibiotics are frequently prescribed everywhere in both empiric and regular therapy for UTI [6]. At the hospital in the present study, UTIs were of serious clinical concern for adult patients due to causative multidrug resistant (MDR) bacteria, which are resistant to routinely used antibiotics [7]. This hospital reported that in an 18 month period, 2 Gram-positives (GPs) (*Enterococcus faecalis* and *Staphylococcus aureus*) and 9 Gram-negatives (GNs) (*Acinetobacter baumannii*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, *Proteus mirabilis*, *P. vulgaris* and *Pseudomonas aeruginosa*) were isolated as uropathogens from hospitalized and community adult patients attending the hospital [7]. Device and fomite associated nosocomial infections in hospitals are important factors related to pathogenic spread.

As an extension of previous research on adults conducted in 2011—2012 [7], this study was undertaken in 2013—2014 with pediatric UTI patients who were visiting the outpatient department (OPD) and who were admitted to wards, cabins and neonatal intensive care unit designated as inpatient departments (IPD) over a period of 18 months. This study was undertaken to explore possibilities for a revision of the antimicrobial stewardship program because the rising concern caused by frequent UTI reports in adults and children could be addressed with a newer prophylaxis module. A revised antimicrobial stewardship program would reduce nosocomial spread of certain isolates of bacteria reported earlier from this hospital [8—10] as well as morbidity and hospitalization costs. Obviously, empiric therapy is usually formulated on epidemiological data based on regional surveillance reports; however, the spread of drug resistant bacteria may undermine empiric therapy. The present study should help inform empiric therapy for preventing child mortality from UTI and enteric infections in India [11].

Methods

Isolation and identification of pathogenic bacteria

Over a span of 18 months (January 2013 to June 2014) 510 isolates of pathogenic bacteria belonging to 9 genera (2 GP and 7 GN bacteria) were isolated by culturing 1054 urine samples of OPD and IPD pediatric patients attending/admitted to the Institute of Medical Sciences and Sum Hospital with complaints of fever and foul urine. Strains were identified using media, HiCrome UTI agar (HiMedia, Mumbai) and standard biochemical tests [7] and were maintained as pure cultures in nutrient agar (HiMedia). Corresponding Microbial Type Culture Collection (MTCC) strains were used as reference controls during biochemical identification of isolated bacteria. Two GPs and 7 GNs were isolated from culturing urine samples and were used in this study (Table 1).

Antibiotic susceptibility test

All bacterial isolates including the standard isolates from MTCC of each bacterium were subjected to

Table 1 Bacteria isolated from urine samples of IPD and OPD pediatric patients.

Bacteria	MTCC strain number	January—June 2013	July—December 2013	January—June 2014	Total
Enterococcus faecalis	439	20	27	35	82
Staphylococcus aureus	7443	15	22	28	65
Citrobacterfreundii	1658	14	18	09	41
Enterobacter aerogenes	2990	22	27	15	64
Escherichia coli	443	48	25	36	109
Klebsiella oxytoca	2275	16	22	12	50
Klebsiella pneumoniae	4031	12	15	18	45
Proteus vulgaris	1771	10	7	5	22
Pseudomonas aeruginosa	1688	14	10	08	32
Grand total		171	173	166	510

Note: Total number of urine samples cultured was 1054; MTCC — Microbial Type Culture Collection strains were used as reference controls during biochemical identification of isolated bacteria; IPD, inpatient department; OPD, outpatients department.

antibiotic sensitivity tests by Kirby—Bauer/disk diffusion method, using a 4 mm thick Mueller—Hinton agar (HiMedia) medium [7,12]. Fifteen prescribed antibiotics of 4 groups were used. Plates were incubated for 18 h at 37 °C and were examined for size-measurements of zones of inhibition around each disk, following the standard antibiotic susceptibility test chart of CLSI guidelines [12]. The susceptibility limit of resistance was above 20 mm in agar plates.

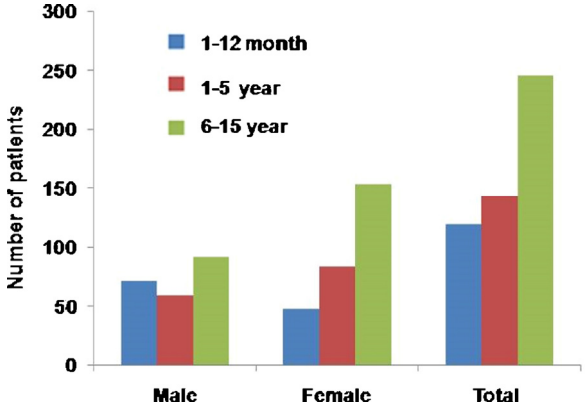

Figure 1 Prevalence of UTI in pediatric patients over an 18 month time period.

Results

Overall, 510 isolates of pathogenic bacteria belonging to two GPs and seven GNs were collected from a total of 1054 urine samples from community OPD and IPD pediatric patients over 18 months. In total, there were 82 isolates of *E. faecalis*; 65 isolates of *S. aureus*; 41 isolates of *C. freundii*; 64 isolates of *E. aerogenes;* 109 isolates of *E. coli*; 50 isolates of *K. oxytoca;* 45 isolates of *K. pneumoniae;* 22 isolates of *P. vulgaris;* and 32 isolates of *P. aeruginosa*. Based on the isolate numbers, bacteria could be arranged in the following decreasing order: *E. coli* > *E. faecalis* > *S. aureus* > *E. aerogenes* > *K. oxytoca* > *K. pneumoniae* > *C. freundii* > *P. aeruginosa* > *P. vulgaris* (Table 1).

From 510 positive samples in the 1—12 month age group, 120 samples were collected from which 72 samples were from males and 48 samples were from females. In the 1—5 year age group, there was a total of 144 positive samples were collected from 60 males and 84 females. In the 6—15 year age group, 246 clinical samples were collected 92 males and 154 female patients. These results indicate that in the age group of 1—12 months, males were more predisposed to UTI than females. However, in age groups, 1—5 and 6—15 year females were more predisposed than males to UTI (Fig. 1).

Among aminoglycosides, the maximum values of 46%, 43% and 50% of *S. aureus* isolates were resistant to the antibiotics amikacin 30, gentamicin 10 and netilmicin 30 μg/disk, respectively. The percent resistant values of the β-lactam group were similar (Table 2). Among the β-lactam antibiotics, piperacillin 100 μg/disk had the highest percent resistant isolates; the resistance pattern slightly decreased in the following order: ceftazidime 30, cefuroxime 30, piperacillin/tazobactam 100/10, ampicillin 10, ceftriaxone 30 and amoxyclav 30 μg/disk. For amoxyclav 30 μg/disk, 36% of *E. coli* isolates had the highest percent of resistance. For ampicillin 10 and piperacillin 100 μg/disk, 40% of *E. aerogenes* isolates were resistant. Approximately 38% of *E. coli* isolates had the highest percent value of resistance over piperacillin/tazobactam 100/10 μg/disk. A 36% percent resistance value in *E. coli* isolates was recorded as the highest value against ceftriaxone 30 μg/disk. For ceftazidime

Table 2 Percentage of resistance of bacterial isolates to 15 antibiotics belonging to 4 groups.

Bacterium	Antibiotics (μg/disk)														
	Aminoglycosides			General β-lactams							Fluoroquinolones			Stand alones	
	AMK 30	GEN 10	NET 30	AMC 30	AMP 10	PIP 100	TZP 100/10	CRO 30	CAZ 30	CXM 30	LVX 5	NOR 10	OFX 5	COT 25	NIT 300
E. faecalis	38	35	38	23	29	32	37	26	35	30	29	Nd	32	37	Nd
S. aureus	46	43	50	25	32	39	28	32	28	32	35	Nd	39	39	Nd
C. freundii	23	33	32	34	34	33	34	33	34	23	34	34	23	33	34
E. aerogenes	40	34	34	34	40	40	34	33	26	34	40	33	34	40	27
E. coli	31	36	31	36	39	36	38	36	30	31	38	36	36	31	28
K. oxytoca	25	33	25	28	33	42	33	18	25	33	25	28	28	25	33
K. pneumoniae	22	33	27	22	38	33	26	27	33	27	27	27	26	38	33
P. vulgaris	20	28	30	28	30	20	0	20	0	0	28	38	32	20	22
P. aeruginosa	32	29	25	31	34	28	32	31	35	32	30	32	35	32	34

Note: Antibiotics (μg/disk), AMC: amoxyclav 30; AMK: amikacin 30; AMP: ampicillin 10; CAZ: ceftazidime 30; COT: co-trimoxazole 25; CRO: ceftriaxone 30; CXM: cefuroxime 30; GEN: gentamicin 10; LVX: levofloxacin 5; NET: netilmicin 30; NIT: nitrofurantoin 300; NOR: norfloxacin 10; OFX: ofloxacin 5; PIP: piperacillin 100; TZP: piperacillin/tazobactam 100/10. Nd, not done.

30 μg/disk, 35% of *E. faecalis* and *P. aeruginosa* recorded the individual highest resistance value. For cefuroxime 30 μg/disk, 34% of *E. aerogenes* recorded the highest resistance value.

Similarly, for the fluoroquinolone group, *E. aerogenes* was found to be most resistant organism to levofloxacin 5 μg/disk with 40% and *K. oxytoca* the least, with 25%. Again, for norfloxacin 10 μg/disk, *P. vulgaris* was the most resistant organism (38%) and *K. pneumoniae* the least with a resistance percentage value of 27%. Further, for ofloxacin 5 μg/disk, *S. aureus* isolates had the maximum resistance values with 39%, whereas *C. freundii* had the least resistance with 23%. Surprisingly, co-trimoxazole 25 μg/disk was found resistance for 40% of isolates of *E. aerogenes* and 39% of isolates of *S. aureus* in this hospital. For nitrofurantoin 300 μg/disk, the maximum resistance percent value was found as 34% for *C. freundii* and *P. aeruginosa* isolates (Table 2).

Discussion

Isolates of both GPs were vancomycin resistant and all GNs were resistant to nitrofurantoin and co-trimoxazole, the most preferred antibiotics prescribed in empiric therapy against UTI in this region [7]. In another study based in India, UTI-causing bacteria were reported to be resistant to antibiotics to the following degrees: 83.3% to trimethoprim/sulfamethoxazole, 80.6% to nalidixic acid, 67.3% to amoxicillin, 61% to co-trimoxazole, 48.8% to gentamicin, 46% to ciprofloxacin and 43% to cephalexin [13]. Community surveillance for uropathogens in a rural setting was conducted in Tamil Nadu, India; from this, 22.78% of 1359 urine samples were found positive for some of the most common bacterial uropathogens: *Staphylococcus* sp., *Streptococcus* sp., *Enterococcus* sp., *Klebsiella* sp., *Proteus* sp. and *E. coli*. Furthermore, antibiograms of all the reported genera revealed multiple drug resistance within each [14]. Previous studies conducted in different types of Indian rural settings make clear that environment plays a significant role in the spread of MDR pathogenic bacteria [15—17]. From Iran, it was reported that adult patients in ICU with sepsis had higher prevalence of MDR bacteria causing UTIs [18]. UTI is known to cause significant levels of morbidity in developed countries [19]; thus, morbidity of MDR UTI-causing bacteria has become a global concern.

Resistance to aminoglycosides and β-lactams, including cephalosporins and fluoroquinolone, is of great concern in clinical management, particularly as it applies to children because their immune

systems are undeveloped [20]. The unfortunate situation is that most pathogenic bacteria have drug-resistant characters exchanged through the operative genetic exchange mechanisms which promote survival in a new host. Further, a report from London described how urine dipstick analysis, which measures the presence or absence of nitrites, can serve as a prognostic criterion in antibiotic-sensitivity pattern in most common bacterial uropathogens. It was observed that in nitrite positive infants and children, certain groups of bacteria were significantly resistant to cefixime (third generation cephalosporin, 3GC), whereas nitrite negative patients had significantly increased resistance rate with other bacteria. For example, the London study observed amoxicillin and amoxicillin clavulanate resistance in nitrite negative UTI cases [21]. While nitrofurantoin and 3GCs were effective among nitrite negative afebrile pediatric UTI cases, they were ineffective among febrile infants with UTI [21]. In the present study, 34% of isolates were resistant to nitrofurantoin in vitro. In a study conducted in Iran, hospitalized children with UTI problems were given chemoprophylaxis with trimethoprim/sulfamethoxazole, nitrofurantoin or cephalosporins. The recorded resistant pattern was according to the particular antibiotic used; nitrofurantoin was resistant to 100% of *Pseudomonas* sp. isolates [22]. In a study in Belgium, infants less than 3 months old were found to be at risk for UTI (21% of all children); the study population was made up of 26% females and 74% males, with the usual occurrence of *E. coli* as the predominate causative organism [23]. In the present study, in the age group of 1—12 months, males were more predisposed to UTI than females; however, in age groups 1—5 years and 6—15 years, females were more predisposed than males to UTI. Overall, 48% of children had a UTI. Longer hospital stays (6 days versus 4 days) caused infections from extended spectrum β-lactamase producing organisms in UTI cases in Israel, with the predominance of *E. coli* and *Klebsiella* sp. [24]. UTI was reported to occur in 1—5% of children with recurrence in Oulu, Finland [25]. In a Nigerian hospital, it was recorded that UTI occurred in 9% of febrile children aged 1—60 months with a higher prevalence among girls [26]. In Abidjan (Western Africa), it was reported that common uropathogens including *E. coli* and *Klebsiella* sp. had considerably higher rates of resistance for amoxicillin > tetracycline > trimethoprim/sulfamethoxazole, in this order [27].

MDR isolates of GPs (Staphylococci and Enterococci) precipitate episodes of suppurative infection that are notoriously difficult to control [9,10] because most isolates remain resistant to β-lactams. The superbug of the health domain, MRSA, is widespread [28]. Moreover, for the control of *E. coli* infections aminoglycosides, β-lactams and fluoroquinolones are generally used everywhere. When *E. coli* isolates are simultaneously resistant to several antibiotics of the cited groups, the consequent therapeutic problems challenge the cleanly state of hospital indoor units [7,29]. Indeed, the emergence of MDR isolates of *E. coli* threaten the use of antibiotics which poses a major challenge to the health care system. The present antibiogram of *E. coli* confirms such resistance in this region. The hospital in this study reported a fatal neonatal case of septicemia due to MDR *K. pneumoniae* [30]; clearly, antibiotic resistant bacteria have consequences in pediatric patients. The present study and similar studies clearly indicate that the high prevalence of MDR strains of pathogenic bacteria are a cause of morbidity in patients of the pediatric age group.

As a limitation, it could be stated that previous history of use of antibiotics for older children (6—15 years of age) were not known, while the admitted infants and under-5 children had no history of antibiotic use.

Conclusion

All bacterial isolates from urine samples of infants and children of a typical community were resistant to most current antibiotics. The 18 month surveillance of pediatric UTI revealed that MDR isolates of 9 pathogenic GP and GN bacteria were prevalent in the environment around the hospital. These findings suggest a need for revisions to the present antimicrobial stewardship program and the use of nitrofurantoin, ceftriaxone and cefuroxime in this area of the country. This would ensure clinician confidence in empiric therapy, which is commonly used, e.g., for surgical sites including UTI cases.

Funding

This work was supported by a major research project on ''Development of standardized herbal extracts against urinary tract bacterial infection'' (grant no. BT/PR8214/PBD/17/863/2013), from the Department of Biotechnology, Government of India, New Delhi.

Competing interest

None declared.

Ethical approval

Not required.

Authors' contributions

R.S. and R.N.P. conceived and designed the study. M.P.M. collected, analyzed and interpreted the data. M.P.M., R.S. and R.N.P. were involved in drafting the manuscript. All authors read the manuscript and approved the final copy for submission.

Acknowledgements

This work is a part of Ph.D. thesis of M.P. Mishra in Biotechnology from Siksha 'O' Anusandhan University, Bhubaneswar. We are grateful to Prof. Dr. M.R. Nayak, Honourable President, Siksha 'O' Anusandhan University, Bhubaneswar for extended facilities.

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