DOI: 10.7860/JCDR/2018/30228.11106

Original Article

Paediatrics Section

Antibiotic Resistance in Community Acquired Urinary Tract Infection in Children: Data from a Tertiary Center in Eastern India

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ABSTRACT

Introduction: Antibiotic resistance is an increasing global problem which hampers appropriate treatment of Urinary Tract Infection (UTI) in paediatric population, rendering the developing kidneys vulnerable for scarring and long-term complications. The present study stressed upon the most severely affected patients who required hospitalisation for treatment of UTI. Authors conducted this study observing the higher degree of drug resistance in patients admitted to general paediatric ward lately, suffering from UTI.

Aim: To observe different clinical presentations of paediatric patients hospitalised with UTI. Authors also intended to identify locally prevalent community acquired bacterial uropathogens of clinical importance and note the sensitivity and resistance patterns of the isolated organisms against different antibiotics.

Materials and Methods: This prospective observational pilot study was conducted at the Institute of Child Health, Kolkata, a tertiary care paediatric referral hospital. A total of 950 urine samples (single sample per patient) were collected from hospitalised children (from neonatal age group, upto 12 years) with suspected UTI/sepsis, between October 2014 to April 2016. Of 132 culture positive samples, 35 were excluded as per exclusion criteria, and 97 isolates had antimicrobial sensitivity performed on them. Clinical presentation was documented. Statistical analysis was done using the Chi-Square test.

Results: The most common clinical presentations were fever, pain abdomen and anorexia. The most common isolates were *Escherichia coli* 59/97 (60.82%), followed by *Enterococcus* spp. 19/97 (19.59%) and *Klebsiella pneumoniae* 9/97 (9.28%). The majority of *E. coli* (n=59) isolates showed resistance against all Cephalosporins: 49-52 (83.1-88.1%), meropenem: 39 (66.1%), cotrimoxazole: 42 (71.1%), amoxycillin-clavulanic acid: 55 (93.2%) and quinolones: 50-51 (84.8-86.4%). Most *Enterococcus* spp. (n=19) isolates were resistant to amikacin: 17 (89.5%). Overall, a large proportion, 79/97 (81.4%) of uropathogens isolated showed Multidrug-Resistance (MDR).

Conclusion: The alarming rates of resistance of uropathogens to commonly used antibiotics calls for review of empiric treatment guidelines and emphasises the need for preventing antibiotic misuse in day-to-day practice.

Keywords: Antimicrobial agents, Bacteriological profile, Uropathogens

INTRODUCTION

Urinary tract infections are common bacterial infections, most of the times causing febrile illness in children. It has been observed that at least 8% of girls and 2% of boys suffer from UTI in their childhood [1]. UTI not only causes acute morbidity, but also is associated with renal scarring, hypertension and chronic kidney disease in the long run, if not treated at an appropriate time with the right antimicrobial agent [2]. Symptoms and signs of UTI are often non-specific and clinical suspicion must be confirmed by urine culture. The standard care of practice in India is that antibiotic therapy is initiated empirically after collection of a urine sample for culture, particularly in children ill enough to require admission. Later, according to the bacteriological sensitivity antimicrobial therapy is modified [2].

So, an upto-date knowledge of the local bacteriological profile and antibiotic susceptibility is required to optimise therapy from the very starting point of patient care. The aetiology of paediatric UTI and the antibiotic susceptibility of urinary pathogens in both the community and hospitals have been changing and drug resistance has become a major problem worldwide [3,4].

Recent data on UTI in children from eastern India is lacking, so this study was done at our institute to analyse the susceptibility pattern of microorganisms causing UTI among infants and children.

MATERIALS AND METHODS

This prospective observational study was conducted among children up to 12 years of age admitted in the paediatric wards of Institute of Child Health, Kolkata, a charitable tertiary care teaching hospital.

All children with unexplained fever, specific symptoms of UTI (dysuria, frequency, abdominal pain, flank pain, dribbling of urine with/without nausea/vomiting, headache, myalgia) and neonates or infants with suspected sepsis (poor feeding, lethargy, vomiting, irritability, dribbling of urine, cry during micturition) admitted between October 2014 to April 2016 were included.

Final sample size was calculated to be 97 [by using necessary algorithm: Sample size (SS) = Z2* p*(1-p)/C2; Z= Z-value e.g. 1.96 for 95% confidence level; p= percentage of picking a choice, expressed as decimal; C= margin of error, expressed as decimal. Appropriate correction was done to determine the sample size for finite population using the hospital data for community-acquired UTI]. Patients were excluded if they had received antibiotics prior to urine sampling, had previous history of UTI, known structural or functional anomalies of the urinary tract, were on antibiotic prophylaxis or had urethral catheter in situ.

Community acquired UTI was defined as UTI detected at hospital admission or within first 48 hours without fulfilling any of the following

criteria: History of (i) receiving any parenteral drug therapy within last 30 days, (ii) attending a hospital or hemodialysis ward within last 30 days, (iii) being hospitalised for two or more days within last 90 days, (iv) residing in a nursing home or health facility or (v) being subjected to invasive urinary tract procedure within last 30 days [5].

The study enrolled a number of 950 patients to achieve the necessary sample size. Freshly voided midstream clean catch urine samples for older children and suprapubic aspiration or urethral catheter specimens in infants were obtained. Microscopic examination (for white blood cells, red blood cells etc.) was performed for all the samples. Semi-quantitative urine culture (single sample per patient) using calibrated loop was used to inoculate Blood agar and MacConkey plates. Samples were incubated in normal body temperature (37°C) and stamped negative if there was no growth till 48 hours of incubation. Isolates from positive culture colonies were identified by gram stain, motility and routine biochemical reactions. 'Urine culture positivity' was taken as growth of a single species at a concentration of $>10^5$ colony forming units/mL (cfu/mL). Sensitivity was determined by Kirby-Bauer modified disc diffusion method following the Clinical Laboratory Standard Institute guidelines (CLSI, 25th supplementary literature) [6] using *E. coli* ATCC 25922, *S. aureus* ATCC 25923 and *P. aeruginosa* ATCC 27853 as quality controls. Antibiotic Sensitivity Testing (AST) was carried out and reported (separate sets for gram-positive and negative ones as mentioned in [Table/Fig-1,2]) using the following antibiotics as per the CLSI guidelines: ceftriaxone, cefotaxime, ceftazidime, cefixime, cefoxitin, oxacillin, amoxicillin-clavulanate, piperacillin-tazobactam, cefoperazone-sulbactam, ciprofloxacin, ofloxacin, gentamicin, amikacin, imipenem, meropenem, co-trimoxazole, nitrofurantoin, linezolid, vancomycin, colistin, polymyxin-B, teicoplanin.

Multidrug-resistance has been defined as in-vitro reistance to three or more antimicrobial classes and Extensive Drug-Resistance (XDR) has been taken as resistance to almost all antimicrobial categories [7]. If a particular isolate is found to be resistant to at least three structurally different antimicrobial categories according to the antibiogram, it has been labelled as MDR.

STATISTICAL ANALYSIS

Statistical analysis used Chi-Square test, conducted with SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) to detect intergroup differences, p-value <0.05 was considered significant. Institutional Ethics Committee clearance was obtained before this study. Informed consent from the guardian was taken before inclusion into the study.

RESULTS

Out of 950 samples collected, 132 (13.9%) were culture positive, of which 35 were excluded (Recurrent UTI with functional vesicoureteric reflux, structural problems like posterior urethral valve, hydronephrosis due to pelviureteric junction obstruction, ectopic ureter, duplex ureteric system were the observed underlying disorders) following exclusion criteria. Of the 97 included for data analysis, 54 were from males and 43 from females. There were 31 infants, 40 between one and five years and 26 above five years of age.

Fever was the most common presenting symptom in 85 out of 97 (88%) patients [Table/Fig-1].

Statistically significant male preponderance was seen in infants and one to five year age group and female preponderance in those above five years (p=0.003).

Microscopic examination of urine samples showed presence of less than five white blood cells/high power field (wbc/hpf) in 3/97 (3.09%), 5-10 wbc/hpf in 24/97 (24.74%) and more than 10 wbc/hpfin 72/97 (74.23%). More than 5 red blood cells/hpf were present in 78/97 (80.41%) samples.

Age (years)		0-1	>1-5	>5	Total (%)
Number (%)		31 (32)	40 (40.2)	26 (26.8)	97 (100)
Sex	Male (%)	17 (54.8)	29 (72.5)	8 (30.8)	54 (55.7)
	Female (%)	14 (45.2)	11 (27.5)	18 (69.2)	43 (44.3)
p-value: 0.003 (<0.05)					
Number (percentage-%)					
Fever		24 (77.4)	35 (87.5)	26 (100)	85 (88)
Pain abdomen		02 (6.5)	34 (85)	15 (57.7)	51 (53)
Anorexia		16 (51.6)	16 (40)	15 (57.7)	47 (48)
Urinary frequency		01 (3.2)	17 (42.5)	23 (88.5)	41 (42)
Dysuria		06 (19.4)	16 (40)	17 (65.4)	39 (40)
Nausea/Vomiting		17 (54.8)	11 (27.5)	08 (30.8)	36 (37)
Flank pain		-	08 (20)	12 (46.2)	20 (21)
Headache		-	02 (5)	05 (19.2)	07 (7)
Others*		04 (12.9)	05 (12.5)	02 (7.7)	11 (11)

[Table/Fig-1]: Clinical features of patients with positive urine culture.
*poor feeding, irritability, dribbling, myalgia.

Antibiotics (Disc Potency)	*E. coli* (n=59)	*Klebsiella* spp. (n=9)	*Pseudomonas aeruginosa* (n=4)	*Proteus mirabilis* (n=2)
Number (Percentage-%)				
Ceftriaxone (30 mcg)	51 (86.4)	7 (77.8)	4 (100)	1 (50)
Cefotaxime (30 mcg)	52 (88.1)	7 (77.8)	4 (100)	1 (50)
Ceftazidime (30 mcg)	49 (83.1)	7 (77.8)	2 (50)	1 (50)
Cefixime (05 mcg)	50 (84.7)	7 (77.8)	4 (100)	1 (50)
Cefoperazone-Sulbactam (75/30 mcg)	29 (49.2)	4 (44.4)	2 (50)	1 (50)
Piperacillin-Tazobactam (100/10 mcg)	16 (27.1)	3 (33.3)	2 (50)	0 (0)
Gentamicin (10 mcg)	14 (23.7)	2 (22.2)	3 (75)	1 (50)
Amikacin (30 mcg)	4 (6.8)	1 (11.1)	2 (50)	1 (50)
Imipenem (10 mcg)	7 (11.9)	1 (11.1)	2 (50)	1 (50)
Meropenem (10 mcg)	39 (66.1)	3 (33.3)	3 (75)	1 (50)
Colistin (10 mcg)	6 (10.2)	0 (0)	1 (25)	2 (100)
Polymyxin B (300 mcg)	6 (10.2)	0 (0)	1 (25)	2 (100)
Ciprofloxacin (05 mcg)	51 (86.4)	4 (44.4)	4 (100)	1 (50)
Ofloxacin (05 mcg)	50 (84.8)	4 (44.4)	4 (100)	1 (50)
Nitrofurantoin (300 mcg)	5 (8.5)	6 (66.7)	3 (75)	2 (100)
Sulfamethoxazole-Trimethoprim (25 mcg)	42 (71.1)	5 (55.6)	4 (100)	1 (50)
Amoxycillin-clavulanic acid (20/10 mcg)	55 (93.2)	8 (88.9)	4 (100)	2 (100)

[Table/Fig-2]: Resistance patterns of gram-negative organisms.

Of all isolates, gram-negative bacteria 75/97 (77.31%) were common than gram-positive 22/97 (22.68%) ones. The most frequent isolat ewas *Escherichia coli* 59/97 (60.82%) followed by *Enterococcus* spp. 19/97 (19.59%), *Klebsiella pneumoniae* 9/97 (9.28%), *Pseudomonas aeruginosa* 4/97 (4.12%), *Staphylococcus aureus* 3/97 (3.09%), *Proteus mirabilis* 2/97 (2.06%) and *Acinetobacter* spp. 1/97 (1.03%).

E. coli showed resistance rates ranging from 42/59 (71.1%), 55/59 (93.2%) to common oral antibiotics like amoxycillin-clavulanic acid, cefixime, cotrimoxazole and fluoroquinolones. Resistance to intravenous drugs like ceftriaxone, cefotaxime, cefoperazone-sulbactam and meropenem varied between 29/59 (49.2%) 88.1% (52/59). Low resistance rates (6.8-27.1%) were seen against the oral antibiotic nitrofurantoin, parenteral antibiotics such as aminoglycosides, imipenem, piperacillin-tazobactam and reserve antibiotics like colistin and polymyxin B [Table/Fig-2].

Among other gram-negative organisms, Klebsiella isolates showed resistance rates of 5/9 (55.6%)-8/9 (89%) to cephalosporins, amoxycillin-clavulanic acid, nitrofurantoin and cotrimoxazole.

Among the four *Pseudomonas aeruginosa* isolates, all showed 4/4 (100%) resistance to quinolones and two of them 2/4 (50%) showed additional resistance to ceftazidime, amikacin, piperacillin-tazobactam and imipenem. The single *Acinetobacter* spp. isolate was resistant to every other antibiotic tested apart from colistin and polymyxin B [Table/Fig-2].

Enterococcus species, the second most common pathogen isolated, showed 14/19 (73.7%)-19/19 (100%) resistance to oxacillin, cefoxitin, amikacin, fluoroquinolones and cotrimoxazole, but good susceptibility to linezolid, vancomycin and teicoplanin [Table/Fig-3].

Overall 79/97 (81.4%) microorganism isolates were MDR strains. Fifty four (91.5%) isolates of 59 *E. coli*, the most predominant uropathogen and all 22 isolates (100%) of gram-positive organisms were found to be MDR in this study. One *Klebsiella* spp. and two *Pseudomonas aeruginosa* isolates were also found to be MDR. The single *Acinotobacter* spp. isolate was XDR.

Antibiotics (Disc potency)	*Enterococcus* spp. (n=19)	*Staphylococcus aureus* (n=3)	OVERALL (n=22)
Number (percentage-%)			
Oxacillin (01 mcg)	19 (100)	1 (33.3)	20 (90.9)
Cefoxitin (30 mcg)	19 (100)	1 (33.3)	20 (90.9)
Vancomycin (30 mcg)	2 (10.5)	0 (0)	2 (9.1)
Linezolid (30 mcg)	1 (5.3)	0 (0)	1 (4.5)
Teicoplanin (30 mcg)	2 (10.5)	0 (0)	2 (9.1)
Amikacin (30 mcg)	17 (89.5)	0 (0)	17 (77.3)
Ciprofloxacin (05 mcg)	18 (94.7)	3 (100)	21 (95.5)
Ofloxacin (05 mcg)	18 (94.7)	3 (100)	21 (95.5)
Sulfamethoxazole-Trimethoprim (25 mcg)	14 (73.7)	1 (33.3)	15 (68.2)
Nitrofurantoin (300 mcg)	1 (5.3)	2 (66.7)	3 (13.7)

[Table/Fig-3]: Resistance patterns of gram-positive organisms.

DISCUSSION

This study from a tertiary paediatric hospital, is probably the first exclusive study of paediatric population in recent times from eastern India and it demonstrates an alarmingly high resistance rate of community acquired uropathogens, to conventional antibiotics. Gram-negative organisms especially *E. coli* (59/97, isolated in 60.82% of our samples) are globally, the most common uropathogens documented [1,8,9]. Thus, changing resistance patterns of *E. coli* are of paramount importance in planning empiric UTI treatment.

The culture positivity rate (13.9%) is at par with other studies conducted in this part of the world [10,11]. Also, male to female ratio (1.3:1) and age distribution (majority between one to five years) in our study, are similar to reports from other parts of the world [18,9,12,13]. While the predominance of gram-negative, particularly *E. coli* isolates is similar to prior reports, most older studies have described very low incidences of gram-positive organisms, though recently their incidence appeared to be rising [2].

Nineteen of 97 (20%) of our isolates were *Enterococcus* spp. - only a handful of studies from North India and Iran have shown similar results [1,2,8]. Lower incidence of UTI due to *Pseudomonas* and *Acinetobacter* spp. have been noted which is similar to the findings of previous studies that excluded nosocomial UTIs just like this one [2,12].

E. coli isolates were only susceptible to polymyxins, imipenem, piperacillin-tazobactam, cefoperazone-sulbactam and amikacin. These findings are contrary to those from Africa, south Asia and some Middle-East countries where these antibiotics showed high resistance against *E. coli* [13,14].

The low susceptibility of gram-negative organisms to oral antibiotics like fluoroquinolones, amoxicillin-clavulanic acid and cotrimoxazole demonstrated in our study, is also similar to previous reports [1, 6]. However, their high resistance rates to oral and intravenous cephalosporins has not been reported before [2,15], particularly for community acquired UTI. According to Dash M et al., with increasing resistance to ampicillin and cotrimoxazole, physicians were inclined towards using quinolones and cephalosporins more and more as first line antimicrobials, but unfortunately due to their overuse resistance is mounting against these agents very rapidly [16]. Another alarming observation was the resistance to meropenem 39/59 (66.1%) and high degree of MDR 54/59 (91.53%) among *E. coli* isolates. The MDR data is way worse than those last reported from other parts of the world like Spain (20.6%) and United States (7.1%) [17,18].

In our country, antibiotics are often misused for trivial paediatric symptoms, most commonly occurring due to viral illnesses [19]. A study by Ganguly NK et al., documented a steep increment in antibiotics sale by 40% between 2005 to 2009 with the sale of cephalosporins strikingly increasing by about 60%. According to a review article published in 2016, India was the largest consumer of antibiotic sales globally [19]. Seventy six percent increase in global antibiotic use was shown to be contributed by "BRICS" countries (Brazil, Russia, India, China and South Africa) and India also topped "retail antibiotic sales" by contributing 23% increase alone among the five countries [20]. Apart from overuse, erratic dosing and inadequate durations of therapy are also not uncommon as observed in day to day practice. These may be important causes for the high level of antibiotic resistance seen in our study. An added reason may be that only patients ill enough to require admission were included in this study, in comparison to several other studies that focussed on outpatients also.

The results of this and other regional studies require the formulation of a modified antibiotic protocol for empiric therapy of patients admitted with suspected UTI [1,2,12]. The Indian Society of Paediatric Nephrology guidelines [21] advocate that empiric therapy for UTI should be guided by local culture and sensitivity patterns and may include 3rd generation cephalosporins, aminoglycosides (if renal function normal), amoxicillin-clavulanic acid and quinolones.

However, going by our results, a different regime is required. Nitrofurantoin seems to be an oral option for the treatment of uncomplicated UTI. For parenteral therapy, amikacin or piperacillin-tazobactam may be the first-line antimicrobial options while drugs like imipenem, colistin and polymyxin-B should be reserved for those who are critically ill. After getting the final bacterial sensitivity report from the laboratory, antibiotic therapy should be modified (up or downgraded) accordingly for optimum therapaeutic outcome.

LIMITATION

This study is limited by including only admitted patients from single centre. Additionally, there may be in-vitro and in-vivo difference in antibiotic susceptibility, however, we did not assess the clinical response to therapy. Also this study did not take Extended Spectrum Beta Lactamase (ESBL)/Metallo Beta Lactamase (MBL) into account.

CONCLUSION

Our results underline the importance of developing periodic regional bacteriological surveillance programs to guide empiric antibiotic therapy of UTI. It also underlines the alarming emergence of resistant uropathogens and emphasizes the need for preventing antibiotic misuse among paediatric patients.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **May 18, 2017**
Date of Peer Review: **Jul 25, 2017**
Date of Acceptance: **Nov 11, 2017**
Date of Publishing: **Jan 01, 2018**