Pediatric urinary tract infections in a tertiary care center from north India

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**Background & objectives:** Paediatric urinary tract infections (UTI) are associated with high morbidity and long term complications like renal scarring, hypertension, and chronic renal failure. A cause of occult febrile illness, they often remain undiagnosed. We studied the clinical and microbiologic profile and antibiotic resistance profile of such infections in paediatric UTI patients at our center.

**Methods:** Clean catch mid-stream urine samples for culture were received from 1974 children aged < 12 yr over a period of 6 months. Quantitative wet mount microscopy and semiquantitative culture on cysteine lactose electrolyte deficient medium were done to diagnose UTI. Isolates were identified by standard biochemical tests and antimicrobial sensitivity was determined. Clinical details including risk factors and underlying illness were noted.

**Results:** Significant bacteriuria was found in 558 children (28.3%). Male gender (25.6%), age < 1 yr (77.5%), vesicoureteric reflux disease (VUR) (19.9%) and posterior urethral valve (PUV) (27.6%) were common risk factors in children suffering from UTI. Pyuria was detected in 53.6 per cent of infections. Common uropathogens isolated were *Escherichia coli* (47.1%), *Klebsiella* spp. (15.6%), *Enterococcus fecalis* (8.7%), members of tribe *Proteae* (5.9%), *Pseudomonas aeruginosa* (5.9%) and *Candida* spp. (5.5%). Against lactose fermenting *Enterobacteriaceae*, *in-vitro* resistance was least against amikacin (32.5%), nitrofurantoin (26.7%) and imipenem (3.7%). Among enterococci, vancomycin resistant enterococci constituted 12 per cent of the strains. 93.4 per cent of the UTI detected was nosocomial.

**Interpretation & conclusion:** Paediatric UTI was common in children with male gender, age < 1 yr, and in children suffering from VUR and PUV. Spectrum of pathogens causing paediatric UTI in our center had a preponderance of nosocomial multi-drug resistant pathogens.

**Key words** *Escherichia coli* - *Klebsiella* spp. - paediatric - uropathogens - UTI

Pediatric urinary tract infections (UTI) are associated with high morbidity and long term complications like renal scarring, hypertension, and chronic renal failure. A cause of occult febrile illness in up to 5 per cent of young children often remains undiagnosed, documented in cases associated with vesicoureteral reflux (VUR). Gram negative enteric bacilli, especially *Escherichia coli* and *Klebsiella* spp. are the leading pathogens though *Enterococcus* spp., yeasts and *Staphylococcus aureus* have...
emerged as prominent agents in recent years\textsuperscript{3-5}, many of them resistant to multiple antibiotics\textsuperscript{4-5}. Therapy for these children requires urine culture and appropriate antimicrobial sensitivity testing. Recent studies on paediatric UTI in India are limited. In a retrospective analysis, of the 52 children treated for posterior urethral valves (PUV), 34 had renal scarring\textsuperscript{3}. A significant correlation was seen between the occurrence of renal scarring and breakthrough UTI\textsuperscript{1}. UTI in children with symptomatic unilateral pelvi-ureteric junction obstruction (PUJO) was shown to be associated with poor somatic growth in another study from India\textsuperscript{6}. In the present study, we report the clinical, microbiological, and antimicrobial resistance profile of all consecutive paediatric UTI patients, presented at 304 bed advanced paediatric centre at Postgraduate Institute of Medical Education & Research, Chandigarh, from July to December 2006.

**Material & Methods**

For all cases of suspected UTI, urine culture was done by semi-quantitative technique on cysteine lactose electrolyte deficient medium (CLED agar – (Hi-Media, Mumbai)\textsuperscript{6} and quantitative unspun wet mount microscopy done to detect pyuria (> 1 pus cell/7 high power fields of well mixed uncentrifuged urine samples)\textsuperscript{6}, bacteriuria, haematuria or candiduria. One \textmu l urine was cultured using a calibrated bacteriological loop on CLED agar, and colonies were counted after overnight incubation at 37\textdegree C. Number of colonies obtained was multiplied by 1000 to obtain the colony forming units (cfu) / ml. For boys and girls, 10\textsuperscript{3} and 10\textsuperscript{4} cfu/ml of bacterial growth of a single type was taken as threshold (significant bacteriuria) respectively\textsuperscript{7,9}. In case of girls with mid-stream urine showing 10\textsuperscript{4}-10\textsuperscript{5} cfu/ml, repeat samples were asked for\textsuperscript{8-9}. Any number of colonies from a suprapubic sample were considered significant\textsuperscript{8,9}. Guidelines by Hellerstein et al\textsuperscript{8} were strictly adhered to for diagnosis of paediatric UTI. Isolates were identified by Gram stain, motility test and routine biochemical reactions. Antibiotic sensitivity was put up by the Kirby Bauer method following the clinical laboratory standards institute (CLSI) guidelines\textsuperscript{10}. All *Enterobacteriaceae* and *Acinetobacter* spp. were tested against first line agents: gentamicin (10\textmu g), amikacin (30\textmu g), cefoperazone (75\textmu g), cefotaxime (30\textmu g), nitrofurantoin (300\textmu g), trimethoprim-sulphamethoxazole (1.25-23.75\textmu g), nalidixic acid (30\textmu g), norfloxacin (10\textmu g) and ciprofloxacin (5\textmu g); *Enterococcus* spp. against amoxycillin (10\textmu g), vancomycin (30\textmu g), nitrofurantoin (300\textmu g), ciprofloxacin (5\textmu g) and high level aminoglycoside resistance gentamicin (HLAR-G, 120\textmu g); *Pseudomonas aeruginosa* against amikacin (30\textmu g), cefoperazone (75\textmu g), gentamicin (10\textmu g), ceftazidime (30\textmu g) and ciprofloxacin (5\textmu g). Second line antibiotics were tested only for organisms in those isolates resistant to all 1\textsuperscript{st} line antimicrobials or specifically requested for by the attending physician. These included: imipenem (10\textmu g), cefoperazone-sulbactam (75\textmu g) and piperacillin-tazobactam (100/10\textmu g) for all *Enterobacteriaceae*, *Acinetobacter* spp. and *Pseudomonas* isolates. *E. coli* ATCC 25922, *E. coli* ATCC 35218 and *P. aeruginosa* ATCC 27853 were used as controls. Apart from demographic data, risk factors and underlying illness were recorded in 428 cases of UTI. Symptomatic UTI was defined and further characterized as community acquired or hospital acquired as per CDC case definition\textsuperscript{11}. Cases (n=203) with PUV and VUR were followed up during the study period to determine the frequency of repeat infections. Statistical analysis was done using Microsoft Excel software version 2003 and Students t test done to check the significance of proportions.

**Results & Discussion**

A total of 1974 children (age <12 yr) with suspected UTI (Ward: OPD ratio - 5.8:4.2) were evaluated in the study, of whom 558 (28.3\%) children [434 male (77.8\%) and 124 female (22.2\%)] had culture proven UTI [538 due to a single uropathogen (508 bacterial, and 30 due to yeasts) and 20 bi-microbial infections (18 bacterial co-infections and 2 mixed bacterial and yeast infections)]. Of them, 143 (25.6\%, 116 male, and 27 female) were infants, 216 (38.7\%, 155 male, and 61 female) between 1-5 yr age, and 199 (35.7\%, 163 male, and 36 female) between 5-12 yr age. These children presented to the paediatric surgery (234, 41.9\%), paediatric medicine (238, 42.7\%), paediatric intensive care unit (PICU) (45, 8.1\%), and paediatric emergency (41, 7.3\%) departments. A significantly greater proportion of surgical patients were below one year age (P<0.05). There was an overall male preponderance in cases of UTI (77.8\%). The incidence of UTIs in the PICU during this period was 20 episodes / 1000 patient days while none were recorded from the neonatal ICU.

Wet mount microscopy for presence of bacteria/yeast or pus cells in significant amount per field was positive in 459 patients with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 82.3, 58.3, 43.4 and 89.3 per cent respectively in detecting infections. Significant pyuria alone was found in 299 patients with sensitivity,
specificity, PPV and NPV of 53.6, 62.6, 36.1, and 77.4 per cent respectively. Of the 428 patients in whom information about underlying disease was available, commonest underlying illnesses were PUV (118, 27.6%), VUR (85, 19.9%), neurogenic bladder (22, 5.1%), PUJO (15, 3.5%), hydronephrosis (10, 2.3%), percutaneous nephrostomy (10, 2.3%), other congenital anomalies of the urinary tract (14, 3.3%), stricture urethra (9, 2.1%), recurrent UTI (7, 1.6%), urinary tract trauma (5, 1.2%), renal stone disease (4, 0.9%), and post surgical patients (on systems other than genito-urinary tract) (11, 2.6%). The remaining 118 (27.6%) children had no predisposing conditions known to cause UTI. According to CDC case definitions, 28 of these 428 UTI cases were community acquired (6.6%) while the remaining were nosocomial infections (400, 93.4%). When the 203 UTI cases with PUV and VUR were followed up, 152 (74.9%) showed complete cure and no relapse; 9 (4.4%) reported reinfection with same microbe with same antibiogram; 19 (9.4%) reinfection with same species but more resistant antibiogram; and lastly 23 (11.3%) with infections due to a different pathogen.

Commonest uropathogens isolated included \textit{E. coli} (47.1%), and \textit{Klebsiella pneumoniae} (14.5%) (Table). In the PICU, \textit{Candida} spp. were isolated significantly more commonly (\(P<0.001\)) and \textit{E. coli} significantly less commonly (\(P<0.05\)) compared to other units. \textit{In vitro} resistance (R) and intermediate susceptibility (IS) in lactose fermenting and late lactose fermenting (LF and LLF) \textit{Enterobacteriaceae} (including \textit{E. coli, Klebsiella, Enterobacter} spp., and \textit{Citrobacter} spp., \(n=392\)) was as follows: (cefotaxime-75.5%,0.8%), (cefoperazone-72.7%,1.3%), (gentamicin-74.2%,1.3%), (amoxicillin-32.7%,9.2%), (nalidixic acid-94.4%,0.3%), (norfloxacin-86%,2%), (ciprofloxacin-79.6%,0.5%), (trimethoprim-sulphamethoxazole-89%,0.8%), and (nitrofurantoin-26.8%,7.4%). \textit{In vitro} R and IS in \textit{P. aeruginosa} (\(n=34\)) were as follows: (cefoperazone-88%,4%), (nitrofurantoin-32%,12%), (amoxicillin-72%,12%), (vancomycin-12%,0%); and HLAR-G in 86 per cent isolates. \textit{In vitro} R and IS in \textit{Enterococcus fecalis} (\(n=50\)) were as follows: (ciprofloxacin-88%,4%), (nitrofurantoin-32%,12%), (amoxicillin-72%,12%), (vancomycin-12%,0%); and HLAR-G in 86 per cent isolates. Among 108, 8, and 5 isolates of \textit{Enterobacteriaceae}, \textit{Acinetobacter}, and \textit{P. aeruginosa} tested for second

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
Organism & Surgical (%) & Medical (%) & PICU (%) & Emergency (%) & Overall (%) \\
\hline
\textit{Escherichia coli} & 118 (48.4) & 118 (47.8) & 13 (28.3) & 23 (56.1) & 272 (47.1) \\

\textit{Klebsiella pneumoniae} & 35 (14.9) & 36 (14.6) & 4 (8.7) & 9 (22) & 84 (14.5) \\
\textit{K. oxytoca} & - & 4 (1.6) & 1 (2.2) & 1 (2.4) & 6 (1.0) \\

\textit{P. mirabilis} & 10 (4.3) & 6 (2.4) & 1 (2.2) & 1 (2.4) & 18 (3.1) \\
\textit{P. vulgaris} & 1 (0.4) & 1 (0.4) & - & - & 2 (0.3) \\
\textit{M. morgani} & 5 (2.1) & 9 (3.6) & - & - & 14 (2.4) \\

\textit{Staphylococcus aureus} & 6 (2.6) & 4 (1.6) & - & - & 10 (1.7) \\

\textit{Pseudomonas aeruginosa} & 19 (7.8) & 10 (4) & 5 (10.9) & - & 34 (5.9) \\

\textit{Enterococcus fecalis} & 15 (6.4) & 25 (10) & 6 (13.2) & 4 (9.8) & 50 (8.7) \\

\textit{Acinetobacter calcoaceticus-}
\textit{baumanii complex} & 7 (3) & 6 (2.4) & 3 (6.6) & - & 16 (2.8) \\

\textit{Enterobacter aerogenes} & 10 (4.3) & 9 (3.6) & 3 (6.6) & - & 22 (3.8) \\

\textit{Citrobacter spp}. & 1 (0.4) & 1 (0.4) & - & 1 (2.4) & 3 (0.5) \\
\textit{C. freundii} & 1 (0.4) & 1 (0.4) & - & - & 5 (0.8) \\
\textit{C. diversus} & 1 (0.4) & 1 (0.4) & - & - & 10 (1.7) \\

\textit{Streptococcus spp}. & 5 (2.1) & 4 (1.6) & 1 (2.2) & - & 11 (1.9) \\
\textit{haemolytic streptococci} & - & - & - & - & - \\

\textit{Candida spp}. & 7 (3) & 6 (2.4) & 6 (13.2) & 2 (4.9) & 21 (3.6) \\
\textit{C. albicans} & 4 (1.7) & 4 (1.6) & 3 (6.6) & - & 11 (1.9) \\

\textit{C. glabrata} & - & - & - & - & - \\

Total isolates & 244 & 247 & 46 & 41 & 578 \\
\hline
\end{tabular}
\caption{Microbiological profile and percentage distribution of isolates}
\end{table}

PICU= Paediatric intensive care unit
\(P^*<0.05 \quad **<0.001\) compared to other units
line antibiotics in vitro susceptibility to Imipenem, piperacillin, cefoperazone-sulbactam was found in 96.3, 50.9, and 58.3 per cent; 62.5, 50, and 50 per cent; 40, 40, and 80 per cent isolates respectively. There was no statistically significant difference in the susceptibility profiles of the isolates from various categories (surgical, medical, emergency and ICUs). LF Enterobacteriaceae with two different antibiograms (R to cefoperazone, gentamicin, cotrimoxazole, nalidixic acid, norfloxacain, ciprofloxacin, cefotaxime, amikacin; and R to cefoperazone, gentamicin, ceftrioxazole, nalidixic acid, norfloxacain, ciproflaxacin, cefotaxime but susceptible to amikacin) constituted 28 and 22 per cent of the isolates.

Our tertiary centre caters to a group of children at very high risk of UTI as can be estimated from the 28.3 per cent culture positivity. Similar situations exist in other parts of India, albeit the load has not been studied in children12. Important facts emanating from the present study include (i) infants (25.6%) and toddlers (38.7%) represent the group most vulnerable to UTI, (ii) Male gender is clearly a risk factor towards acquiring UTI in infancy, (iii) not surprisingly, majority of culture positive cases were diagnosed in patients attending paediatric surgery OPDs, as a complication of PUV, VUR, other congenital abnormalities, neurogenic bladder and obstructive uropathy. Pre-existing congenital anomalies and physiological voiding disturbances contribute to the high burden of disease as seen in other studies12 (iv) E. coli (47.1%) was the leading aetiology of paediatric UTI at our center, multidrug resistant microbes (Enterococcus spp., K. pneumoniae, P. aeruginosa and Candida spp.) were responsible for a substantial proportion of infections, however, staphylococci were not found to play a major role in UTI at our center (<2%) unlike reports from elsewhere13, (v) incidence of UTI in our PICU was high compared to that reported from the western world14,15, and Candida spp., E. fæcalis and Pseudomonas aeruginosa complex were the major pathogens, (vi) 2nd generation cephalosporins, co-trimoxazole and fluoroquinolones, once the mainstay in treatment of UTIs, were no longer useful at our centre. Previous work from our laboratory has shown very high rates of extended spectrum beta-lactamase and Amp-C beta-lactamase production16 in these isolates, (vii) carbapenem resistance has spread to E. coli and K. pneumoniae and an increase is seen in the isolation of VRE (from 5.8% in 200317 to 12% in 2006), (viii) presence of antibiotype clones of bacteria suggests that resistance to currently useful agents (imipenem and amikacin) may increase with great rapidity in future, (xi) most of the infections were acquired due to nosocomial transmission. Surgical intervention and long term indwelling catheters were recognized risk factors towards UTI acquisition in these patients. Infection control and catheter and bag care practices have a major role in prevention of such infections18. While a majority of our patients with PUV and VUR showed complete cure, a substantial proportion showed relapsed infections. Re-infection due to a more resistant antibiotic (9.4% of these patients) points towards the need for better infection control practices.

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References


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