Original Article

http://journals.sbmu.ac.ir/jpn
https://doi.org/10.22037/jpn.v8i1.29701

Bacteriuria in Children with Special Reference to Structural Abnormalities of Urinary Tract

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Abstract

Background and Aim: Urinary tract infection (UTI) can lead to adverse renal outcomes in the form of renal scarring and its consequences in children. Underlying congenital abnormalities of the kidney and urinary tract (CAKUT) play a crucial role in UTI recurrence and its outcome.

Methods: This study was conducted to evaluate children aged 1 month to 18 years with bacteriuria retrospectively to assess recent trends of antimicrobial resistance, underlying structural abnormalities of the urinary tract, and severity of symptoms associated with it. Ultrasonography was done in children under 2 years with a history of recurrent UTI to exclude associated structural abnormalities of the urinary tract.

Results: Of 255 studied children, 58% were female. Ultrasonography of the kidney and bladder was performed in 116 children, which revealed CAKUT in 38% (n=44). Children with CAKUT commonly presented with fever (36%) alone or in combination with other features. The most common pathogen was *E coli* (60%), which was very sensitive to intravenous aminoglycosides (95-100%) and carbapenems (96%) but had less sensitive to cephalosporins (43%). *E coli* showed higher resistance to oral cephalosporins and quinolones (62% and 54%, respectively). *E coli* had a high (93%) and *Klebsiella spp* had a low (63%) sensitivity to nitrofurantoin.

Conclusion: This study revealed that about one fifth of the children with bacteriuria had CAKUT. A higher resistance pattern was observed to commonly used oral antimicrobial agents, which eventually narrows down the choice of empirical antibiotic.

Keywords: Children; Bacteriuria; Urinary Tract Infection; Urinary Tract Abnormalities.

Received: March, 2020
Revised: March, 2020
Accepted: March, 2020

Conflict of interest: The authors declare no conflict of interest.
Please cite this article as: Qader A, Hasan J, Hasan Z. Bacteriuria in Children with Special Reference to Structural Abnormalities of Urinary Tract. J Ped Nephrol 2020;8(1):1-7. https://doi.org/10.22037/jpn. v8i1.29701

Introduction

Urinary tract infection (UTI) is one of the common infections in children. According to different studies, the prevalence of UTI is between 7-8% in children presenting to the hospital and around 3.7% in febrile children presenting to the emergency department (1, 2). The risk factors include the skin or intestinal flora under the nappy of an infant, short female urethra, and foreskin of an uncircumcised boy (3). Voiding disorders are another important cause of UTI in children. Voiding disorders can be structural (e.g. congenital abnormalities of the kidney and urinary tract) or functional (e.g. neurogenic bladder, constipation, and behavioral withholding).

Children with congenital abnormalities of the kidney and urinary tract (CAKUT), especially vesicoureteral reflux (VUR), are at increased risk of acute pyelonephritis and renal scar formation (4, 5). Those with higher grades of VUR suffer from recurrent UTI, which eventually leads to the development of hypertension and renal function impairment (6, 7, 8). About 10% of children with preexisting renal scarring will develop hypertension by adolescence or early adulthood. Female children with renal scarring are particularly at increased risk of toxemia of pregnancy (9, 10, 11). Early diagnosis and treatment of UTI can prevent the formation of renal scarring and further renal damage (12).

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CAKUT is one of the leading causes of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in children and VUR is prominent among them. An abnormal dimercaptosuccinic acid (DMSA) scan after the first episode of febrile UTI increases the risk of UTI recurrence (13). Children with recurrent UTI and VUR require long-term antibiotic prophylaxis to prevent recurrent UTI. Narasimhan et al. found that renal scarring had a significant correlation with breakthrough UTI (14). *Escherichia coli* (*E coli*) is reported to be the most common organism in different studies with a prevalence of as high as 70%. Other common organisms include *Enterococcus*, *Klebsiella* and *Proteus* (15, 16, 17). Common antimicrobial agents used for empirical therapy to treat UTI include cephalosporins, quinolones, or co-trimoxazole (18, 19, 20, 21, 22). However, the choice of drug therapy also depends on the local antibiotic resistance pattern. The increasing trend of antibiotic resistance is the most concerning challenge for physicians. The most common resistance pattern is related to beta lactamase among which extended spectrum beta-lactamase (ESBL) producing bacteria are the greatest concern. ESBL producing bacteria are resistant to penicillin, extended cephalosporins, and aztreonam (24). Treatment of UTI caused by carbapenem resistant *Enterobacteriaceae* (CRE) is also a challenge. It is reported that UTI accounts for about one fourth of the CRE infections (25). Considering the burden of antimicrobial resistance, it is important to know the recent trends of antimicrobial susceptibility. Taking the above factors in consideration, this study was conducted to evaluate the severity of the symptoms and bacterial susceptibility of childhood UTI and its association with unrevealed CAKUT.

Methods

This retrospective observational study was conducted in the department of paediatrics and microbiology of a tertiary care hospital, Dhaka city, Bangladesh. Children aged 1 month to 18 years that presented to the hospital between January and December 2018 and had a positive urine culture were included in the study. Children with a bacterial colony count of less than $5x10^4$ and/or with a primary diagnosis other than UTI, sepsis or pyrexia of unknown origin were excluded from the study.

Definition of UTI:

UTI was defined according to our institutional UTI guideline, which is based on the definition presented by the American Academy of Pediatrics (26). The following criteria were used to define UTI: isolation of $\geq 10^5$ colony-forming units (CFU)/ml of a single organism in a freshly voided midstream sample, $5x10^4$ CFU in a catheter sample, or any growth of single organism in suprapubic aspiration sample. Urine bag samples were excluded.

Data collection:

Demographic data including age, gender, past medical history, duration of hospitalization, and treatment history were collected from the medical records. Laboratory data including type of specimen, urinary pathogen(s), and antimicrobial sensitivity were retrieved from the records of the microbiology laboratory.

Laboratory procedure:

In the hospital setting, urine samples collected for culture and sensitivity testing are transferred immediately to the microbiology lab at room temperature. Urine samples are cultured on blood and MacConkey's agar. The plates are incubated at 37°C for 48 hours and bacterial identification and susceptibility testing are performed. As per CLSI guideline, bacterial susceptibility is tested for amoxicillin- clavulanic acid, amikacin, cefuroxime, cefixime, ceftriaxone, cefepime, ciprofloxacin, colistin, gentamicin, meropenem, nitrofurantoin, piperacillin-tazobactam, and co-trimoxazole for Gram-negative organism and penicillin, cefuroxime, cefoxitin, ciprofloxacin, nitrofurantoin, co-trimoxazole, linezolid, vancomycin, clindamycin, erythromycin and gentamycin for Gram-positive organisms (26).

Children aged 2- 24 months that presented with features of upper urinary tract infection (fever with or without abdominal pain, persistent vomiting or shock and laboratory evidence of sepsis) and a previous history of urinary tract infection underwent an ultrasonography of the kidney and urinary bladder (27, 28, 29).

Results

In 2018, 287 children aged 1 month to 18 years had a positive urine culture. Of 287 patients, 225 met the inclusion criteria and joined the study.

The mean age± SD of the study population was 6.16±5.61 years. Moreover, 54% of the children were below 5 years and only 11% were above 15 years. The study population was female dominant with girls constituting 58% of the subjects (Table 1). Of 225 children, 116 underwent ultrasonography of the kidney and urinary bladder to find any underlying structural abnormality. Table 2 shows the presenting features of the children and their relationship with congenital abnormalities of the kidney and urinary tract (CAKUT). Children with CAKUT (n=44) mostly presented with a fever alone (36%) followed by fever and dysuria (10%) and fever plus other symptoms (7%). Children without a CAKUT presented with fever (22%) and dysuria (18%).

Of 44 children with CAKUT (Table 3), 22 (50%) had unilateral and 11 (25%) had bilateral hydronephrosis. Thirteen patients underwent micturating cystourethrography (MCUG), which showed normal results in 3 and VUR in 10 patients. Of 10 children with VUR, 3 had primary VUR, 4 had duplex collecting systems with VUR, 2 had posterior urethral valves with

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Table 1. Demographic details of the study populations (n=225)

	Male		Female		Total	
	No	%	No	%	No	%
Less than 5 years	68	56	54	44	122	54
5 to 10 years	8	20	32	80	40	18
10 to 15 years	10	26	28	74	38	17
More than 15 years	8	32	17	68	25	11
Total	94	42	131	58	225	100

Table 2. Presenting features of children who underwent USG (n=116)

	Fever No (%)	Dysuria No (%)	Fever& Dysuria No (%)	Others No (%)	Missing information No (%)	Total No (%)
Presence of CAKUT	16 (36) *	6 (14)	5 (11)	5 (11)	12 (27)	44 (38)
No CAKUT	16 (22) $	13 (18)	5 (7)	18 (25)	20 (28)	72 (62)
Total	32 (28)	19 (16)	10 (9)	23 (20)	32 (28)	116 (100)

CAKUT Congenital abnormality of kidney and urinary tract
* Percentages out of CAKUT
$ Percentages out of No CAKUT

Table 3. Type of CAKUT among USG positive children (n=44)

Type of CAKUT	No.	%
Unilateral Hydronephrosis	22	50
Bilateral Hydronephrosis	11	25
Duplex collecting system with vesico-ureteric reflux (VUR)	4	9
Vesico-ureteric reflux (VUR)	3	7
Posterior urethral valve with vesico ureteric reflux	2	5
Horshoe kidney with urethral duplication with bilateral VUR	1	2
Crossed fused ectopia	1	2
Total	44	100

VUR and 1 had a Horshoe kidney with urethral duplication and VUR.

Table 4 shows the antimicrobial sensitivity pattern of Gram-negative (Table 4a) and Gram-positive (Table 4b) bacteria. The most common bacteria in this study was *E coli* (n-133), which was highly sensitive to intravenous agents like colistin (100%), polymyxin B (100%), tigecycline (100%), nitrofurantoin (98%), meropenem (96%), amikacin (95%), and piperacillin- tazobactam (90%), but it had a lower sensitivity to cephalosporins like ceftriaxone and cefepime (resistance to both was 57%). The sensitivity of *E coli* to oral antimicrobials was below par as this pathogen showed higher resistance to most of the oral agents like ciprofloxacin (54%), cefixime (59%), cefuroxime (62%), and amoxicillin-clavulanic acid (63%). *Klebsiella spp.* and *Enterobacteria spp.* were 100% sensitive to both of the aminoglycosides, i.e. amikacin and gentamycin, 60-100% sensitive to 3rd and 4th generation cephalosporins, and 80-100% sensitive to ciprofloxacin. *Pseudomonas spp*. was 100% sensitive to colistin, polymyxin B and co-trimoxazole, 88% sensitive to amikacin and gentamycin, and 78% sensitive to ceftazidime.

The most common Gram-positive organism was *Enterococcus spp.* (n=17), which was sensitive to linezolid (100%), vancomycin (94%), nitrofurantoin (94%) and ciprofloxacin (40%).

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Table 4a. Antimicrobial sensitivity pattern of gram -ve bacteria (n=185)

	Escherichia coli (n=133)	Klebsiella spp (n=19)	Enterobacter spp (n=12)	Proteus spp (n-10)	Pseudomonus spp (n=9)	Citrobacter spp (n=1)	Serratia spp (n=1)
Moxaclav	37	53		70			
Cefuroxime	38	58		70			
Cefixime	41	63	25	`90		100	100
Ceftriaxone	43	68	100	90		100	100
Ceftazidime					78		
Cefipime	43	68	100	90		100	100
Gentamycin	86	100	100	80	88	100	100
Amkacin	95	100	100	100	88	100	100
Co-Trimoxazole	42	74	100	40	100	100	100
Ciprofloxacin	46	82	100	89			
Piptazo	90	100	88	100	88	100	100
Nitrofurantoin	98	63	38			100	
Meropenem	96	100	100	100	63	100	100
Colistin	100				100		
Polymixin-B	100				100		
Tigacyclin	100						

NB: Numbers are percentages of susceptible organisms

Table 4b. Antimicrobial sensitivity pattern of gram +ve bacteria (n=40)

	Enterococcus spp (n=17)	Streptococcus spp (n=11)	CONS* (n=7)	Staphylococcus aureus (n=5)
Cefuroxime			57	40
Ceftriaxone		100		
Gentamycin			88	71
Amikacin			100	
Co-trimoxazole			71	60
Ciprofloxacin	40	64	86	20
Clindamycin		73	100	20
Nitrofurantoin	94	100	100	100
Linezolid	100	100	100	100
Vancomycin	94	100	100	100

NB: Numbers are percentages of susceptible organisms
*Coagulase negative Staphylococcus aureus

Other Gram-positive organisms included *Coagulase negative staphylococcus* (CONS) and *staphylococcus aureus*, which were 100% sensitive to linezolid, vancomycin, and nitrofurantoin as well as amikacin and clindamycin for CONS.

In this study, 68 participants had ESBL producing bacteria among which *E coli* (n=59) was predominant; other bacteria were *Klebsiella pneumonia* (n=7), *Pseudomonas aeruginosa* (n=1), and *Proteus mirabilis* (n=1). CRE positive *E coli* was found in 5 participants. None of the subjects had vancomycin resistant *Enterococcus* (VRE) or methicillin resistant *Staphylococcus aureus* (MRSA).

Discussion

UTI is a frequent infection in children, which may lead to adverse events like renal scar formation and long-term consequences. The long-term impact of UTI is more marked in in children less than 2 years old as it is most commonly associated with structural abnormalities of the kidney and urinary tract (CAKUT); these patients

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frequently develop acute pyelonephritis, which may eventually lead to renal scar formation and renal damage (30, 31, 32). In this study, most of the participants were below five years (54%), which was similar to some other studies (16, 33). This study showed an expected predominance of female participants (58%), which was consistent with earlier studies (1, 16, 33, 34). Ultrasonography was performed in febrile children of less than 2 years with a history of previous UTI to find any underlying structural abnormality and to differentiate between complicated and uncomplicated UTI. This study found that 38% (n= 44) of the subjects who underwent an ultrasound evaluation had CAKUT whereas a study by Kalaitzidou et al. found CAKUT in 14.4% of the subjects (35). Children with a dilated upper urinary tract have 15% higher risk of developing pyelonephritis compared to children with a normal urinary tract (36). Children who have a preexisting CAKUT are at increased risk of developing pyelonephritis, which may lead to renal insufficiency in the future (37). Renal hypoplasia-dysplasia and high-grade VUR are more frequently associated with renal scar formation following a UTI episode (38, 39). It has been reported that up to 5% of girls and 13% of boys develop renal scarring following the first episode of a febrile UTI (40, 41, 42). Other risk factors of renal scar formation include recurrent pyelonephritis, delayed initiation of antimicrobial treatment, bacterial virulence, and host factors (43, 44, 45, 46, 47). Children, particularly those below 2 years, are at increased risk of renal scar formation and need attention for early initiation of antimicrobial treatment (40).

The most common structural abnormality in patients undergoing ultrasonography is unilateral hydronephrosis (50%, n= 22). A vesicoureteral reflux was found in 10 patients (22%), of whom 7% (n= 3) had primary VUR and the rest had a posterior urethral valve, urethral duplication, or a duplex collecting system. The detection rate of VUR was lower in our study compared to 61% in a study by Kalaitzidou et al (36).

In this study, *E coli* (60%) was the most common organism isolated from the urine followed by *Klebsiella spp*. (8%), *Enterobacteriaceae spp*. (5%), and *Proteus spp*. (4%). Gram-positive organisms such as *Streptococcus spp*. (5%) and *Staphylococcus spp*. (3%) were also isolated from urine specimens. Earlier pediatric UTI studies from different geographical regions also found similar results, indicating the predominance of *E Coli* (36, 48, 49, 50, 51, 52). Nazme et al. conducted a single center in the same city and reported a similar bacterial profile with *E Coli* being the most common (62%) followed by *Enterococcus* (19.2%) and *Klebsiella spp*. (10%) (16). *Pseudomonas spp*. caused 4% of the UTIs in this study (n= 9), which was similar to the study by Nazme et al. (3.4%) (16)

Regarding antimicrobial sensitivity, *E coli* was 100% sensitive to colistin, polymyxin B and tigecycline and 90-98% sensitive to amikacin, meropenem and nitrofurantoin. It was 43% sensitive to intravenous cephalosporins, which presents a poor picture for commonly used antimicrobials similar to a study by Nazme et al. (16). Considering oral antimicrobials for empirical therapy, resistance to amoxicillin-clavulanic acid, ciprofloxacin, and oral cephalosporins like cefuroxime and cefixime was 60%, 56%, and about 60%, which challenges decision-making in this situation. *Klebsiella spp*. was 100% sensitive to aminoglycosides, meropenem and piperacillin- tazobactam, 60-70% sensitive to cephalosporins, and 80% sensitive to quinolones, which offers a better picture compared to an earlier study by Nazme et al. and studies conducted in neighboring countries (16, 50). Considering the above scenario, cephalosporins and amoxicillin- clavulanic acid are not a good choice for empirical therapy whereas quinolones such as ciprofloxacin can be administered for initial therapy.

E coli was 98% sensitive and *Klebsiella spp* was 63% sensitive to nitrofurantoin. On the other hand, nitrofurantoin was a good fit for all the gram-positive organisms as the sensitivity rate was 94 -100%, suggesting that it can be considered as a drug of choice for treatment and prophylaxy. The sensitivity of *E coli* and *Klebsiella spp* to co-trimoxazole was 42% and 74%, respectively. Therefore, co-trimoxazole is not a good choice for treatment of UTI but it may be used for prophylaxis with careful regular monitoring for breakthrough UTI.

Conclusion

This study found that about one fifth of the participants had CAKUT and a higher percentage of resistance to commonly used antimicrobial agents. This resistance pattern narrows the choice of empirical therapy and antibiotic treatment. In order to prevent the long-term consequences of CAKUT, pediatricians are required to pay sincere attention to careful evaluation and management.

Acknowledgements

The authors wish to thank the Department of Microbiology and Pediatrics for helping us by providing data for this study.

Conflict of Interest

The author declares no conflicts of interest.

Financial Support

None.

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