ETIOLOGY AND ANTIBIOTIC RESISTANCE PATTERN OF COMMUNITY-ACQUIRED URINARY TRACT INFECTIONS IN CHILDREN

Samin Ullah Shah, Ambreen Ahmad, Islam Gul, Gohar Rehman

ABSTRACT

Objective: To find out the causative agents of community-acquired urinary tract infections and their antibiotic sensitivity pattern in pediatric patients.

Methods: This study was conducted at Pediatric department, Khyber Girls Medical College/Hayatabad Medical Complex, Peshawar from 1st July 2014 to 30th June 2015. All children from 2 months to 15 years of age with provisional diagnosis of UTI based on history and urinalysis findings were included in the study after taking consent. Urine samples for cultures were obtained by suprapubic aspiration, transurethral bladder catheterization or clean-catch midstream method. The bacterial agents which caused UTI were isolated, characterized & identified using standard microbiological tests. Antibiograms of all the isolates were performed by the disc-diffusion technique using Ampicillin, Amoxycillin + Clavulanic acid, Cephalexin, Cefixime, Ceftriaxone, Cefotaxime, Co-Trimaxazole, Ciprofloxacillin, Nalidixic acid, Nitrofurantoin, Amikacin, Gentamycin, Cefoperazone/Sulbactam, Piperacillin/Tazobactam and Meropenem.

Results: Out of 230 positive urine cultures, 225 (97.8%) were gram negative bacilli and 5 (2.2%) were gram positive cocci. Among gram negative bacteria, E.coli was the predominant isolate (165/225) followed by Klebsiella sp (30/225) and Pseudomonas (13/225). All gram negative bacteria in general were found to be resistant to the commonly used antibiotics and were sensitive to amikacin, nitrofurantoin, imipenem, cefoperazone/sulbactam and piperacillin/tazobactam. Moreover, 50.9% of the E-coli were extended spectrum beta lactamase (ESBL) producer.

Conclusion: The resistance pattern of uro-pathogens causing urinary tract infections to common antimicrobial agents is changing and must be taken into account when selecting treatment strategies.

Such studies will guide clinicians to choose accurate empirical treatment options and will help to reduce the mortality and morbidity. Moreover, a change in empiric therapy should be considered.

Key Words: Urinary tract infections, E.coli, Klebsiella, Antibiotic sensitivity/resistance pattern, Empirical treatment, Pediatrics.

INTRODUCTION

Urinary tract infection (UTI) is common in pediatric practice and an important cause of morbidity and mortality in children. It is associated with significant acute morbidity and long-term illnesses such as arterial hypertension and chronic renal failure; that is why it is necessary to make an early diagnosis, provide effective treatment and appropriate follow-up[1,2]. Because the clinical presentation tends to be nonspecific in infants and reliable urine specimens for culture cannot be obtained without invasive methods (urethral catheterization or suprapubic aspiration [SPA]), diagnosis and treatment may be delayed. Most experimental and clinical data support the concept that delays in the institution of appropriate treatment of pyelonephritis increase the risk of renal damage[3].

Pediatric urinary tract infections (UTI) account for 0.7% of physician office visits and 5–14% of emergency department visits by children annually. The epidemiology of UTI varies according to age and sex. About 5% of girls and 2% of boys experience at least one episode of urinary tract infection. The global prevalence in children under two years of age is 7%[4].

If UTI is suspected, urinalysis and urine culture should be performed. Collection methods used in clinical practice can be either invasive or non invasive, yet all carry a risk of contamination by bacteria not present in the bladder. Clean voided methods are preferable as they are quite easy to perform and reliable, while invasive methods should be limited to children in poor general health[5]. In the presence of clinical signs and positive urinalysis, while awaiting the results of antimicrobial sensitivity testing, antibiotic treatment should be started as soon as possible, considering local resistance patterns. The need for imaging after a first febrile UTI has long been debated. New insights have led us to

Department of Pediatric Khyber Girls Medical College/ Hayatabad Medical Complex, Peshawar

Address for Correspondence:
Dr. Samin Ullah Shah
Associate Professor,
Pediatric A Unit,
Hayatabad Medical Complex, Peshawar.
Ph: 03339364507.
E-mail: saminushah@yahoo.com

consider less aggressive imaging strategies, given the high rate of spontaneous resolution of vesico- ureteral reflux with age and the good renal outcome for patients with acquired scarring. Therefore, voiding cystography and renal dimercaptosuccinic acid scintigraphy are not routinely recommended. As regards preventive interventions, the most controversial is the use of antibiotic prophylaxis and currently none of the recently published guidelines recommend a routine use[6,7].

The most common organism causing UTI in children is Escherichia coli, accounting for up to 80% of infections. Other bacterial pathogens include Pseudomonas aeruginosa, Enterococcus faecalis, Klebsiella pneumoniae, group B Streptococcus (predominately in neonates), Staphylococcus aureus (consider other sites of infection via hematogenous spread, renal abscess, and pyelonephritis), Proteus mirabilis (boys > 1 year old and associated with renal calculi), or coagulase-negative Staphylococcus. Fungal UTI can be caused by Candida albicans (associated with instrumentation of the urinary tract); viral UTIs can be caused by adenovirus and BK

virus (hemorrhagic cystitis). In hospitalized patients, the common nosocomial pathogens are E coli, C albicans, and P aeruginosa[8,9].

Treatment is often started empirically based on the local prevalence of organisms and susceptibility pattern. Presently this situation is challenging to the treating pediatricians as multidrug resistant (MDR) organisms are on the rise among children. Multidrug resistance is defined as resistance to two or more different structural classes of antimicrobial agents. Multidrug resistance has become a universal phenomenon across organisms and may complicate the therapeutic management of infections. Antibiotic resistance can cause serious disease and is an important public health problem[10].

Drug resistance has been a common occurrence in infections among adults and elderly, but now it is frequently seen in children as well. Overuse and use of incomplete course of antibiotics as well as empirical antibiotic therapy have been the major contributing factors in the development of multidrug resistant bacteria[10]. To reduce the rate of resistance it is pertinent to initiate antibiotic therapy after microbiological confirmation.

Hence, knowledge of antibiotic sensitivity pattern of the common etiological agents is of great importance. The knowledge will serve as a guide to first line treatment while the results of culture and sensitivity are being awaited. Prompt treatment will reduce the risk of renal scaring and other sequelae of UTI[11]. Moreover, the microbial isolates and their sensitivity pattern need to be analyzed at regular interval to monitor the changing pattern of microbial flora and the development of resistance to drugs, which may help the physician to treat UTI in a better way and to prevent further complications[12].

There are various studies on the prevalence of drug resistance in adults with urinary tract infections, but there are very few studies in children. Hence this study was taken up in our hospital to know the bacteriological profile and susceptibility pattern of organisms causing UTI among children and also to know the prevalence of multidrug resistant uropathogens and to formulate guidelines for the empiric antibiotic treatment of childhood UTI while awaiting the results of culture and sensitivity pattern for our region.

MATERIALS AND METHODS

This was a prospective hospital-based study carried out at Pediatric department, Hayatabad Medical Complex, Peshawar from 1st July 2014 to 30th June 2015 after ethical approval from institutional review committee. Verbal consent was taken from the parents before enrolling them in study. Patients from 2 months to 15 years who were admitted to the pediatric ward and visited the outpatient department (OPD) with diagnosis of UTI based on history and routine and microscopic examination of urine were considered for this study. Urine samples for cultures were obtained by suprapubic aspiration, transurethral bladder catheterization or clean-catch midstream method; bag-collected urine samples were not included. Midstream urine specimen were carefully collected in children older than 2 years who had achieved bladder control, while suprapubic bladder aspiration and catheter samples were collected in children less than 2 years old.

Identification of microbial growth and determination of antimicrobial susceptibility pattern was done by the disk diffusion technique, with the recommended media and standard control strains[13]. Organisms were identified by standard microbiological procedures. Susceptibility was routinely tested for the following antimicrobial agents:

Ampicillin, Amoxycillin + Clavulanic acid, Cephalexin, Cefixime, Ceftriaxone, Cefotaxime, Co-Trimaxazole, Ciprofloxacillin, Nalidixic acid, Nitrofurantoin, Amikacin, Gentamycin, Cefoperazone/Sulbactam, Piperacillin/Tazobactam and Meropenem.

UTI was defined according to the AAP guidelines[14]. Cultures were considered positive when there was growth of a single pathogen of 50,000 colony forming units/ml in a urine specimen collected by midstream catch; of $>10^4$ colony forming units/ml in urine collected by bladder catheterization; and any growth in urine obtained by a suprapubic aspiration. Mixed pathogen growth results were considered unreliable and been excluded.

The UTI occurring in the presence of catheterization, functional or anatomical abnormalities of the urinary tract, in children with altered defenses, chronic renal failure, renal transplantation, and those receiving peritoneal and hemodialysis were excluded.

RESULTS

Out of 230 positive urine cultures, 225 (97.8%) were gram negative bacilli and 5 (2.2%) were gram positive cocci. Among gram negative bacteria, E.coli was the predominant isolate (73.5%) followed by Klebsiella sp (13%) and Pseudomonas (5.6%). Among gram positive cocci, Staphylococcus aureus (1.3%) was the predominant isolate followed by Streptococcus faecalis. The isolation of various pathogens is depicted in table 1.

The sensitivity pattern of various organisms is shown in table 2. The majority of isolates of E.coli was found to be highly resistant to co-trimoxazole (100%) followed by ampicillin (97%). It was also found to be resistant to amoxycillin-clavulanic acid, ceftriaxone (77.5%) and cefotaxime (75.7%). All gram negative bacteria in general were found to be highly sensitive to nitrofurantoin, amikacin, imipenem, cefoperazone/sulbactam and piperacillin–tazobactam. Moreover, 50.9% of the E coli isolates were positive for the extended spectrum beta lactamase (ESBL).

Table 1: Pattern of isolates

Organisms	Isolates	Percentage
Gram negative bacilli (225/230)		
E coli	169	73.5%
Klebsiella	30	13%
Pseudomonas sp	13	5.6%
Proteus	6	2.6%
Acinetobacter	3	1.3%
Providentia	2	0.9%
Citrobacter sp	2	0.9%
Gram positive Cocci (5/230)		
Staphylococcus Aureus	3	1.3%
Enterococcus faecalis	2	0.9%
Total	230	100%

Table 2: Antimicrobial Sensitivity Pattern of Isolates

Antibiotic	E. coli (no: 169)		Klebsiella sp (no: 30)		Pseudomonas (no: 13)		Proteus sp (no: 6)	
	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)
Ampicillin	3	97	6.7	93.3	11.1	88.9	0	100
Amoxycillin + Clavulanic acid	4.1	95.9	20	80	11.1	88.9	16.7	83.3
Cephalexin	1.8	98.2	13.3	86.7	0	100	0	100
Cefixime	23.7	76.3	23.3	76.7	22.2	77.7	16.7	83.3
Ceftriaxone	22.5	77.5	20	80	22.2	77.7	16.7	83.3
Cefotaxime	24.3	75.7	20	80	22.2	77.7	16.7	83.3
Co-Trimaxazole	0	100	6.7	93.3	0	100	0	100
Ciprofloxacillin	23.7	76.3	30	70	11.1	88.9	33.3	66.7
Nitrofurantoin	100	0	100	0	100	0	100	0
Amikacin	100	0	100	0	100	0	100	0
Gentamycin	88.2	11.8	90	10	11.1	88.9	100	0
Cefoperazone/Sulbactam	93.5	6.5	93.3	6.7	100	0	100	0
Piperacillin/ Tazobactam	97	3	96.7	3.3	100	0	100	0
Meropenem	98.8	1.2	100	0	100	0	100	0

Table 3: Showing percentage (%) of gram negative and gram positive isolates with multidrug resistant organisms

Organisms	Isolates	MDR Isolates no (%)
Gram negative bacilli (225/230)		
E coli	169	126 (74.5%)
Klebsiella	30	8 (26.7%)
Pseudomonas sp	13	6 (46%)
Proteus	6	2 (33.3%)
Acinetobacter	3	1 (33.3%)
Providentia	2	1 (50%)
Citrobacter sp	2	1 (50%)
Total	225	145 (64.4%)
Gram positive Cocci (5/230)		
Staphylococcus Aureus	3	0
Enterococcus faecalis	2	0

Among 225 isolates of gram negative bacilli, 145 isolates (64.4%) were found to be resistant to 2 or more drugs and hence considered to be multidrug resistant. Multidrug resistance was not found among gram positive organisms. Among gram negative organisms, MDR was more prevalent in E. coli (74.5%) followed by Klebsiella sp (26.7%).

DISCUSSION

The appropriate choice of empiric antibiotic for a child with UTI requires adequate knowledge of the prevalence of organisms and their resistance pattern. Moreover, the emergence of multidrug resistant organisms is a cause of concern worldwide. Our study evaluated the types of bacterial pathogens and their patterns of antimicrobial susceptibility in children presenting with UTI. Moreover, this study also describes the prevalence of multidrug resistant organisms among children.

In the present study, E.coli was the commonest bacterial pathogen causing UTI in children. Klebsiella was the second most predominant organism followed by Pseudomonas which is consistent with earlier studies[12,15-18]. With regard to sensitivity pattern, E.coli was found to be sensitive only to meropenem (99%) piperacillin/tazobactam (97%), cefoperazone/sulbactam (93%) and amikacin (100%) while the commonly used antibiotics like ampicillin, cotrimoxazole, amoxycillin + clavulanic acid, cefexime, ciprofloxacillin, ceftriaxone, and cefotaxime, which are often used by pediatricians to treat UTI, showed a high resistance. Klebsiella and Pseudomonas, like E.coli were sensitive to amikacin, meropenem, piperacillin/tazobactam and cefoperazone/sulbactam and were resistant to 3rd generation cephalosporins, ciprofloxacillin, ampicillin and amoxycillin + clavulanic acid. These findings are in agreement with recent studies from other countries as well[19-21].

Our study showed that all the gram negative organisms causing UTI in children were sensitive to nitrofurantoin, a fact which was observed in other studies as well[10, 22, 23]. As E. coli resistant to trimethoprim-sulphamethoxazole and Fluoroquinolones have become more common, nitrofurantoin has become an important oral agent in the treatment of uncomplicated urinary tract infection.

With increasing resistance to ampicillin, co trimoxazole and amoxycillin + clavulanic acid, physicians started using quinolones and cephalosporins as first line agents. But unfortunately due to excessive use of these agents, the uropathogens developed resistance to these agents too[24]. A study conducted by Ganguly et al[25] showed that one of the main reasons for antibiotic resistance seems to be widespread and inappropriate use of antibiotics.

The emergence of resistant bacteria is a significant problem in UTI chemotherapy, especially the isolation of fluoroquinolone-resistant E. coli from patients with UTI is a serious therapeutic problem. The resistance rate for ciprofloxacin has been increasing over decades. Though the bacterial spectrum causing community-acquired UTI remained the same over time, the antibiotic susceptibility pattern has changed[16,26]. Although, quinolones were considered as one of the drugs of choice for the treatment of UTI, the increasing resistance rate necessitates a change in the empirical treatment against community-acquired UTI.

In the present study prevalence of multidrug resistant organisms among gram negative bacilli was about 64.4%, which means that 145 organisms out of 227 were resistant to two or more different structural classes of antibiotics. Among 145 MDR isolates, maximum isolates (74.5%) were E.coli. Similar studies conducted elsewhere also showed that maximum MDR isolates were seen in E.coli[27]. Since E.coli is the major causative organism causing UTI across age groups,

various drugs are being used in hospitals empirically for treating E.coli which leads to drug resistance. The situation is worsening everyday as no new antibiotics against these multidrug-resistant organisms are in advanced stages of clinical development.

In the present study, 50.9% (86/169) of the isolates were ESBL-positive uropathogens. Eshwarappa et al[28] in a community based study from India reported that 52.2% of the isolates were ESBL producers while Akram et al[29] in a multi centre study in our country reported 61% positivity rate. ESBL producers do not respond to the usually prescribed empirical therapy. Also, there is an increased risk of associated morbidity and mortality and cost of therapy when these patients are put on the standard empirical therapy. Presently, alternative antimicrobial therapy to treat ESBL-positive UTI on outpatient basis is limited. Carbapenems are the most effective in this situation but need to be administered parenterally. The experimental use of fosfomycin in treating ESBL-positive UTI has also shown promising results in the recent past[30]. All this and the high rate of ESBL positivity in the present study warrant a change in the empirical therapy for UTI to prevent the complications.

Resistance by the extended spectrum betalactamase (ESBL) mechanism is an important emerging problem in E.coli. ESBLs are betalactamase that hydrolyze penicillin and extended spectrum cephalosporins with an oxyimino side chain that includes ceftazidime, ceftriaxone, cefotaxime, and aztreonam. Antibiotic utilization patterns, including widespread cephalosporin use, have been associated with the emergence of ESBLs and a decrease of administration of these antibiotics has been associated with control of ESBL emergence[31].

A perceived limitation of this study is that it was limited only to one centre which is a known tertiary referral hospital. This may not reflect the overall antibiotic susceptibility trends across the province and country and hence emphasizes the need for a future multi-centre prospective study.

CONCLUSION

E. coli was the most common organism isolated and was found to be highly sensitive to amikacin, imipenem, nitrofurantoin, cefoperazone/sulbactam and piperacillin-tazobactam and resistant to ciprofloxacillin, ceftriaxone, cefotaxime and cefixime. Pediatricians can hence defer using cefexime, ceftriaxone and ciprofloxacin as first line agents and rather prefer nitrofurantoin and amikacin to treat UTI in children. The only disadvantage being that amikacin has to be administered parenterally and that nitrofurantoin is not available freely. As susceptibility pattern is changing around the globe, a regular monitoring of antibiotic resistance pattern is required to ensure proper therapy for children with urinary tract infections.

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