A Study on Antibiotic Usage Pattern in Pediatric Population for Urinary Tract Infection

Divya V Nair, Gopika S Kumar, Remya Raghu*
Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi-682041, Kerala, India.

Article History:
Received on: 23 Oct 2020
Revised on: 12 Nov 2020
Accepted on: 23 Nov 2020

Keywords:
Antimicrobials, Escherichia coli, Pediatric population, Urinary tract infection, Uropathogens

Abstract
A prospective observational cohort study was conducted on 144 patients admitted with UTI for a period of 1 year and observed for the recurrence for next 1 year. The objective was to study the antibiotic resistance pattern of uropathogens in UTI and to assess the antimicrobial utilization pattern in the pediatric ward of a tertiary care hospital. The confirmatory test used for UTI was urine culture. The most common causative agent for UTI was found to be Escherichia coli followed by Klebsiella. Antibiotic testing of E.coli and other isolates was done which showed greater sensitivity to meropenem and amikacin compared to other antibiotics tested. This isolates showed increasing resistance to commonly used antibiotics. Most of the children (74.31%) were treated with a single antimicrobial agent. Cephalosporins (n = 87; 60.41%) were prescribed to majority of the children, followed by Penicillin derivatives (n = 42; 29.17%) and Carbapenems (n = 16; 11.11%). The percentage of antimicrobials administered by parenteral route was found to be 79.17%. The major problems encountered in the management are relapse of UTI and treatment failure. Out of 144 children, 40 children had recurrent UTI. Among them for 25 children, antibiotics were not given according to the culture sensitivity pattern during their first UTI. Recurrent UTI can occur if adequate antimicrobial therapy based on antimicrobial susceptibility test is not given during initial UTI. This demonstrates the need for rational use of antimicrobials and judicious prescribing. The implementation of antibiotic policy and treatment guidelines based on regional data on antimicrobial susceptibility of uropathogens with periodic assessment of the clinical pharmacist in the study area is recommended.

*Corresponding Author
Name: Remya Raghu
Phone: +91 9847881842
Email: remyareghu@aims.amrita.edu

INTRODUCTION

UTI can occur at any age-group, from neonates to geriatrics. Incidence of UTI varies with the age of the child, is a clinical condition affecting the urinary tract. It occurs due to the colonisation of a pathogen anywhere in the kidney, ureter, bladder, or urethra. Gram-negative bacteria predominantly cause UTIs, Escherichia coli being the most common one (>75% of UTIs) (Pullanhi et al., 2019). Proteus, Klebsiella, Enterobacter, Citrobacter, Enterococcus and Staphylococcus saprophyticus are some of the other pathogens that cause UTI. Recent antibiotic therapy, urinary catheterisation or immuno-
suppression are usually co-related with fungal UTIs (Candida albicans infection). Symptomatic viral UTIs are rare. Recurrent UTI in children is known to cause acute morbidity, which may develop into hypertension and renal insufficiency later in life, to reduce delayed complications, early diagnosis, and effective treatment of UTI in the pediatric population has been proven essential, wing to the number of non-specific clinical characteristics, it can be quite tricky to diagnose the condition based on clinical features. A categorisation of UTI as the first infection versus recurrent infection is a more simplified and rational approach in children. The first infection is the initial UTI which is recorded by an ethical culture of urine. Recurrent infections can be classified as unresolved bacteriuria, bacterial persistence, and reinfection. For most children, urinary tract infections usually resolve with proper medical care. UTI recurrence can be attributed to many factors. Insufficient antimicrobial treatment seems to be the most frequent source of unresolved bacteriuria. Noncompliance, malabsorption, suboptimal drug metabolism, and resistant uropathogens are the critical factors for sub-therapeutic levels of the antibacterial agents. In such cases, infection normally resolves based on antimicrobial sensitivities which are assessed by proper culture of the urine after the treatment has been modified.

Pathogens found and the pattern of antibiotic sensitivity between different geographical areas in the same country can be distinctly differentiated. In India, the resistance pattern of community-acquired UTI, particularly in children, are reported occasionally. By comparing the antibiogram trends from various studies, it is understood that the resistance of uropathogens against antibiotics has increased tremendously over the years (Reghu et al., 2016). There is a need to gain knowledge about the types of uropathogens and their resistance patterns for the rational use of antimicrobials. Moreover, there is a need to know whether antimicrobial is selected based on antimicrobial susceptibility test to prevent recurrent infections, using this context, the current study will help to evaluate the antimicrobial utilisation pattern and resistance trends of isolated uropathogens from children having community-acquired UTI in our region (Mishra et al., 2014).

Method

This observational, prospective study was carried out in the department of paediatrics of a 1250 bedded tertiary care hospital, teaching and super speciality referral hospital located in Kochi, Kerala for one year from May 2016 to May 2017. The study was conducted after obtaining approval from the institutional ethics committee. Before the initiation of the study, appropriate information was provided to the study participants (and parents) and written either parent duly signed informed consent forms. Children aged ≤18 years with culture-proven UTI were included as the study participants. The standard laboratory test used for diagnosis of UTI was a growth of single uropathogenic bacteria in a urine culture from a properly collected urine sample. The study was carried out by reviewing a computerised and networked Amrita Hospital Information System (AHIS) and case files. Data like patient’s demographic characters, antibiotics prescribed, dose, route of drug administration, frequency and duration of treatment were collected from patient records. All data were recorded in data collection form and analysed to answer the objectives of this research. Data were analysed using descriptive analysis, and results were presented using tables.

RESULTS AND DISCUSSION

Out of 2187 patients admitted in the paediatrics department during May 2016- May 2017, 144 children had culture-positive UTI, making the prevalence of 6.58 %. Since our study was conducted at a tertiary care hospital and included only children with positive urine culture test, the prevalence of UTI in our study population was found to be lower: 65.28% of the study participants ( = 94) were in the age group of 1-5 years and the remaining were <1 year ( = 24; 16.67%) (Table 1). Our findings were similar to the study conducted by Rad LV et al. (Rad and Alekhya, 2015), where they observed that the majority of the patients were of the age group of 1-5 years. The main reason may be because of an immature immune system in early childhood. Considering certain anatomical and physiological factors like vesicoureteric reflux (VUR), children of this age group are also at risk of developing recurrent UTI (Mandal et al., 2015).

In <1 year age group, the males (n = 15) outnumbered females (n = 9) whereas in the second group including the 1-5 year age group was mainly female predominant (females= 63, males= 57). Similarly, the study by Gupta P et al. and Kiran et al. (Mandal et al., 2015; Kiran et al., 2017) concluded that more culture-proven cases were observed in males during their first year of life and beyond that females outnumbered the males as females have a short urethra, which is found closer to the anus, allowing the easy ascent of microbes to the urinary tract from the gastrointestinal tract leading to easy contraction of UTI in females. Since males have a longer course of the
### Table 1: Age distribution of patients observed in our study

| Age distribution     | Number (%) of patients |
|----------------------|------------------------|
| Less than one year   | 24 (16.67%)            |
| 1-5 years            | 94 (65.28%)            |
| 5-10 years           | 17 (11.81%)            |
| 10-15 years          | 3 (2.08%)              |
| 15-18 years          | 6 (4.17%)              |
| Total number of patients | 144 (100%)         |

### Table 2: Isolated uropathogens during the study period

| Pathogens             | Number (%) |
|-----------------------|------------|
| Escherichia coli      | 72 (50%)   |
| Klebsiella species    | 32 (22.22%)|
| Proteus species       | 4 (2.78%)  |
| Pseudomonas           | 8 (5.56%)  |
| Enterococcus species  | 20 (13.89%)|
| Others                | 8 (5.56%)  |
| Total                 | 144        |

### Table 3: Comparison of sensitivity and resistance patterns of E.coli and Klebsiella for various antimicrobials in urinary tract infection

| Drug                    | E.coli Sensitive | E.coli Resistant | Klebsiella Sensitive | Klebsiella Resistant |
|-------------------------|------------------|-----------------|----------------------|---------------------|
| Amikacin                | 86.11            | 13.89           | 71.88                | 28.12               |
| Gentamycin              | 59.72            | 40.28           | 59.38                | 40.62               |
| Tobramycin              | 65.28            | 34.72           | 68.75                | 31.25               |
| Ceftriaxone             | 19.44            | 80.56           | 40.63                | 59.37               |
| Cefotaxime              | 13.89            | 86.11           | 34.38                | 65.62               |
| Ceftazidime             | 16.67            | 83.33           | 37.5                 | 62.5                |
| Cefoperazone/Sulbactam  | 68.06            | 31.94           | 62.5                 | 37.5                |
| Cefixime                | 1.39             | 98.61           | 0                    | 100                 |
| Cefuroxime              | 15.28            | 84.72           | 25                   | 75                  |
| Cefazolin               | 15.28            | 84.72           | 25                   | 75                  |
| Ampicillin/Sulbactam    | 1.39             | 98.61           | 0                    | 100                 |
| Ampicillin/Amoxicillin  | 6.94             | 93.06           | 0                    | 100                 |
| Amoxicillin/Clavulanic acid | 8.33         | 91.67           | 9.38                 | 90.62               |
| Piperacillin/Tazobactam | 66.67            | 33.33           | 53.13                | 46.87               |
| Ticarcillin/Clavulanic acid | 25            | 75              | 12.5                 | 87.5                |
| Meropenem               | 95.83            | 4.17            | 81.25                | 18.75               |
| Nitrofurantoin          | 84.72            | 15.28           | 28.13                | 71.87               |
| Co-trimoxazole          | 23.61            | 76.39           | 56.25                | 43.75               |
| Ofloxacin               | 34.72            | 65.28           | 53.13                | 46.87               |
urethra and bacteriostatic secretion by the prostate gland, the percentage of UTI among males is generally found to be low.

Results indicated that E. coli (50%) and Klebsiella (22.22%) are the most common pathogens found in our hospital (Table 2). This was following other studies done by (Jitendranath, 2015; Gidabadya et al., 2017) in which E. coli (46.2% to 69%) was the predominant isolate followed by Klebsiella (15.2% to 30.8%). The sensitivity of these bacteria towards different antibiotics are found to be E. coli (95.83%) and Klebsiella (81.25%) for Meropenem, E. coli (86.11%) and Klebsiella (71.88%) for Amikacin, E. coli (84.72%) and Klebsiella (28.13%) for Nitrofurantoin, E. coli (68.06%) and Klebsiella (62.5%) for Cefoperazone/ Sulbactam, E. coli (66.67%) and Klebsiella (53.13%) for Piperacillin/ Tazobactam. The resistance of these bacteria towards different antibiotics are found to be E. coli (98.61%) and Klebsiella (100%) for Ampicillin/Sulbactam, E. coli (91.67%) and Klebsiella (90.62%) for Amoxicillin/Clavulanic acid, E. coli (98.61%) and Klebsiella (100%) for Cefixime, E. coli (86.11%) and Klebsiella (65.62%) for Cefotaxime, E. coli (84.72%) and Klebsiella (75%) for Cefuroxime, E. coli (83.33%) and Klebsiella (62.5%) for Ceftazidine, E. coli (80.56%) and Klebsiella (59.37%) for Ceftriaxone (Table 3).

The isolated organisms exhibited a greater level of resistance to frequently used antibiotics like penicillin derivatives, cephalosporins, quinolones and co-trimoxazole. In all cases, the patients were found to be resistant to more than five antibiotics. According to the study done by Nisha KV et al. (Nisha et al., 2015), E. coli displayed a higher level of resistance to generally used antibiotics like ampicillin, cephalosporins (cefixime, cefotaxime), fluoroquinolones (ciprofloxacin, norfloxacin) and co-trimoxazole. Another study by Taneja N et al. (Taneja et al., 2010) consisting of 558 E. coli isolates concluded that 32.7% were resistant to ampicillin, and 75.5% were resistant to cephalosporin. In the study by Ghadage DP et al. (Ghadage et al., 2014) over 390 culture-positive samples, about 98% was found to be resistant to ampicillin, and 87% was found to be resistant to cephalosporin. Similarly, Rao SP et al. (Rao et al., 2014) has documented 89% resistance to cephalosporins in their 857 culture-positive urine samples. Indiscriminate prescription and high prevalence of ESBL producing organism may have caused the resistance of E. coli to commonly used antibiotics to go higher (Prakasham et al., 2012).

In our study, Cephalosporins (n = 87; 60.41%) were mainly prescribed to the children, followed by Penicillin derivatives (n = 42; 29.17%) and Carbapenems (n = 16; 11.11%), which comprised of Ceftriaxone (n = 55; 38.19%), Cefotaxime (n = 11; 7.64%), Ceftazidime (n = 8; 5.56%), Cefoperazone (n = 6; 4.17%), Cefixime (n = 3; 2.08%), Cefpodoxime (n = 2; 1.38%), Cefuroxime (n = 2; 1.38%), Piperacillin/ tazobactam (n = 17; 11.81%), Amoxicillin/clavulanate (n = 15; 10.42%), Benzylpenicillin (n = 8; 5.56%), Ampicillin/cloxicillin (n = 2; 1.39%), and Meropenem (n = 16; 11.11%) respectively. Among Cephalosporins third-generation cephalosporins (59.02%) were antibiotics of choice for pediatric patients.

In this study, Piperacillin/tazobactam and Amoxicillin/clavulanate were the most prescribed drugs among penicillin derivatives. Among Carbapenems, Meropenem was the only drug which was prescribed for the pediatric patients in this study. A study conducted by Rad LV et al. (Rad and Alekhy, 2015) reported that Cephalosporins (58.06%) followed by beta-lactamase inhibitors (19.35%) were choice of antimicrobial agents for pediatric patients, and Ceftriaxone (67.77%) was the most commonly prescribed cephalosporin. A considerable rise in the use of third-generation cephalosporins for the treatment of UTI was acknowledged in our study which was similar to that conducted by Copp HL et al. and Prabahar K et al. (Copp et al., 2011; Prabahar, 2017). They reported that approximately one-third of UTI patients were treated using broad-spectrum antibiotics. This is one of the classic examples of overprescribing broad-spectrum antibiotics in pediatric patients as part of empirical therapy. According to Berild D et al. (Berild et al., 2006), the emergence of antibiotic resistance can be avoided or delayed by modifying antibiotic therapy based on blood culture findings resulting in the narrowing of antibiotic therapy.

A high percentage of patients (74.31%) were prescribed at least one antibiotic, two antibiotics were prescribed in 18.75% patients, and three antibiotics were prescribed in only 6.94% cases. Similarly, a study conducted by Shankar PR et al. (?) pointed out that, 98% of patients were prescribed a single antimicrobial agent. But on the contrary, another study conducted by Palikhe N et al. (Palikhe, 2004) two antibiotics were prescribed in most cases (37%).

In 67 children (46.53%), antibiotics were prescribed for a period of 1-5 days, in 64 children (44.44%) for 6-10 days, and 13 children (9.03%) for more than ten days. For 79.17% of patients, antibiotic was administered through IV route, 15.28% patients by oral route and 5.55% cases, both oral and IV routes of drug administration were used. The most preferred dosage form was injectables.
excessive use of injectable is common in many developing countries (Tomson et al., 1990). Injectables are given more because for immediate control of infections, to decrease morbidity and to avoid in compliance issues as compared to oral route (Kanish et al., 2014). Another study conducted by Ramesh L et al. Ramesh et al. (2012) had proven that injections (58.25%) were the most standard route of administration followed by oral route (38.20%).

Out of 144 children, for 77 children antibiotic was not given based on culture sensitivity pattern during the first UTI. Among them 40 children had recurrent UTI, in which the same organism was isolated in 19 children and the different organism was observed in 21 children during subsequent UTI episodes. The frequency of antibiotic prescription or modification based on urine culture result was low. Since the patients are doing well on empirical therapy, the findings of urine cultures were often overlooked.

UTI recurrence can be attributed to many factors. For most kids, urinary tract infections usually recover with adequate medical care. Insufficient antimicrobial treatment seems to be the most frequent source of unresolved bacteriuria. The bacterial retention and reinfection following urine sterilisation have been recorded. The uropathogens mostly remains at a spot sheltered from antimicrobial therapy. These sheltered sites are quite often anatomical abnormalities, which include infected urinary calculi, necrotic papillus, or foreign objects, such as a ureteral stent or urethral catheter that may not be sterilised once infected. It is important to detect anatomical defects as surgery (extirpation) might be required to eliminate the cause of the infection. Reinfection is determined by various pathogens recorded on proper urine cultures for each new UTI, as opposed to bacterial persistence (Chang and Shortliffe, 2006).

CONCLUSIONS

The prevalence of UTI with multi-drug resistance is increasing in the hospitalised pediatric population. The study concluded that E.coli and other isolates showed greater sensitivity to Meropenem and Amikacin when compared to other antibiotics tested. But most of the children were prescribed with Cephalosporins, followed by Penicillin derivatives. In all cases, the patients were found to be resistant to more than five antibiotics. The study helps to obtain information on the antibiotic usage pattern in the pediatric population, focusing on the prevalence of antibiotic misuse in our set-up. Recurrent UTI can occur if adequate antimicrobial therapy based on antimicrobial susceptibility test is not given during initial UTI. This shows the requirement for rational use of antimicrobials and judicious prescribing.

The clinical pharmacist plays a crucial role in monitoring adherence to antimicrobial susceptibility of uropathogens while selecting antibiotics for treatment of UTI. Close co-operation between pharmacists, clinicians and microbiologists are essential to monitoring the use of reserved antibiotics. This study aids to promote the need for appropriate use of antibiotics and also acts as a checklist to the health-care professionals for efficient monitoring. It is imperative to generate antibiogram based on the regional data to select appropriate therapy. Hence, continuous monitoring of antimicrobial susceptibility of uropathogens is necessary. The periodic assessment of this data and monitoring the clinical use of these medications in the study area is the responsibility of the clinical pharmacist.

Acknowledgement

We thank the Dept. of Pediatrics of Amrita Institute of Medical Sciences and Research Centre and the Dept. of Pharmacy Practice of Amrita School of Pharmacy for their support in the preparation of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

Funding Support

The authors declare that they have no funding support for this study.

REFERENCES

Berild, D., Mohseni, A., Diep, L. M., Jenseniuss, M., Ringertz, S. H. 2006. Adjustment of antibiotic treatment according to the results of blood cultures, leads to decreased antibiotic use and costs. Journal of Antimicrobial Chemotherapy, 57(2):326–330.

Chang, S. L., Shortliffe, L. D. 2006. Pediatric Urinary Tract Infections. Pediatric Clinics, 53(3):379–400.

Copp, H. L., Shapiro, D. J., Hersh, A. L. 2011. National ambulatory antibiotic prescribing patterns for pediatric urinary tract infection, 1998–2007. Pediatrics, 127(6):1027–1033.

Ghadage, D. P., Nale, S. S., Kamble, D. S., Muley, V. A., Wankhade, A. B., Mali, R. J. 2014. Study of aetiology and anti-biogram of uropathogens in children—a retrospective analysis. Journal of Clinical and Diagnostic Research: JCDR, 8(1):20.

Gidabayda, J. G., Philemon, R., Abdallah, M. S., Saajan,
A. M., Temu, T., Kunjumu, I. 2017. Prevalence, Aetiology, and Antimicrobial Susceptibility Patterns of Urinary Tract Infection Amongst Children Admitted at Kilimanjaro Christian Medical Centre. *EA Health Research Journal*, 1(1):53–61.

Jitendranath, A. 2015. Microbiological Profile of Urinary Tract Infection in Pediatric Population from a Tertiary Care Hospital in South Kerala. *J Bacteriol Mycol Open Access*, 1(1):4–7.

Kanish, R., Gupta, K., Juneja, S., Bains, H. S., Kaushal, S. 2014. Prescribing pattern of antibiotics in the department of pediatrics in a tertiary care medical college hospital in Northern India. *Asian Journal of Medical Sciences*, 5(4):69–72.

Kiran, R. C. H., Reddy, T. A., Kumar, R. B. 2017. A study of culture and sensitivity pattern in urinary tract infections of febrile children. *International Journal of Contemporary Medical Research*, 4(6):1258–1261.

Mandal, J., Krishnamurthy, S., Barathi, D., Pandit, N., Gupta, P. 2015. Profile of urinary tract infections in paediatric patients. *Indian Journal of Medical Research*, 141(4):471–473.

Mishra, H., Mishra, R., Mondal, A. 2014. Prescription pattern of antimicrobial drugs in paediatrics outpatient department of a tertiary care teaching hospital of North India. *International Journal of Basic and Clinical Pharmacology*, 3(2):385–388.

Nisha, K. V., Shenoy, R. D., Shetty, A. V., Shenoy, V. M., Shetty, A. K. 2015. Trends in antimicrobial resistance among uropathogens with particular reference to escherichia coli in community-acquired pediatric urinary tract infections from Kerala. *J of Evolution of Med and Dent Sci*, 7:9313–9319.

Palikhe, N. 2004. Prescribing pattern of antibiotics in Paediatric Hospital of Kathmandu Valley. *Kathmandu University Medical Journal (KUMJ)*, 2:6–12.

Prabahar, K. 2017. Antibiotics Utilisation Pattern in Pediatrics in a Tertiary Care Teaching Hospital. *Asian Journal of Pharmaceutics (AJP): Free full-text articles from Asian J Pharm*, 11(01).

Prakasam, K. A., Kumar, K. D., Vijayan, M. 2012. A cross-sectional study on the distribution of urinary tract infection and their antibiotic utilisation pattern in Kerala. *Int J PharmTech Res*, 4(3):1310–1316.

Pullanhi, U., Khan, S., Vinod, V., Mohan, K., Kumar, A. 2019. The outcome of acute urinary tract infections caused by uropathogenic Escherichia coli with phenotypically demonstrable virulence factors. *Annals of African Medicine*, 18(3):138.

Rad, L. V., Alekhya, M. 2015. Prescribing pattern of antibiotics in pediatric inpatient department of a tertiary care teaching hospital in Bangalore. *IOSR J Pharm Biol Sci*, 10:26–32.

Ramesh, L., Sangeeta, S., Hussainy, S. R. 2012. Analysis of antimicrobial prescriptions in pediatric patients in a teaching hospital. *Asian Journal of Pharmaceutical and Clinical Research*, 5:124–128.

Rao, S. P., Rama, P. S., Gurushanthappa, V., Manipura, R., Srinivasan, K. 2014. Extended-spectrum beta-lactamases producing Escherichia coli and Klebsiella pneumoniae: A Multi-centric Study Across Karnataka. *Journal of Laboratory Physicians*, 6(1):7.

Reghu, R., Padma, U. D., Sasankan, V., Puthur, S., Jose, J. 2016. A microbiological study of diabetic foot ulcer in a south Indian tertiary care hospital. *Int. J. Pharm. Sci. Res*, 37(1):167–170.

Taneja, N., Chatterjee, S. S., Singh, M., Singh, S., Sharma, M. 2010. Pediatric urinary tract infections in a tertiary care centre from north India. *Indian journal of medical research*, 131(1):101–106.

Tomson, G., Diwan, V., Angunawela, I. 1990. Paediatric prescribing in out-patient care. *European Journal of Clinical Pharmacology*, 39(5):469–473.