Irish Journal of Medical Science (1971 -) (2022) 191:279–282
https://doi.org/10.1007/s11845-021-02531-4

ORIGINAL ARTICLE

Rising resistance of urinary tract pathogens in children: a cause for concern

Mansoor Ahmed[1] · Wan Norafifah Wan Long[1] · Sidra Javed[1] · Timothy Reynolds[2]

Received: 29 December 2020 / Accepted: 26 January 2021 / Published online: 18 February 2021

Abstract

Background Urinary tract infection (UTI) is one of the common infections in childhood. Prompt diagnosis and treatment reduces the risk of complications. The choice of antibiotic to treat UTI varies from region to region. Rational use and appropriately chosen antibiotic reduces the emergence of resistant uropathogens.

Objective We investigated the resistance pattern of uropathogens for commonly used antibiotics to treat UTI locally.

Methods Data was collected between 2009 and 2019 on all infants and children under 16 years of age with culture proven UTI. Results were compared with previously published figures between 2002 and 2008.

Results A total of 1002 samples were analysed (91/year). Male to female ratio was 1:4.6. About 94% of the samples grew *E. coli*. As before, high resistance rates were recorded to Amoxicillin and Trimethoprim ($Z = -0.325$: $P = 0.7452$; not significant). Overall, average resistance has decreased for Nitrofurantoin from 10% between 2002 and 2008 to 5.84% between 2009 and 2019 ($Z = 3.002$: $P = 0.0027$). On the other hand, Cefalexin resistance has increased from 7.4 to 14.56% between the two study periods ($Z = -4.2$: $P = < 0.0002$).

Conclusion Despite rising resistance rates, we recommend that Cefalexin should cautiously remain the antibiotic of choice for empirically treating uncomplicated urinary tract infections in secondary care pending urine culture. Nitrofurantoin should be reserved for treating non-coliform/atypical UTIs or multi-drug resistant UTIs. There is an ongoing need for clinicians in all geographic regions to continue to monitor antibiotic resistance rates every few years.

Keywords Antibiotics · Resistance · Urinary tract infection · Uropathogens

Introduction

Urinary tract infection (UTI) is very common in children. Around 1 in 10 girls and 1 in 30 boys develop UTI by the age of 16. About 2% of children have a UTI by the age of two [1]. Overall, the outcome of childhood UTI is good. However, prompt diagnosis and appropriate treatment are essential in reducing complications such as renal dysfunction, renal scarring, and hypertension [1, 2]. Empirical antimicrobial treatment should be commenced in symptomatic children with suspected UTI while awaiting urine culture results. Traditionally, many organisations recommend Trimethoprim as first-line empiric antibiotic treatment for suspected UTI. However, first-line empirical antimicrobial treatment in children less than 16 years old is usually dictated by guidance based on local antimicrobial resistance pattern.

Routine and unjustifiable empirical antibiotics for treating various ailments along with easy availability of antibiotics over the counter in many countries have increased the prevalence of antimicrobial resistance globally. Likewise, antibiotic resistance to common uropathogens such as *E. coli* has also risen over the recent decades. Studies have also shown that urinary tract pathogens in children with previous primary care prescriptions for antibiotic were more likely to be resistant to treatment. This increased risk can persist for up to 6 months after treatment [3]. Therefore, it is essential for organisations to continuously monitor and evaluate antimicrobial prescribing and provide guidance which

✉ Mansoor Ahmed
mansoor.ahmed2@nhs.net

[1] Department of Paediatrics, Queen's Hospital, Belvedere Road, Burton upon Trent, UK

[2] Clinical Chemistry, University Hospitals of Derby and Burton NHS Foundation Trust, Queen's Hospital, Burton upon Trent, Staffordshire DE13 0RB, UK

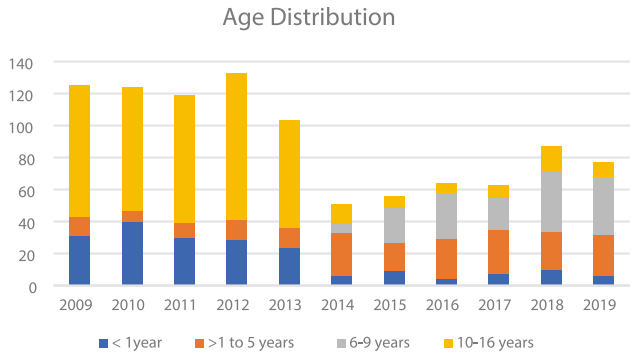

Fig. 1 Age distribution of the culture proven urinary tract infections

relates to local resistance patterns as part of their antimicrobial stewardship programme [4]. To fulfil this aim, we evaluated the resistance pattern of commonly used antibiotics to treat UTI locally.

Methods

Retrospective data analysis was carried out in infants and children between 0 and 16 years of age with culture proven UTI over a period of 11 years (2009–2019) in a district general hospital setting. All the positive urine culture reports with pure growth of $> 10^5$ of a single organism were included in the analysis. Patients were identified and data extracted using the Meditech V6, hospital electronic patient medical record software. We compared the results of this analysis with the results of a previously published data from same catchment population covering 2002–2008 [5]. Differences in proportions were statistically tested by the *Z*-score method [6].

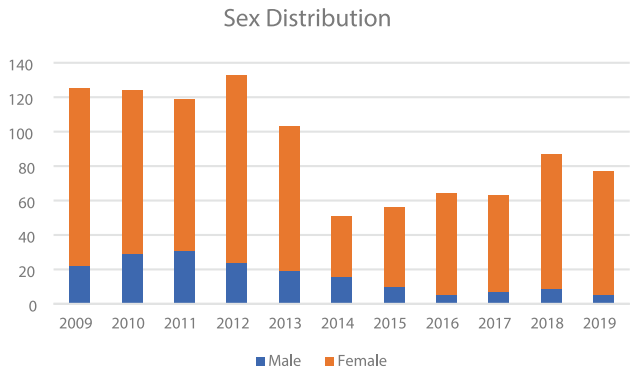

Fig. 2 Sex distribution of the culture proven urinary tract infections

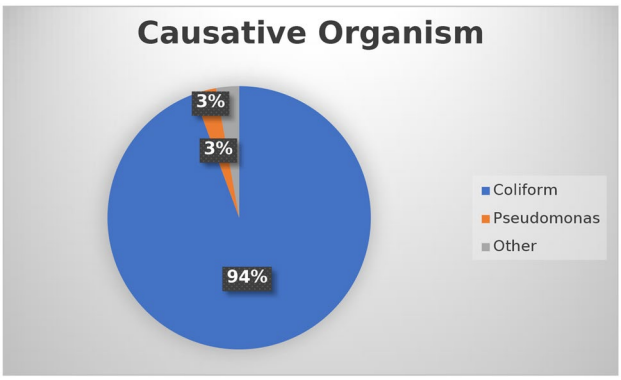

Fig. 3 Causative organism (%)

Results

A total of 1002 samples of culture proven UTI with pure growth $> 10^5$ of a single organism were analysed. Organisms that were considered contaminant were excluded from the analysis. An average of 91 positive cultures per year were analysed, compared with an average of 78 per year in our previous study[5]. It is difficult to ascertain if this truly reflected increase in the incidence of UTI in the local population or low threshold of primary care physicians to refer presumed UTI children to secondary care over the recent years. Figures 1 and 2 show the age and sex distribution of the culture proven UTI respectively. A total of 455 out of 1002 (45%) of all the cases involved children more than 10 years old. A total of 825 out of 1002 (82%) samples were received from female patients and 177/1002 (18%) from male subjects with male to female ratio of approximately 1:4.6. In the previous survey there were 547 cases and male:female ratio was 1:3. Compared with 2002–2008 data; the decrease in male cases between 2009 and 2019 was statistically significant $\{Z = 3.454; P = 0.0006$ (2-tailed)$\}$.

Coliform (*E. coli*) were grown in 946/1002 (94.4%) samples as depicted in Fig. 3. In the previous survey, 92% (503/547) +ve cultures were due to *E. coli* $\{Z = 1.879$;

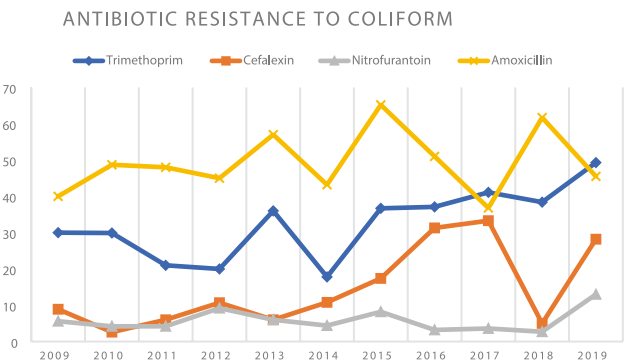

Fig. 4 Antibiotic resistance pattern (%) to Coliform (2009–2019)

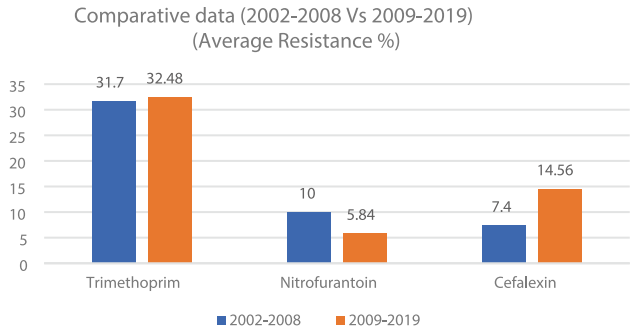

Fig. 5 Antibiotic resistance comparison between two study periods (2002–2008 vs 2009–2019)

$P = 0.062$ (2-tailed) = not significant}. Figure 4 shows Coliform (*E. coli*) resistance pattern to commonly used antibiotics over an 11-year period. Resistance to Amoxicillin has remained steadily high with the highest resistance rates of 65.2% recorded in 2015. Similarly, resistance rates for Trimethoprim seem to be progressively rising over the recent years with peak resistance of 49.3% documented in 2019. Resistance pattern to Nitrofurantoin has largely remained below 10% except in 2019 where the 10% mark was surpassed with registered resistance of 13%. Worryingly, there has been a gradual rise in resistance to Cefalexin over the last few years with maximum resistance of 33.3% logged in 2017.

Figure 5 depicts the comparison of overall/average resistance pattern of our current data (2009-2019) with our previously published analysis between 2002 and 2008[5]. Average resistance for Trimethoprim has largely remained similar between the two study periods {$Z = -0.325$; $P = 0.7452$ (2-tailed), not significant}. On the other hand, overall average resistance has decreased for Nitrofurantoin from 10% (2002–2008) to 5.84% (2009–2019) which is statistically significant {$Z = 3.002$: $P = 0.0027$ (2-tailed)}. Sadly, Cefalexin resistance has increased from 7.4% (2002–2008) to 14.56% (2009–2019) which is statistically significant {$Z = -4.2$: $P \leq 0.0002$ (2-tailed)}. We were unable to compare the Amoxicillin resistance between the two study periods as during 2002–2008 era, pathology laboratory only reported resistance to co-amoxiclav which seemed to have rapidly risen towards the latter half of the study period with 48% resistance recorded in 2008. Comparatively, cumulative Amoxicillin resistance during 2009–2019 was noted to be 49.3%.

Discussion

This study follows our previously published comprehensive data analysis which examined resistance of urinary tract pathogens to commonly used antibiotics to treat UTI between 2002 and 2008 [5]. *E. coli* remains the most prevalent pathogen isolated in the current data analysis, and this is consistent with data published in the literature. There has been no statistically significant change in the proportion of samples positive for *E. coli*. It is important to predict the risk of antibiotic resistance before prescribing empiric antibiotics. In on our previous analysis (2002–2008), based on the resistance pattern, we recommended using Cefalexin as first-line empiric antibiotic for treating urinary tract infection. The analysis of the current data (2009–2019) has shown high resistance to Amoxicillin and Trimethoprim and persistently low resistance to Nitrofurantoin. Although not very high, resistance to Cefalexin has doubled to 14.56% in the last 11 years (Fig. 5). Retrospective analysis dependent upon patient data from electronic health record is the limitation of our study. Moreover, due to technical difficulties, we were unable to capture urine cultures submitted directly from primary care general practices between 2014 and 2019 which resulted in reduced number of urine samples analysed during the last six years (Figs. 1 and 2).

Secondary analysis conducted by Bryce et al. revealed 43% *E. coli* resistant to at least one tested antibiotics with highest resistance to Amoxicillin (49%) [7]. Multi-drug resistance to three or more tested antibiotics was noted in 17% of pathogens. High resistance rates to Amoxicillin (49–62%) and co-amoxiclav (42-43%) were also recorded in two Irish regions by Allawendy SA et al. [8]. Erol and colleagues carried out a retrospective analysis of 6515 urine cultures between 2009 and 2014 and documented high *E. coli* resistance to Ampicillin (70%) and Trimethoprim-Sulfamethoxazole (56%) but low resistance to Cephalosporins [9]. Eremenko R et al. retrospectively analysed antibiotic resistance rates to uropathogens in Israel and recommended first-generation cephalosporins as preferred empiric antibiotic choice to treat children with febrile UTI in out-patient setting [10]. Authors also identified increasing resistance rates in children with urinary tract abnormalities and those who have had recurrent UTIs. Similarly, low resistance rates to first- and second-generation cephalosporins to *E. coli* were observed in their study of 769 children by Sheikh et al. [11]. Children at higher risk of antibiotic resistance included those with history of previous UTIs, recent antibiotic exposure and those with urogenital abnormalities [12–14]. In these children, urine microscopy and culture must be sent to ascertain the uropathogen and its sensitivity pattern. Moreover, selective and restrictive use of uro-prophylaxis in high-risk childhood population such as those with high grade vesico-ureteric reflux and significant hydronephrosis with emphasis on compliance may also aid in reducing or controlling the mounting resistance rates [15].

Antibiotic resistance is one of the major hazards to the world-wide health economy today. Even though antibiotic

resistance develops due several factors, misuse and overuse of antibiotics are most important reasons in speeding up its progression. Consequently, it leads to worsening morbidity/mortality, increased burden on health services, rising treatment costs, and longer duration of in-patient admissions. World Health Organisation (WHO) recommends joint efforts and multi-pronged approach between policy makers, health professionals, healthcare industry, and agriculture sector to prevent and curb the spread of antibiotic resistance [16]. WHO global action plan on antimicrobial resistance was endorsed in 2015. It consists of five aims which include raising awareness of antimicrobial resistance, consolidating surveillance/research, reducing the incidence of infection, effective use of antimicrobials, and investing in combating antimicrobial resistance [16]. Equally, development of new generation antibiotics to combat multidrug resistant infections remains the need of the hour and a mounting challenge for researchers.

The National Institute for Health and Care Excellence (NICE) Clinical Guidance pathway [CG54] for urinary tract infection in children recommends first choice therapy to be trimethoprim when risk of resistance is low, or nitrofurantoin for lower urinary tract infection [17]. Similarly, for pyelonephritis, first-line therapy recommended by NICE is either oral cephalexin or co-amoxiclav [17]. Since referral to secondary care is due to severe infection or pyelonephritis, we recommend that Cefalexin should cautiously remain the antibiotic of choice for empirically treating uncomplicated urinary tract infections in secondary care pending urine culture results because the incidence of Amoxicillin and Trimethoprim resistance is very high. However, if urine culture report is already available, then the choice of most appropriate narrow spectrum antibiotic (e.g., Trimethoprim) should only be based on the sensitivity pattern. Nitrofurantoin should be reserved for treating non-coliform/atypical UTIs or multi-drug resistant UTIs. There is an ongoing need to continue to monitor antibiotic resistance rates every few years by clinicians in all geographic regions as the rising resistance can be limited by improving antibiotic prescribing practices and antibiotic stewardship programmes through the implementation and use of local antibiotic policies.

Acknowledgements Authors would like to thank Dr DN Sobithadevi and Dr Yasmin Jolly for their help in data collection.

Author contribution All authors have participated in data collection, data analysis, writing the manuscript, and approval of the submitted version of the manuscript.

References

1. NICE (2019) Clinical knowledge summaries: urinary tract infection—children. National Institute for Health and Care Excellence. https://cks.nice.org.uk/topics/urinary-tract-infection-children/. (last accessed on 29.12.2020)
2. Coulthard MG, Lambert HJ, Vernon SJ et al (2014) Does prompt treatment of urinary tract infection in preschool children prevent renal scarring: mixed retrospective and prospective audits. Arch Dis Child 99(4):342–7
3. Bryce A, Hay AD, Lane IF et al (2016) Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association with routine use of antibiotics in primary care: systematic review and meta-analysis. BMJ 352:i939
4. NICE (2015) Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NG15). https://www.nice.org.uk/guidance/ng15. (last accessed on 29.12.2020)
5. Chakupurakal R, Ahmed M, Sobithadevi DN et al (2010) Urinary tract pathogens and resistance pattern. J Clin Pathol 63:652–654
6. http://vassarstats.net/vsprops.html. (last accessed on 29.12.2020)
7. Bryce A, Costelloe C, Wootton M et al (2018) Comparison of risk factors for, and prevalence of, antibiotic resistance in contaminating and pathogenic urinary *Escherichia coli* in children in primary care: prospective cohort study. J Antimicrob Chemother 73(5):1359–67
8. Allawendy SA, Farhan M, Biagini A et al (2019) Uropathogen profile in the paediatric population—a comparative study between two geographically distinct regions in Ireland. Arch Dis Child 104:A393
9. Erol B, Culpan M, Caskurlu H et al (2018) Changes in antimicrobial resistance and demographics of UTIs in pediatric patients in a single institution over a 6-year period. J Paed Urol 14(2):176.e1-176.e5
10. Eremenko R, Barmatz S, Lumelsky N et al (2020) Urinary tract infection in outpatient children and adolescents: risk analysis of antimicrobial resistance. Isr Med Assoc J 22(4):236–240
11. Shaikh N, Hoberman A, Keren R (2016) Predictors of antimicrobial resistance among pathogens causing urinary tract infection in children. J Pediatr 171:116–121
12. Sotto A, De Boever CM, Fabbro-Peray P et al (2001) Risk factors for antibiotic-resistant *Escherichia coli* isolated from hospitalized patients with urinary tract infections: a prospective study. J Clin Microbiol 39(2):438–44
13. Cheng CH, Tsai MH, Huang YC et al (2008) Antibiotic resistance patterns of community-acquired urinary tract infections in children with vesicoureteral reflux receiving prophylactic antibiotic therapy. Pediatrics 122(6):1212–7
14. Allen UD, MacDonald N, Fuite L et al (1999) Risk factors for resistance to "first-line" antimicrobials among urinary tract isolates of *Escherichia coli* in children. CMAJ 160(10):1436–40
15. Edlin RS, Copp HL (2014) Antibiotic resistance in pediatric urology. Ther Adv Urol 6(2):54–61
16. World Health Organisation (2020) Antibiotic resistance. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. (last accessed on 29.12.2020)
17. NICE (CG54) Urinary tract infection in under 16s: diagnosis and management. https://www.nice.org.uk/guidance/cg54/resources/urinary-tract-infection-in-under-16s-diagnosis-and-management-pdf-975507490501. (last accessed on 29.12.2020)