Can We Predict Antibiotic-resistance in Urinary Tract Infection?

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Summary

In this study, 769 children (age 2-71 mo) enrolled in the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) or Careful Urinary Tract Infection Evaluation (CUTIE) studies were included to determine the risk factors of having pathogens resistant to narrow spectrum antimicrobials in urinary tract infection (UTI). The authors used logistic regression models to test the associations between demographic and clinical characteristics and resistance to narrow spectrum antimicrobials. Of the included patients, 91% were females, and 76% had vesicoureteral reflux. The odds of resistance to narrow-spectrum antibiotics in uncircumcised males were approximately 3 times that of females (OR 3.1; 95% CI 1.4, 6.7); in children with bladder bowel dysfunction, the odds were 2 times that of children with normal function (OR 2.2; 95% CI 1.2, 4.1). Children who had received one course of antibiotics during the past 6 months also had higher odds of harboring resistant organisms (OR 1.6; 95% CI 1.1, 2.3). Hispanic children had higher odds of harbouring pathogens resistant to some narrow-spectrum antimicrobials. The authors concluded that uncircumcised males, hispanic children, children with bladder bowel dysfunction, and children who received a course of antibiotics in the past 6 months were more likely to have a urinary tract infection caused by pathogens resistant to one or more narrow-spectrum antimicrobials.

Commentaries

Evidence-based Medicine Viewpoint

Relevance: Urinary tract infection (UTI) is a fairly common clinical problem, occurring in upto 10% female and 3% male infants and toddlers [1]. Children with vesico-ureteric reflux (VUR) have greater risk of recurrent episodes and potentially serious consequences, including renal scarring [2]. Appropriate administration of antibiotic therapy is therefore vital, and guidance for choice of initial empiric antibiotics is important.

Critical appraisal: In a sense, this report represents analysis of data obtained from the primary studies. The commendable aspects include clear definitions of UTI and VUR. The primary studies included infants and children with their first or second episode of UTI, yet none were receiving antibiotic prophylaxis. This is somewhat unusual considering that the bulk of evidence and clinical guidelines recommend VUR screening and antibiotic prophylaxis following the first episode of (confirmed) UTI [3].

In this analysis, antibiotics were appropriately grouped according to class, taking care to exclude cephalothin from the first generation cephalosporins, on account of its inconsistent association of resistance with the other agents in the same class. As data were pooled from sites participating in the primary studies, and antibiogram protocols were not uniform across sites, it is difficult to assess whether some of the geographic differences could be explained by this. The investigators examined data separately for *E. coli* and other organisms; although their type and frequency are not described.

The investigators examined the effect of presence, and grade of VUR on antibiotic resistance, but the results are presented only for the grade of VUR. Analysis of patterns among those with (and without VUR) would have helped to understand differences in the pattern of pathogens, antibiotic sensitivity pattern(s), and clinical implications for corresponding episodes of UTI in those without VUR. It is unclear whether the data of the relatively few boys in this analysis could be representative of the whole sex, especially considering that boys often have other underlying conditions predisposing to UTI episodes.

What can we learn from this data analysis? It is difficult to confirm whether the differences are mere statistical artifacts, or clinically meaningful. This is because none of the 'predictors' showed consistency across all antibiotics studied. Similarly some differences are difficult to explain, such as why one prior course of

antibiotic increases the likelihood of resistance; whereas two or more courses (within the same time frame) have no apparent effect. Some observations could have a genetic basis; for example Hispanic children could have different pharmacokinetics for trimethoprim-sulphamethoxazole, compared to other groups. But in the absence of further information, no meaningful conclusions can be drawn. Similarly, the observation of more frequent resistance in one geographic region is unhelpful without additional data.

Therefore, it is pertinent to examine the data from this analysis [4] against the backdrop of other available data. In this analysis, *E. coli* was the most prevalent organism, and it showed variable degrees of resistance to different antibiotics, but especially high resistance to amoxicillin. This is in consonance with data from various developing countries, including India [5-13].

Prior antibiotic therapy has been associated with subsequent infection by resistant organisms in diverse settings. This is a pattern consistent with UTI as well as other infections [14-19]. The pattern seems consistent irrespective of age, site of initial infection, or whether the subsequent infection is with the same or a different organism. In this light, this analysis [4] does not provide new information. There is ample evidence that antibiotic therapy results in selection of organisms that are resistant (or can develop resistance). Recent hypotheses suggest that the gap between the minimum inhibitory concentration (MIC) of antibiotic and the mutant prevention concentration (MPC) called the 'mutant selection window' creates a range wherein resistant mutants are more likely to thrive [20]. Against this backdrop, the investigators' recommendation [4] that children having characteristics associated with greater resistance to specific narrow-spectrum antibiotics should be treated with broader spectrum agents or another antibiotic, appears too simplistic. Although this may work in the short-term reducing the risk of treatment failure in individual children, it would likely create greater problems with resistant organisms in the long term.

A previous retrospective analysis [14] in infants and pre-school children showed a significantly higher risk of UTI with a resistant organism among those who had received amoxicillin in the preceding 30 as well as 60 days, but not those who received it earlier than 60 days. Based on this information, it would have been very helpful if this analysis [4] had provided more detailed description of the relationship with time. This may be especially important, because another analysis of data from the RIVUR trial (on which the current report also is based) suggested that, even though trimethoprim-sulphamethoxazole resistance increased with prior usage, it decreased over time, and there was no significant difference in recurrence of UTI episodes between those children whose first episode was with resistant organisms, *versus* those with sensitive organisms [21].

Previous studies have shown that circumcision of infants with antenatally detected hydronephrosis [22] and posterior urethral valves [23], can help to prevent frequent UTI episodes. Data from systematic reviews also suggest that circumcision is associated with lower frequency of first [24] and subsequent [25] UTI episodes, although the number-needed-to-treat for the latter benefit is very high. Against this backdrop, the data from this analysis [4] showing higher frequency of UTI with resistant organisms among uncircumcised boys is interesting. However, it would have been more helpful if the data were compared with uncircumcised boys rather than girls, and more information on underlying conditions in both sets of boys were presented. Of course, it must be emphasized that circumcision under consideration, is that performed by qualified personnel using aseptic techniques, as UTI appears to be more frequent following ritualistic/traditional circumcision procedures [26].

Extendibility: What lesson can be learnt from this analysis, for the Indian context? Considering the rampant, relatively unregulated, and often inappropriate use of (prescribed and unprescribed) antibiotics in our country, selection of resistant clones of almost every pathogen is inevitable. Further, many of these 'antibiotic courses' are not completed, thereby further encouraging selection of resistant organisms. Perhaps the most important lesson from this analysis [4] relates to antibiotic stewardship and restraint policies, which are otherwise outside the scope of this discussion. The other conclusions from the authors [4] are not very useful for application in the Indian context.

Conclusion: This analysis of data from two prospective studies suggests that prior antibiotic usage could result in (first or subsequent) UTI with resistant organisms in infants and toddlers. However there are limitations that preclude drawing specific conclusions for evidence-based management and/or prophylaxis decisions.

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Pediatric Nephrologist's Viewpoint

Delayed treatment of urinary tract infection (UTI) may aggravate renal damage [1]. Hence early initiation of a sensitive antibiotic is important, but this should be balanced by avoiding inappropriate use of broad spectrum antibiotic [2]. Keeping this in perspective, the study by Shaikh, *et al*. [3] analyzing the antibiotic resistance pattern among children with UTI assumes importance.

In a sub-analysis of data gained from the large RIVUR

and the parallel run CUTIE studies, the authors found that none of the narrow spectrum antibiotics [first generation cephalosporin (1stGenC), trimethoprim-sulfamethoxazole, nitrofurantoin and amoxicillin] covered significantly both *E Coli* and non-*E Coli* pathogens. It recommended the use of 2nd/3rdGenC for UTI with suspected kidney involvement whereas in an afebrile child 1stGenC may suffice. As this has potential to change practice, it is important to assess its applicability in Indian scenario.

Indian studies although few in numbers have also demonstrated high incidence of resistance even in community-acquired UTI [4]. Although resistance to most of the narrow spectrum antibiotics are similar, organisms have been found to be resistant to even broader spectrum antibiotics, including 2nd/3rdGenC [4,5]. The findings by Shaikh, *et al*. [3] that certain group of children are more prone to have antibiotic resistance can be a useful guide while selecting antibiotic, but local antibiotic sensitivity patterns are to be considered. Lastly, we have to remember that even the RIVUR's cohort has been questioned regarding its true representativeness for the population we commonly encounter [6].

In summary, the publication by Shaikh, *et al*. [3], though interesting, has to be interpreted in light of local practice/population, and may not be completely reproducible in the practice of an Indian paediatric nephrologist.

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