Continuous Antibiotic Prophylaxis in Infants with Grade III, IV, or V Vesicoureteral Reflux

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SUMMARY

In this multicentric, open label, randomized trial performed across 39 European centers, the investigators randomly assigned infants 1 to 5 months of age with grade III, IV, or V vesicoureteral reflux (VUR) and no previous episode of urinary tract infection (UTI) to receive continuous antibiotic prophylaxis (prophylaxis group) or no treatment (untreated group) for 24 months. The primary outcome was the occurrence of the first UTI during the trial period. Secondary outcomes included new kidney scarring and the estimated glomerular filtration rate (GFR) at 24 months. A total of 292 participants underwent randomization (146 per group). Approximately 75% of the participants were male; the median age was 3 months, and 235 participants (80.5%) had grade IV or V VUR. In the intention-to-treat analysis, a first UTI occurred in 31 participants (21.2%) in the prophylaxis group and in 52 participants (35.6%) in the untreated group [hazard ratio 0.55; 95% confidence interval (CI) 0.35 to 0.86; $P = 0.008$]; the number needed to treat for 2 years to prevent one UTI was 7 children (95% CI 4 to 29). Among untreated participants, 64.4% had no UTI during the trial. Pseudomonas species, other non–*Escherichia coli* organisms, and antibiotic resistance were more common in UTI isolates obtained from participants in the prophylaxis group than in isolates obtained from those in the untreated group. The investigators concluded that in infants with grade III, IV, or V VUR and no previous UTIs, continuous antibiotic prophylaxis provided a small but significant benefit in preventing a first UTI despite an increased occurrence of non–*E.coli* organisms and antibiotic resistance.

COMMENTARIES

Evidence-based Medicine Viewpoint

This randomized controlled trial (RCT) examined the efficacy and safety of a long-term antimicrobial prophylaxis strategy among infants with high(er) grades of vesicoureteric reflux (VUR) [1]. The elements of the research question are as follows. *Population* (P): 1-5-month-old infants having VUR grades III, IV, or V (confirmed by either voiding cystourethrography or ultrasonography), with no previous episode of symptomatic urinary tract infection (UTI); *Intervention* (I): Long-term antimicrobial administration; *Comparison* (I): No long-term antimicrobial administration; *Outcomes* (O): Symptomatic UTI episodes, time to first UTI episode, new renal scarring, glomerular filtration rate (GFR), UTI organisms isolated, antimicrobial resistance pattern amongst isolated organisms, and serious adverse events; *Time-frame* of the outcome measurements (T): Two years, although the trial protocol mentioned that the infants would be followed-up for five years [2,3]; and *Study setting* (S): Multiple European institutions managing children with VUR.

In addition to the eligibility criteria described above, infants had to have gestation > 35 weeks, and GFR > 15 mL/min/1.73^2 surface area. Infants were excluded if they had episode(s) of previous UTI, or other conditions predisposing to VUR (and/or UTI) *viz*. neurogenic bladder, posterior urethral valves, or other obstruction at the uretero-pelvic or uretero-vesical junctions. The trial protocol additionally mentioned that the receipt of (unspecified) "experimental drugs" during the month prior to enrolment was an exclusion criterion [2,3].

The intervention was two continuous years of once-daily oral antibiotic administration. Study site investigators could choose the antimicrobial (based on the local patterns of sensitivity of *E. coli*) from one of the four options *viz*. nitrofurantoin, coamoxiclav, cefixime, or cotrimoxazole. There were criteria laid down for changing the chosen antimicrobial. Infants in the comparison arm did not receive the antimicrobial.

Follow-up visits were scheduled at 4 monthly intervals during the first year after enrolment, and 6 monthly intervals during the second year. These visits were used to confirm adherence to the prescribed regimen by reviewing diaries completed by families. The occurrence of symptomatic UTI or adverse events prompted additional visits.

Critical appraisal: The methods for generating the allocation sequence, and concealment of allocation, were not described in the publication [1]. As the online supplementary files and trial protocol were inaccessible, the relevant trial registries [2,3] were examined, but the information was unavailable there also. However, individual infants were randomized with stratification based on the presence of renal parenchymal damage. The randomization process appears to have been effective as there were no inter-group baseline differences in the gender distribution, age at enrolment, proportion with abnormal antenatal ultrasonography, distribution of VUR grade, prevalence of bilateral VUR, and the distribution of DMSA as well as ultrasonography scan abnormalities. In terms of renal function, blood pressure and GFR were comparable. There were also no statistically significant differences in the proportion of infants who had received antibiotic prophylaxis prior to enrolment.

The participating infants and caregivers were not blinded to the allocation. The investigators suggested that the primary outcome, did not necessitate blinding. However, this may not be true, because the outcome was 'symptomatic' UTI (and not any UTI). The trigger for parents to suspect UTI and approach the healthcare system was the presence of fever >38.0° C, unwell appearance, irritability, or loss of appetite. Therefore, a scenario can be envisaged wherein parents of infants receiving antimicrobial prophylaxis, were more confident/secure in not reporting the appearance of these symptoms, compared to those not receiving prophylaxis. In this situation, UTI could be missed, especially if infants recovered uneventfully. Therefore, ideally blinding should have been attempted in this trial.

The investigators did not report adherence to the prescribed antibiotic prophylaxis regimen. More important, they did not report whether there were deviations from the intended interventions. Thus, it is unclear whether all infants continued to receive whatever was allocated at randomization (i.e. antimicrobial or no antimicrobial). Given that almost 50% infants had taken antibiotic prophylaxis before enrolment into the trial (although the duration and interval were not specified), it is likely that infants in the comparison arm could have taken antibiotics independent of the trial (assuming that this is feasible in the trial countries). However, had this happened, we would expect to observe less difference in the outcome of symptomatic UTI between the two trial arms. This suggests that the observed reduction in UTI is a robust result.

Although a CONSORT diagram was not published [1], the attrition rate was reportedly low and comparable between the trial arms. Further, intention-to-treat analysis was undertaken. However, the dropout rates for all the outcomes were not published.

The methods for measuring the outcomes were appropriate, and there was no inter-group differences in this. All the outcomes reported were clinically relevant and most were also patient-centric. However, it is unclear why only serious adverse events were recorded, rather than all potential adverse events. Two years' oral antibiotic consumption (albeit in lower than therapeutic doses) is expected to be associated with a wide range of known side effects besides other events (difficult to classify as caused by antibiotics). However, this important information was not recorded.

The authors did not comment about selective outcome reporting. However, a glance at the trial registries [2,3] identified several outcomes that were not reported [1]. For example, hypertension and proteinuria were to be measured and reported at each of the scheduled follow-up visits. Similarly, gut microbiome evaluation was planned not only at these scheduled visits, but also annually until five years after enrolment. Even the secondary outcomes such as serum creatinine, and others like serum cystatin were to be measured annually until five years after enrolment. Similarly, body mass index was to be reported at the end of 2 and 5 years. More importantly, renal scarring was to be evaluated at the end of five years, and not two years alone. It is possible that some of these observations may appear in other publications.

It is interesting that while the publication [1] suggested that antimicrobial prophylaxis was the intervention, and 'no prophylaxis' was the comparison, the trial registries [2,3] described it the other way around; no antimicrobial prophylaxis was the experimental arm, and antimicrobial prophylaxis was the active comparator. Although this switch does not impact the interpretation of the data, it suggests that prior to the trial, antimicrobial prophylaxis use was not uncommon in the study settings, and the effort was to assess whether its omission would make a difference. However, it can be argued that in such a situation, a noninferiority trial design would be appropriate. This would have implications on the sample size calculation and data interpretation.

The trial had several methodological refinements. The main outcome, 'symptomatic UTI' was clearly defined on the basis of a combination of clinical symptoms, urinalysis findings, and quantitative bacterial culture with specimen-specific cut-offs. This fosters confidence of a low likelihood of misclassifying symptomatic UTI. However, it appears that only about 80% of those diagnosed with UTI had fever. This raises two important issues. First, there

were no UTI-specific symptoms (for want of a better term) such as crying during micturition, increased frequency, etc. Second, the symptoms were mostly non-specific for UTI. In other words, the triggers for urinalysis and culture could have missed some episodes of UTI. As there was no recording of asymptomatic UTI through serial cultures, the overall prevalence of UTI in the two groups is unclear.

The pre-trial sample size calculation necessitated 218 infants in each arm to detect a 20% difference in symptomatic UTI with 90% power. A pre-planned analysis when approximately half the sample size was enrolled, suggested the need to continue the trial (as there were no detectable benefits or harms warranting early cessation of the trial). At this point (inexplicably), power of 80% was deemed sufficient and the sample size was re-calculated, slashing it to half of the original. The stated justification of "steady accrual of 50 participants per year" is unclear. Of course, sample size calculation was undertaken only for the primary outcome, and not all the reported outcomes.

Renal scarring was identified by the observations on DMSA scans, and the abnormalities consistent with scarring were clearly defined. The DMSA scans were secured in a central database for blinded re-reporting. There was also a process for handling disagreements between the reporting of individual observers. These refinements enhance confidence in the reporting. However, this elaborate process was not standard procedure and only those images uploaded to the database were re-reported.

The investigators reported that 867 infants were screened to finally enrol the required sample size. However, the criteria for screening potentially eligible infants were not described. This information is especially important because the inclusion criteria were infants with confirmed VUR (III, IV, or V) but without prior UTI. Further, several conditions resulting in high(er) grade VUR were excluded. As the median age of enrolment was about 3 months, it appears that antenatally diagnosed urinary tract anomalies and/or early postnatal identification of this, would have been necessary. This perception is supported by the facts that over half of the screened infants already had renal scan abnormalities, and only one-third of the infants had experienced UTI. Perhaps this explains how/why over half the enrolled participants had already received antibiotic prophylaxis by the age of enrolment. This makes the enrolled cohort a carefully selected subgroup of infants with VUR, thereby limiting generalizability.

How to interpret the results of this trial? On one hand, there was an impressive relative decline in the frequency of symptomatic UTI with long-term antimicrobial prophylaxis; on the other hand, there was no impact on renal scarring, or renal function (serum creatinine, or GFR). This raises several troubling questions for physicians managing children with VUR. For example, could renal scarring be independent of UTI (at least symptomatic UTI, as this trial suggests)? If so, are previous data focusing on UTI prevalence meaningful? Should (harder to document) anatomic and/or functional renal outcomes having long-term consequences, be given precedence over the (easier to measure), shorter-term consequences of UTI episodes? Could there be a subgroup of patients wherein there may be a relationship between UTI episodes and renal scarring, within this and/or other trials? Unfortunately, there are no ready answers to these vexing questions. Since the time interval to the first episode of symptomatic UTI was not reduced with antibiotic prophylaxis, and the proportion with UTI requiring hospitalization was comparable (suggesting similar severity of episodes), the statistically significant, clinically meaningful reduction in symptomatic UTI, suggests that there could be a subgroup with better response.

Similarly, how to explain that prophylaxis was associated with fewer infants having ≤ 2 episodes of symptomatic UTI, but more infants having ≥ 3 episodes? Is this an artefactual finding? Or could the local microbiome be altered in such a manner that a few children were predisposed to have greater episodes of UTI? Again, in the absence of data, it is difficult to clarify these issues.

Third, it is interesting that only about one-third of infants developed symptomatic UTI over two years' follow-up, despite not receiving prophylaxis. This by itself makes a strong case to suggest that antimicrobial prophylaxis may not be required in all such infants, and that the observed reduction in symptomatic UTI is probably driven by a subgroup with better response.

The authors themselves did not focus exclusively on the beneficial effect of antibiotic prophylaxis, but weighed it against the potential harms of this approach [1]. Therefore, they unequivocally stated that their results argue against long-term antimicrobial prophylaxis. Their balanced approach is laudable. However, this evidence-based viewpoint is in divergence with the authors on a couple of subtle, but important points. The trial documented reduction in *symptomatic* (emphasis added) UTI, therefore the authors' statement that "the number needed to treat to prevent one UTI was 7" [1] is incorrect. More accurately, 7 children would need to receive prophylaxis to prevent one *additional* episode of *symptomatic* UTI. The importance of the distinction between symptomatic UTI, and UTI, has been highlighted already.

What is the impact of this study on Indian infants with this condition? First, unless there is meticulous antenatal and/or postnatal screening (with ultrasonography, radionuclide scanning, and cystourethrography), it is very difficult to identify asymptomatic infants with high grades of VUR. Second, VUR is generally detected when episode(s) of UTI are identified, with or without additional risk factors. The results of this trial are not extrapolatable to such infants. Third, continuous antibiotic consumption for two years among infants in our setting, is likely to create more harm than good, both to individual infants and also the community at large. However, the consequences of symptomatic UTI in our setting may be different from that in European countries, making a case for considering long-term antibiotic prophylaxis in some infants. Thankfully, the lack of benefit on most outcomes in this trial, with additional demonstration of harm, tips the scales against antimicrobial prophylaxis.

Conclusion: This elaborate RCT among young infants with pre-confirmed renal dysplasia (but no episode of UTI) demonstrated a statistically significant reduction is *symptomatic* (emphasis added) UTI, with two years of continuous oral antibiotic administration. However, there was no effect on the risk of developing new renal scars at the end of the trial period. Further, there were clinically important negative effects of antibiotic prophylaxis, notably the emergence of antimicrobial resistance amongst common organisms, appearance of other than usual organisms in urine cultures, and a three-fold higher probability of multidrug resistant organisms. Some clinically important safety outcomes such as the frequency and severity of all/any adverse events, and the impact on the gut microbiome (and its conse-quences) were not reported. Overall, the findings of this trial argue against the use of antimicrobial prophylaxis among infants conforming to those included in this study.

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Pediatric Nephrologist's Viewpoint

Primary VUR is often diagnosed following a UTI or on evaluation of antenatal hydronephrosis [1]. Low-dose antibiotic prophylaxis is the commonest strategy employed to prevent UTI in children with VUR [2]. Considering the risk of antimicrobial resistance (AMR) and modest efficacy, most international guidelines recommend its judicious use [3-5].

The role of antibiotic prophylaxis in prevention of UTI in VUR detected on evaluation of antenatal hydronephrosis is unclear. The PREDICT trial assessed the efficacy of antibiotic prophylaxis in infants with high-grade VUR (III, IV and V) prior to developing UTI [6]. Authors in this multicenter, open-label trial used four different antibiotics for prophylaxis over 24 months. There was a significant reduction in risk of symptomatic UTI (35%) on prophylaxis as compared to no therapy (21%) with no difference in efficacy between different antibiotics. However, similar to previous trials [7-9] in children with VUR, this study also failed to show a significant difference in kidney scarring and function over 24 months. Interestingly, new kidney scars developed even in children who did not have UTI which could be likely due to progression of underlying dysplasia. The study also observed higher AMR in prophylaxis group compared to untreated group [6].

This large trial reaffirms modest benefit of antibiotic prophylaxis for preventing UTI in high-grade VUR. Whereas the benefit was found in girls and not boys, the study was not powered for subgroup analysis. While we agree that only two-thirds of children had UTI, similar rates of UTI are observed in VUR detected following UTI [7]. Authors of the PREDICT trial were cautious in their conclusion about the use of antibiotic prophylaxis due to lack of difference in kidney scarring and AMR associated with this intervention [8]. However, similar to previous trials risk of serious adverse events, hospitalization, or requirement of intravenous antibiotic therapy in intervention group was not higher despite higher AMR. In recently updated evidence-based guidelines, authors have provided weak recommendations for its use to prevent UTI in high-grade VUR detected antenatally [3].

A key message for pediatricians from this study is that every child with antenatal hydronephrosis should not to be given antibiotic prophylaxis except those found to have high-grade VUR.

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Pediatrician's Viewpoint

The PREDICT study group's investigation into antibiotic prophylaxis (AP) for infants with high-grade vesicoureteral reflux (VUR) sheds light on critical considerations for pediatricians. In this study continuous AP significantly reduced the risk of the first symptomatic urinary tract infection (UTI) compared to no treatment (hazard ratio 0.55). The study, conducted in 39 European centres, provides valuable insights into the potential benefits and risks of AP in this vulnerable population [1].

The benefits include a noteworthy 45% reduction in the risk of initial UTIs, potentially sparing children the pain and complications associated with these infections. Preservation of kidney function is another positive outcome, emphasizing the potential long-term advantages of prophylaxis. A landmark study, RIVUR trial, evaluated the impact of trimethoprim-sulfamethoxazole prophylaxis in this population. The study concluded that prophylaxis reduced the incidence of UTIs, but the overall clinical significance of this reduction remained a subject of debate [2].

Pediatricians who support AP argue that preventing UTIs in infants with high-grade VUR is crucial for minimizing the risk of renal scarring and long-term complications. Renal scarring can lead to hypertension and renal insufficiency later in life, making the prevention of UTIs a priority in these cases [3-5].

However, the use of AP must be carefully weighed against associated risks. Antibiotic resistance, a significant concern, may arise from overuse and impact future treatment options. Side effects, including diarrhea, nausea, and vomiting, further underscore the need for a balanced approach. Disruption of the gut microbiota, with potential downstream health implications, adds another layer of consideration [1].

Pediatricians are urged to adopt an individualized approach, considering the child's unique circumstances, risk factors, and family preferences. The decision-making process should involve collaborative discussions with parents, emphasizing the need for a nuanced evaluation of the risks and benefits of AP [6]. Various risk factors (family history, gender, laterality, age at presentation, presenting symptoms, VUR grade, duplication, and other voiding dysfunctions), early stratification help in identification of patients with potential risk of renal scarring and urinary tract infections.

The study's findings prompt a reconsideration of current guidelines, advocating for a case-to-case decision-making approach. While the reduction in UTI incidence is notable, a comprehensive evaluation of each child's risk factors is essential. Ongoing research is needed to optimize the duration and type of prophylaxis.

In conclusion, the PREDICT trial contributes valuable insights into the use of continuous antibiotic prophylaxis for infants with VUR and no prior UTIs. Pediatricians are encouraged to carefully balance the modest yet significant benefits against potential risks, fostering a thoughtful and personalized approach to care for this vulnerable population.

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