Arch Argent Pediatr 2024;122(3):e202310242

Continuous antibiotic prophylaxis in patients with vesicoureteral reflux: Less is more

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The objective of administering continuous antibiotic prophylaxis (CAP) to patients with vesicoureteral reflux (VUR) is to reduce the recurrence of pyelonephritis and prevent the development of kidney scarring. Although this topic has been the subject of several clinical trials, their results are disparate due to the heterogeneity of their designs and the differences in the characteristics of the patients included (sex, VUR grade, age, etc.). Among the most relevant trials, the RIVUR study was a multicenter, double-blind, placebo-controlled clinical trial that assessed 607 patients (only 8% were males) aged 2 to 71 months with grade I–IV VUR diagnosed after an episode of urinary tract infection (UTI). In the intervention group, CAP reduced the risk of recurrence by 50%, with a greater benefit for patients whose index UTI developed with fever and for those with enterovesical dysfunction.[1] The PRIVENT study, another double-blind, placebo-controlled clinical trial involving 576 patients (not all with VUR), demonstrated a modest reduction (6%) of recurrence in the intervention group, regardless of the presence of VUR.[2] It is worth noting that both the RIVUR and the PRIVENT studies had a predominance of women and low-grade VUR (I–III), so they were low-risk populations, making it difficult to generalize their results to patients with greater severity.[1,2] In contrast, other studies showed no benefit or, as observed in the Swedish Reflux Study, which included 203 patients aged 1 to 2 years with grade III–IV VUR, the benefit was observed in girls only. In addition, a Cochrane review that included all the studies mentioned above showed that CAP is not beneficial to prevent recurrence.[3] Recently, the results of the PREDICT study were published, which was a new open-label clinical trial (antibiotic versus no therapy) with 292 patients (77%, males) aged 1-5 months with grade III-V VUR who had not developed UTI.[4] Therefore, the cohort in the PREDICT study differed from previous populations, who were predominantly female, older, had already had at least 1 UTI episode, and had low-grade VUR. As a result, it was observed that CAP significantly reduced the risk of UTI (hazard ratio: 0.55, 95% CI: 0.35–0.86); such benefit was greater in girls with grade IV or V VUR. Notably, 64.4% of untreated patients did not develop UTI, so the number needed to treat was 7 patients for 2 years to prevent an episode of UTI; finally, the authors concluded that although the results were numerically significant, the clinical benefit was doubtful.

In turn, none of those studies proved useful for the other fundamental objective of CAP, which is to prevent kidney damage. However, this outcome measure was a secondary objective of those

doi: http://dx.doi.org/10.5546/aap.2023-10242.eng

To cite: Balestracci A, Beaudoin L. Continuous antibiotic prophylaxis in patients with vesicoureteral reflux: Less is more. *Arch Argent Pediatr* 2024;122(3):e202310242.

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studies, so they lacked adequate power to draw solid conclusions. A meta-analysis that included 1076 children confirmed the findings of the individual studies, however, the sample size analyzed was also insufficient, as 8000 patients would have been necessary to reach an adequate power.[5]

Another, not less important factor in the risk-benefit assessment of this strategy is the possibility of inducing bacterial resistance and modifying the gut microbiota. In this regard, a meta-analysis published in 2018 showed that CAP increased the risk of multidrug resistance by 6.4-fold. Along the same line, in the recent PREDICT study, patients in the intervention group who developed a UTI had a higher level of isolation of non-*Escherichia coli* bacteria and a higher antibiotic resistance.[4] Finally, other factors that should be considered before initiating CAP include sphincter control status, perceived medication adherence, choice of caregivers, treatment duration, and cost of medication.[6] In relation to the latter, a cost-effectiveness analysis based on data from the RIVUR study concluded that treatment in children with low-grade VUR (I–III) was not cost-effective.

We should ask ourselves whether the results of those studies may be extrapolated to the setting in which we conduct our daily clinical practice. Most studies were based on the administration of trimethoprim-sulfamethoxazole, which may not be the best option if local antibiotic resistance to these drugs is high. In addition, the diagnosis of VUR in some patients included was based on prenatal ultrasound findings, without an index UTI; in our experience, many times, a reliable prenatal ultrasound is not available and the vast majority of the patients we see have a history of having already presented 1 or more infections. Another point to consider is the speed with which new infections in enrolled patients have probably been treated. It is to be expected that, when a UTI developed, the patients included in clinical trials would have been treated quickly, both because their caregivers were alerted to the early recognition of the symptoms of infection and because they presumably had high accessibility to medical care. Given that it is known that a delayed treatment initiation favors the development of parenchymal damage,[6] it is likely that this situation influenced the development of new kidney scarring in study participants. Similarly, the possibility of early treatment may also have decreased the likelihood of hospitalization. Finally, it is worth noting that the rate of treatment adherence in the context of a study is usually higher than in the real world, and this is another aspect that may have an impact on the results obtained in routine clinical practice.

To conclude, the available evidence has shifted from the universal indication of CAP in patients with VUR to a selective use in patients at risk.[7] Studies that allow a better stratification of risk groups will further reduce CAP indications, which could be considerably more precise with the contribution of local studies. ■

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