Selective Antimicrobial Prophylaxis for Vesicoureteral Reflux

Tej K. Mattoo, M.D.

The use of continuous antibiotic prophylaxis in the prevention of urinary tract infection (UTI), particularly in children with vesicoureteral reflux, has been studied extensively during the past 15 years. Double-blind, placebo-controlled trials such as the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial and the Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts (PRIVENT) trial showed that continuous antibiotic prophylaxis significantly reduced the risk of UTI among children with vesicoureteral reflux.[1,2] However, other randomized trials showed either no beneficial effect[3-7] or a beneficial effect that was limited to female patients.[8] These variations in trial results have been attributed to considerable differences in trial designs. Systemic reviews and meta-analyses have also yielded mixed results, which to a large extent appear to be due to heterogeneity and quality variations among the included studies, possibly with some selection bias and selective outcome reporting.

In this issue of the *Journal*, Morello et al.[9] report the results of a multicenter, randomized, open-label trial of continuous antibiotic prophylaxis in infants 1 to 5 months of age with grade III, IV, or V vesicoureteral reflux and no previous UTI. Most infants had other congenital anomalies of the kidney and urinary tract. The primary outcome was occurrence of a first UTI, and the secondary outcomes included new kidney scarring and the change in the estimated glomerular filtration rate (GFR) during the trial period of 24 months. Among the 292 participants (77.7% male) in the intention-to-treat population, a first UTI occurred in 31 of 146 participants (21.2%) in the prophylaxis group and 52 of 146 participants (35.6%) in the untreated group; the between-group difference was significant (hazard ratio, 0.55; 95% confidence interval, 0.35 to 0.86; P=0.008). New kidney scars and the estimated GFR at 24 months did not differ substantially between the two groups. The trial was neither blinded nor placebo-controlled, and four different antibiotic options were used for continuous antibiotic prophylaxis. Little was reported about protocol adherence or quality-control measures across the 39 centers in various countries with different health care systems.

Despite these limitations, this trial adds valuable data to the existing literature on continuous antibiotic prophylaxis in children with vesicoureteral reflux. Perhaps most impressive, it included young infants with congenital anomalies of the kidneys and high-grade vesicoureteral reflux, a highly vulnerable patient population already known to be at substantial risk for kidney scarring as well as other complications associated with a febrile illness. Another highlight of this trial is the entry criterion of no previous UTI. Indeed, no preceding UTI is consistent with how most children with vesicoureteral reflux diagnosed because of anomalies on prenatal ultrasonography present when they are considered for antibiotic prophylaxis. However, the entry criterion of no previous UTI inadvertently limits the comparability of the trial with other trials that mostly involved patients with a history of UTI. Other variables that make comparisons between trials less meaningful are the much lower mean age of the trial cohort, the predominance of male participants, the presence of other kidney anomalies in addition to vesicoureteral reflux, the prospects of an earlier resolution of vesicoureteral reflux than in cases diagnosed after a UTI, and the urine-collection method.

The results of this trial once again showed that continuous antibiotic prophylaxis significantly reduced the risk of UTI, although not among all children considered en masse and at the expense of increased antimicrobial resistance. Interpretation of trial results in terms of numbers needed to treat is not helpful: even though it is a valuable metric for treatment effectiveness for the population as a whole, the number needed to treat does not help calculate the individual risk–benefit ratio and cannot be the sole basis for clinical decision making. As in previous trials, this trial was not designed to evaluate kidney scarring as a primary

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outcome and thus cannot take us further on that question. Finally, observing changes in the GFR due to kidney scarring during the trial period would be unlikely, because most such patients have unilateral scarring and studies indicate that it takes much longer to observe changes in the GFR, even in patients with bilateral (substantial) scarring.

Routine use of continuous antibiotic prophylaxis for vesicoureteral reflux is already passé, as reflected in the published guidelines from professional societies such as the American Urological Association, the European Association of Urology–European Society for Pediatric Urology, and the Swedish and the Italian Societies for Pediatric Nephrology. These bodies all recommend a more selective approach for using continuous antibiotic prophylaxis, based on a combination of factors that include patient age and sex, severity of vesicoureteral reflux, and the presence of bladder or bowel dysfunction or renal scarring. Other factors that warrant consideration before initiation of long-term continuous antibiotic prophylaxis include parental choice, anticipated adherence to medication, status of toilet training, and medication expense.[10] Thus, the key takeaway message from this and other trials is that continuous antibiotic prophylaxis should be used judiciously.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Department of Pediatrics, Wayne State University School of Medicine, Detroit.

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Pegozafermin for NASH — A Sprint to Start a Marathon

Mary E. Rinella, M.D.

Pharmacotherapy in patients with nonalcoholic steatohepatitis (NASH) has been a frustrating endeavor, with failures outnumbering successes by some margin, even in late-phase clinical trials. The complex pathobiologic features of NASH, the slow and variable natural history of the disease, and the nefarious nature of assessing histologic end points have contributed to the difficulty of attaining efficacy with pharmacotherapy that is meaningfully distinct from that seen with placebo. In this context, studies that have shown even moderately compelling histologic efficacy are understandably heralded. Therapeutic approaches have broadly dichotomized into those targeting weight loss and those targeting more specific aspects of the lipotoxicity–fibroinflammatory cascade. Fibroblast growth factor 21 (FGF21) has pleiotropic metabolic effects, mediated in part by adiponectin, that improve insulin sensitivity and reduce inflammation, improve vascular function,

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