Antibiotic Prophylaxis in Children with Vesicoureteric Reflux: Has RIVUR Answered All Our Questions?

Abstract:

The interest in urinary tract infections (UTI) and vesicoureteric reflux (VUR), which is the retrograde flow of urine from the bladder into the ureters, started gaining pace in the late 1950s after the introduction of voiding cystourethrography. VUR is present in one third of children presenting with Abdominal urinary tract infections (UTI) and is associated with renal scarring. In an effort to reduce renal scarring as a result of VUR, various surgical repairs of the vesicoureteral junction, and later endoscopic injection techniques were introduced. With the emerging understanding of the strong association between UTI and VUR, antibiotic prophylaxis gained popularity after an observational cohort study showed that VUR improved with long-term, low-dose antibiotic treatment. Smellie et al found that prophylaxis significantly reduced the number of UTI recurrences compared to before prophylaxis. The use of antibiotic prophylaxis became standard practice after two large prospective randomised trials comparing surgical intervention and antibiotic prophylaxis in terms of the two interventions relation to UTI recurrence and new renal damage. Endoscopic and surgical treatments were reserved for severe reflux.

The natural history for lower grades of VUR is spontaneous resolution at a rate of 13% per year.

A prospective 5-year follow-up study of children <5 years of age with primary VUR and radiographically normal kidneys, grade I VUR resolved in 82%, grade II in 80% and grade III in 46% of ureters. Rate of resolution of grades IV and V VUR over 5-year period are approximately 30% and 13% respectively. Recent data suggest that mild and moderate VUR do not increase the incidence of UTI, pyelonephritis or renal scarring, and that antibiotic prophylaxis is associated with increased antibiotic resistance. A well-powered, placebo-controlled, randomized study by Craig et al. involving children from birth to 18 years of age showed a modest decrease in new infections in the prophylaxis group. It found that 14 children would have to be treated to prevent one case of UTI, with its benefit most marked in the first 6 months of treatment (most likely time of UTI recurrence), but found prolonged use of antibiotics resulted in increased risk of symptomatic UTI from resistant bacteria. It was however underpowered to ascertain if antibiotic prophylaxis reduced the incidence of new renal scarring. These conflicting results meant that the value of antibiotic prophylaxis as the standard of care in children with VUR remain controversial four decades after it was introduced.

The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial recently published in the New England Journal of Medicine, was a multicenter, randomized, double-blind, placebo-controlled trial where 607 children (2-71 months of age) with grades I-IV VUR after a first or second UTI, received either trimetoprim-sulfamethoxazole or placebo. The Follow-up longitudinally at 1, 2, 5 and 7 years with technetium-99m sulfur colloid (Tc-99m) scan was performed at baseline and after 1 and 2 years. Fewer recurrent UTIs occurred in the prophylaxis group than in the placebo group (relative risk 0.55; 95% confidence interval 0.38-0.78). However, more children in the prophylaxis group had breakthrough UTI with resistant organisms (63% vs 19%). Antibiotic prophylaxis was particularly effective in children whose index infection was febrile and in those with bladder and bowel dysfunction. They found that 8 children (5%) in the prophylaxis group to be treated for 2 years to prevent one febrile/symptomatic UTI. Such analysis showed that recurrent infection was more common among children with grades III or IV VUR than those with grade I or II VUR (22.9% vs 14.3%) and the number of renal scars reported was low (12.2%) with no significant between group differences in the incidence of renal scarring (11.9% in prophylaxis group vs 10.2% in placebo group), severe renal scars (4.0% vs 2.6%) or new renal scar formation (8.2% vs 8.4%). At the end of the study, VUR resolved in 218 of 428 (50.9%) children.

The participants of the RIVUR study were young children (<6 years of age); the criteria for diagnosis of UTI were strictly met. Treatment was commenced in low-toileted children, and clean, voided urine sample in toilet-trained children; and two radiologists centrally scored renal scarring with radionuclide scanning at baseline and annually for 2 years. Adherence to study medication/placebo was realistic – 85% of parents reported to have followed the study medication/placebo. The management of VUR and UTIs in children, there remains unanswered questions: as only one antibiotic was used, the results only speak for the effectiveness of trimetoprim-sulfamethoxazole in reducing the number of UTI recurrences; with only 2 years of follow-up, the longer term degree of renal injury remains unknown. Very few boys (8%) were enrolled, thus limiting the generalisability of its results to boys. Although primary VUR is more common in girls, such information has not been evaluated outside the United States. This is important because boys did not benefit from prophylaxis in a Swedish trial.

In our opinion, the ‘take home’ message from the RIVUR study is that antibiotic prophylaxis reduces the incidence of recurrent UTIs in children with VUR grades I-IV (especially those with VUR grades II and IV, and bladder/bowel dysfunction), but at the expense of increased antibiotic resistance. Eight children need to be treated for 2 years to prevent one symptomatic UTI – all this with no significant difference in the incidence of new renal scarring. One would have to question whether this ‘trade-off’ is cost-effective. We concur that antibiotic prophylaxis would benefit a selected group of high-risk children with multiple episodes of recurrent UTIs that impact significantly on their well-being. However, we opine that in the vast majority, early diagnosis and treatment of UTIs remain the mainstay of treatment; while antibiotic prophylaxis be used according to risk stratification rather than to the mere presence of VUR.

References

9. Ch Teoh, A Awan
Department of Paediatric Nephrology Transplantation, The Children's University Hospital, Temple St, Dublin 1
Email: cwteoh88@hotmail.com