Recurrent Febrile Urinary Tract Infections in the Anatomically Normal Child: The Greatest “Mundane” Challenge of Pediatric Urology?

FROM THE GUEST EDITOR

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The offices of pediatric urologists are full of children experiencing recurrent febrile urinary tract infections (UTI) despite ostensibly normal genitourinary anatomy and no apparent bowel and bladder dysfunction (BBD). These patients pose a particular challenge given that there are no quick fixes in the form of surgery. Many of these children become chronic patients requiring multiple office visits.

In this Dialogues article I have attempted to conduct a small, informal survey of management strategies for a set of hypothetical patients with recurrent febrile UTI and normal anatomy and elimination behaviors. Although all of our excellent contributors point out that BBD is often an occult condition that can be addressed as a modifiable risk factor for UTI, the variations in the contributors’ proposed management suggests that there is no consensus regarding optimal care for these patients.

To be fair, we have relatively few tools to deal with what I refer to as “microscopic risk factors” for recurrent UTI. Whereas “macroscopic” risk factors encompass anatomic anomalies such as ureteroceles and BBD, microscopic risk factors include host epithelial and immune factors which confer susceptibility to infection by uropathogens, as well as microbial factors such as colonization by uropathogenic strains of bacteria. In fact, the theoretical mechanisms of probiotics and cranberry products in the urinary tract are based on these microscopic risk factors.

My hope is that novel UTI therapeutics, and perhaps a vaccine, will be developed as investigators dissect the underpinnings of host-microbial interactions in the urinary tract. However, in the meantime it behooves us to continue to be vigilant for occult BBD in children with recurrent UTI.

FROM THE EDITOR

Anthony A. Caldamone, M.D.

The road to understanding the various factors leading to recurrent febrile urinary tract infections has been winding and undulating. To put this all in perspective, if one reads through the systematic analyses of these cases that our contributors have provided and compare that to approaches in the distant past, our practice had reflected a philosophy that could only be interpreted as “even if there is not an anatomical problem that we can demonstrate, there must be something that we can fix”.

As one reads through these case scenarios and the expert commentary that is provided by our contributors, there are certainly some common themes that we can all learn something from. One of those themes is the relentless search for bladder bowel dysfunction (BBD). In the recently reported AUA Guidelines on vesicoureteral reflux, BBD was recognized as a risk factor in promoting breakthrough urinary tract infections and the development of upper tract scarring. We all suspect that this is true even in the absence of demonstrable reflux. It is also interesting to recognize the subtleties of the differences in approaches by each of these experienced pediatric urologists for such a “mundane challenge” as normal anatomical recurrent febrile urinary tract infections.

We can all take some pointers away from each of the discussions that will help us on a day to day basis in the office. I congratulate Dr. Hsieh and his contributors for an enlightening and
CASE 1: A 4 year old girl with a history of recurrent febrile UTI has a normal physical examination, VCUG and renal-bladder ultrasound, as well as normal elimination behaviors based on history. Would you offer long-term antibiotic prophylaxis, and if so, how would you decide when to stop prophylaxis?

HC: I consider a 4 year old girl with recurrent febrile UTI as having bladder and bowel dysfunction (BBD) until proven otherwise, even with “normal elimination behaviors”. I ensure that such patients are voiding every 2-3 hours and having bowel movements at least twice a day. To assist with the latter I frequently administer oral polyethylene glycol to these children. I see these patients in clinic every 2-3 months and at their second visit I have them bring a 2 day voiding diary (not necessarily consecutive 24 hour periods), with measured outputs and underwear checks for accidents when on a Q2-3 hour voiding schedule. Most of the time, I would start them on antibiotic prophylaxis if they have had more than 2 febrile UTI. If I started prophylaxis and BBD therapy simultaneously, then I potentially would consider stopping prophylaxis in 6 months if they are adherent to the BBD regimen and have not had any infections. If I started prophylaxis because they are having recurrent UTI despite compliance with a BBD regimen then I would consider stopping prophylaxis in 6 months to a year depending on whether breakthrough infections occur while on prophylaxis.

JH: I agree with HC that these patients are dysfunctional voiders until proven otherwise. I do offer antibiotic prophylaxis in these patients. I typically recommend a 6 month prophylaxis period unless there is continued dysfunctional elimination. Once patients have been doing well with these behaviors, I tend to stop prophylaxis. I have these patients undergo uroflow with post-void residuals as well as voiding (2 days) and stooling (7 days) diaries.

TdJ: I would like to have at least 2 uroflowmetries with ultrasound-determined post-void residuals. The chance that such a patient is a dysfunctional voider with incomplete emptying is significant. Moreover, I would like to have a sonographic measurement of the rectum to see whether she is constipated or not (Figure), combined with thorough history taking according to the Rome III criteria. A sonographic diameter of the rectum of more than 3 cm in the absence of urge to pass stools would be considered a strong indicator of fecal retention. I would offer antibiotic prophylaxis for 6 months, combined with advice concerning toileting posture and other issues. Specifically, I advise against straining during voiding and also seek to prevent an overdistended rectum. Before stopping antibiotic prophylaxis I like to have a few uroflowmetries without staccato or interruptions and without residual urine.

I have these patients complete a 3 day frequency/volume voiding diary and a 2 week defecation diary. We would ask specific questions on the direction of the urinary stream because we have learned that many girls with recurrent UTI have an anteriorly deflected stream (ADUS) and wet the toilet rim when voiding in the optimal position (or always have wet buttocks and legs after voiding). In case of an ADUS we would offer dorsal meatotomy to incise the web covering the meatus. We certainly would look into the possibility of constipation. The goal is to achieve daily stools. If necessary, we give laxatives polyethylene glycol (PEG). We would also state to the parents that these problems generally have a chronic character meaning that supervision of voiding and defecation habits is needed for at least one year and often for life.1-4

Guest editorial comment (MH): I would add that a DMSA scan (at least 6 months since the last known UTI) may be helpful for this type of patient. Specifically, the presence of renal scarring can be used to guide recommendations for antibiotic prophylaxis, and to improve patient and family compliance with prophylaxis and behavioral alterations (timed voiding, high fiber and water intake, laxatives, etc.). I agree that uroflows with postvoid residuals and voiding diaries can be useful to detect incomplete emptying that can be addressed with double voiding. Finally, a careful history combined with voiding diaries can reveal vaginal voiding, which can be remedied by having girls sit facing the commode with their legs wide apart while voiding. Obese girls sometimes need to manually spread their labia apart to reduce vaginal voiding.
CASE 2: A 1 year old girl with a history of recurrent febrile UTIs has a normal physical examination, VCUG and renal-bladder ultrasound, with no history of constipation. Would you offer long-term antibiotic prophylaxis, and if so, how would you decide when to stop prophylaxis? Would you give this child alpha blockers?

HC: I would offer prophylaxis. Usually I find that in 6 months to a year the cycle has been broken. I would again really make sure that there are no signs of constipation by looking at the scout film on the VCUG. If there is any concern I would start polyethylene glycol. I would not start alpha blockers in this patient without performing urodynamics and I don’t feel there is any indication to do urodynamics based on previous imaging studies and confirmation of no PVR. I would place the patient on a 3 month period of double prophylaxis of trimethoprim and nitrofurantoin. I would then try resuming single prophylaxis if they have been infection-free. If they begin to have breakthrough infections on this regimen I would revert back to a 6 month course of double prophylaxis. I would consider alternating therapy (1 week cycle of trimethoprim, then 1 week cycle of nitrofurantoin, etc.) after a 6 month course of double prophylaxis with no UTI. I would think about positional instilled cystography (PIC) after 2-3 breakthrough UTIs.

JH: Breakthrough infections? If so, this is a child I would do a PIC cystogram on. I have not used alpha blockers in these children. If a breakthrough, or recurrent after stopping them I would proceed with PIC.

TdJ: I would look very specifically to meatal anomalies; does a meatal web exist that can be corrected? In the case of breakthrough infections on trimethoprim prophylaxis I would give “rotating” prophylaxis with daily trimethoprim alternating with daily nitrofurantoin 2 mg/kg/day. In case of persistent febrile infections I would continue with PIC. The nitrofurantoin elixir that is readily available is not suitable for prophylaxis because it causes nausea in the majority of children when given for more than 1 week. Instead, we ask the pharmacist to prepare capsules containing approximately 2 mg/kg of nitrofurantoin powder. The contents of these capsules can be sprinkled into food or drinks.

Guest editorial comment (MH): Analogous to the first case, for this case a DMSA scan (at least 6 months since the last known UTI) may be helpful for this type of patient. Specifically, the presence of renal scarring can be used to guide recommendations for antibiotic prophylaxis and alpha blockers. DMSA-detected renal scarring may also improve patient and family compliance with medication-based therapy.

Under what circumstances, if any, would you offer positional instilled cystography (PIC) with subureteric injection of an implant for the same patient described above in scenario #1?

HC: I really do not do PICs, as most of the time I have good results with the above. However, just recently I have had a patient in which I may consider this. Despite prophylaxis and BBD treatment she is having recurrent febrile UTIs. I would consider alternating therapy (1 week cycle of trimethoprim, then 1 week cycle of nitrofurantoin, etc.) after a 6 month course of double prophylaxis with no UTI. I would think about PIC cystography after 2-3 breakthrough UTIs. Prior to this I may suggest complementary therapy with cranberry and/or probiotic products which is another approach which I have not incorporated in my practice.

JH: I would offer PIC if the child did not have dysfunctional voiding, or if their dysfunctional voiding was optimally treated and they were still getting recurrent febrile infections - on or off antibiotics. I believe it is a rare patient that benefits from performing PIC cystogram but I have had a handful. When treated with either dextranomer-hyaluronic acid implants or ureteral reimplantation they do not usually have postoperative recurrent infections. I offer either dextranomer-hyaluronic acid implants or ureteral reimplantation and have done both for PIC VUR.

TdJ: We rarely do endoscopic injections for these cases but would certainly suggest it to the parents in case of febrile breakthrough infections or immediate recurrence after stopping of prophylaxis. We would not consider open reimplantation for these cases.

Guest editorial comment (MH): I have offered positional instilled cystography to patients’ families but in my experience parents prefer alternative approaches, including MRI urography, to rule out unlikely, subtle anomalies such as ectopic ureters that may be missed by ultrasonography.
The parents of the patient described above ask you about the role of cranberry juice/extract and probiotics in preventing recurrent UTI. What advice do you give them? If you recommend cranberry juice/extract and/or probiotics, what regimens do you recommend?

HC: I usually tell parents that the data are lacking in this area, but that I do believe in certain patients that complementary medicine is beneficial. Furthermore, as long as it is tolerated (some children have significant GI upset with the cranberry juice in large quantities), I do not believe that it is harmful from the data that we have collected thus far. I recommend either cranberry or probiotic products and typically tell them that from the literature the following regimens have been used: Cranberry supplements: 15 ml/kg cranberry juice/day or 300 ml/day (both 30% cranberry concentrate); Probiotics: *Lactobacillus acidophilus* 10⁶ CFU/g 1 g b.i.d. Many of these products can be purchased over the counter. For example, one product with which I am familiar is BioGaia, which is labeled Child Health at the bottom of the package so the parents know they are purchasing the formulation that is appropriately dosed for children.

JH: I have not recommended probiotics, although when parents ask I let them know I tell them the data does not suggest they are harmful and it is unclear if they help. I support their decision to use it if they choose to. I have recommended cranberry supplements although I tell them there also is insufficient data. Most often I have used Cystex cranberry complex or Cranactin.

TdJ: If parents ask for it, I would answer that there is some scientific proof that Cranberry pills or capsules with a dosage of approximately 500 mg/day may protect against UTI. The same is true for probiotics when taken every day.

Guest editorial comment (MH): I agree with this issue’s participants that the evidence for probiotics is weak at best. The *L. acidophilus* study by Lee et al. is interesting, but suffers from limitations. This equivalence clinical trial (oral *L. acidophilus* versus trimethoprim-sulfamethoxazole daily prophylaxis) studied young children with vesicoureteral reflux, a different patient population from anatomically normal children prone to recurrent UTI. The number of children diagnosed with VUR after a UTI versus after a diagnosis of prenatal hydrenephrosis was not reported. This has important implications, since these patient populations likely differ in terms of their risk of recurrent UTI. Although the authors reported subset analyses of children with and without voiding dysfunction, the criteria they used to make this important diagnosis were incompletely outlined. Finally, *L. acidophilus* is not a common commensal strain found in the vaginas of healthy girls and women. The lactic acid bacterial composition of the preputial and male peri-urethral microbiota is poorly characterized. Furthermore, it is unclear whether and how orally administered lactic acid bacteria in general can exert anti-uropathogenic effects, unless they exit the anus and colonize the vagina, as has been suggested to occur for the candidate probiotics *Lactobacillus reuteri* RC-14 and *Lactobacillus rhamnosus* GR-1.⁹ In a single non-controlled prospective study, *L. reuteri* RC-14 and *L. rhamnosus* GR-1 were reported to prevent recurrent UTI in women.¹⁰ Based on this literature I offer this commercially available strain combination to girls prone to UTI, with the caveat that the evidence for this is weak at best.

With regards to cranberry products, a recent randomized non-inferiority clinical trial reported that prophylactic antibiotics are superior to cranberry capsules in preventing recurrent UTI in infection-prone women.¹¹ Although this trial does not establish that cranberry products are efficacious in preventing recurrent UTI, the associated data does provide ammunition for the argument that prophylactic antibiotics work better than cranberry products. By extension, perhaps prophylactic antibiotics more effectively prevent UTI in children as compared to cranberry products. Certainly, there is no known contraindication to combined use of prophylactic antibiotics and cranberry products.

References