

CLINICAL DECISIONS

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Treatment of a 6-Year-Old Girl with Vesicoureteral Reflux

This interactive feature addresses the diagnosis or management of a clinical case. A case vignette is followed by specific clinical options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. In the online version of this feature, available at NEJM.org, readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A 6-year-old girl was recently referred to your clinic for further evaluation and management of vesicoureteral reflux, which had first been discovered after she presented at 1 year of age with a temperature of 39.5°C and irritability. Culture of a urine specimen at that time showed more than 10^6 colony-forming units of pansensitive *Escherichia coli* per milliliter, and she was treated with intravenous ampicillin for several days, followed by oral ampicillin, for a total of 14 days of therapy. After the patient no longer had a fever and a urine culture was sterile, voiding cystourethrography was performed while the patient was still receiving ampicillin. The voiding cystourethrogram showed bilateral grade III vesicoureteral reflux, and renal ultrasonography revealed normal findings. Radionuclide renal scintiscanning was not performed.

Prophylactic trimethoprim-sulfamethoxazole was administered at bedtime each night, and during the ensuing year, the patient had no urinary tract infections, as judged by sterile surveillance cultures of urine specimens and sterile cultures when she had any febrile episodes. A follow-up radionuclide voiding cystourethrogram when the patient was 2.5 years of age still showed bilateral grade III vesicoureteral reflux.

Subsequently, the family moved a number of times. The patient had several episodes of high fever, but no urine cultures were documented. At 4 years of age, she was seen again at the center where she had been followed, and she still had bilateral grade III vesicoureteral reflux. Continued antibiotic prophylaxis was recommended, but because of the family's moves, the degree of adherence was unclear. However, the child remained well, and her parents decided to stop the prophylactic antibiotics.

The child was toilet trained at 2 years of age,

and she had no history of constipation or bowel irregularities. She had occasional nocturnal enuresis until the age of 4. She has not had enuresis since that time. Studies at the center where she had been followed documented measurements of serum creatinine of 0.3 mg per deciliter (27 μ mol per liter) and blood urea nitrogen of 11 mg per deciliter (3.9 mmol per liter). Family history includes no chronic kidney disease, although the child's mother had a urinary tract infection when pregnant with this child, and the child's maternal grandmother, who is 51 years old, has had hypertension.

The patient, now 6 years of age, and her family have recently moved to your city, and her new primary care pediatrician refers her to you for consultation. She has been well recently, without reports of any medical problems. On examination of the child, you find that the height and weight are at the 50th percentile for age and the blood pressure is 88/50 mm Hg. Results of a general physical examination, including examination of the external genitalia, are normal. You obtain a urine specimen; culture of the specimen shows fewer than 1000 colony-forming units. A urinalysis reveals a specific gravity of 1.018 and a pH of 6.0; urine dipstick testing is negative for leukocytes, nitrites, protein, blood, glucose, ketones, and urobilinogen. The sediment shows no bacteria, 0 to 1 white cells, no red cells, and no casts per high-power field. You also obtain a radionuclide voiding cystourethrogram, which reveals that the patient still has bilateral grade III reflux. A renal ultrasound study shows that the kidney size is normal. A radionuclide renal scan is also normal. The parents ask whether you think the patient needs antibiotic prophylaxis and whether you would recommend any procedure to stop the vesicoureteral reflux.

Which one of the following approaches would you find most appropriate for this patient? Base your choice on the published literature, your own experience, recent guidelines, and other sources of information, as appropriate.

1. Watchful waiting without antibiotics.
2. Continuous antimicrobial prophylaxis.
3. Repair of the vesicoureteral reflux.

To aid in your decision making, each of these approaches to treatment is defended by an expert in the management of urinary tract infections and vesicoureteral reflux in the following short essays. Given your knowledge of the patient's condition and the points made by the experts, which treatment approach would you choose? Make your choice at NEJM.org.



Choose an option and comment on your choice at NEJM.org

TREATMENT OPTION 1

Watchful Waiting without Antibiotics

Uri S. Alon, M.D.

The healthy 6-year-old girl described in the vignette had a single episode of febrile urinary tract infection 5 years earlier, caused by the most common uropathogen. Except for the persistence of vesicoureteral reflux, she has no evidence of anatomical or functional perturbations. The question is, Is any intervention better than no intervention? There are several reasons why observation should be considered as the preferred option.

In most instances, vesicoureteral reflux is an inherited abnormality that resolves over time.¹ The rate of resolution depends on several variables, including the age of the patient at presentation and the grade of reflux. The younger the child and the lower the grade of reflux, the faster the resolution will be. Whether the reflux is unilateral or bilateral can also affect the rate of resolution.

It is reassuring that the renal ultrasound examinations at presentation and follow-up were normal. Most girls with low-grade or medium-grade vesicoureteral reflux who have a normal renal ultrasound examination at presentation will continue to have normal ultrasound studies. Likewise, in the vast majority of children with reflux nephropathy in whom chronic kidney disease and end-stage renal failure develop, the kidneys were most likely damaged in utero. With the routine use of maternal-fetal ultrasonography, obstructive and vesicoureteric reflux nephropathy can be detected prenatally. The knowledge that kidney damage may occur in utero has added to our understanding of the pathophysiology of reflux nephropathy. Furthermore, we have learned that

urinary tract infections might never develop in some children who have kidney damage in utero. Acquired reflux nephropathy has become nearly nonexistent as a cause of end-stage kidney disease in children, which further supports the concept of in utero kidney damage.²

Although older studies involving small numbers of children showed an advantage to the administration of prophylactic antibiotics, more recent studies do not confirm this advantage. Relatively recent meta-analyses showed no or only marginal advantage against recurrent urinary tract infection^{3,4}; a prospective study from Sweden showed that treatment with antibiotics provides better protection against new scarring than no such treatment, but the population studied included children who were younger than 2 years of age and who had severe vesicoureteral reflux and, in most cases, preexisting parenchymal damage.⁵

Abnormal elimination patterns may play a crucial role in delaying the resolution of reflux and increasing the risk of urinary tract infection.⁴ The risk of infection in this child is low, since none of these clinical scenarios apply to her.

Excessive use of prophylactic antibiotics may increase the prevalence of resistance. Many strains of *E. coli* in the community are already resistant to ampicillin and trimethoprim-sulfamethoxazole. Therefore, it might be an advantage in terms of both public health and the individual patient to minimize the use of antimicrobial agents.

This patient has remained free of infection since she stopped taking prophylactic antibiotics. She is healthy and has normal kidney anatomy and function and excellent bladder control and bowel habits. She has an anatomical abnormality that seems to have no clinical consequences; her prognosis is excellent. She may benefit from careful observation, with a high index of suspi-

cision for urinary tract infection, but she may not require any additional evaluation or intervention while she remains free of infection.

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

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TREATMENT OPTION 2

Continuous Antimicrobial Prophylaxis

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Children with vesicoureteral reflux of grade III or more that was diagnosed after a febrile urinary tract infection, like the girl in the vignette, have a risk of renal scarring that is 4 to 6 times as great as the risk among children with grade I or II reflux and 8 to 10 times as great as the risk among children without reflux.⁶ Some recently published trials showed no reduction in the incidence of recurrent infections in children receiving antimicrobial prophylaxis; this finding has led some clinicians to question the role of antimicrobial prophylaxis or even the need to evaluate children for reflux.⁶ However, these trials were small and underpowered to detect even large differences in rates of recurrent infection.

To detect a 10% reduction in the rate of recurrent infection among children receiving antimicrobial prophylaxis (assuming a baseline reinfection rate of 20% with placebo), 600 children would have to be enrolled. Therefore, the lack of observed reduction in recurrences may have resulted from insufficient statistical power, rather than lack of efficacy of antimicrobial prophylaxis. Furthermore, since these studies were conducted outside the United States, a large number of uncircumcised boys were included, thereby limiting the generalizability of the findings to a U.S. population in which most newborn boys are circumcised. Finally, lack of blinding may have led to an underestimation of recurrent infection in the prophylaxis group, whereas the use of non-stringent criteria for urinary tract infections, as well as surveillance cultures of urine specimens — which potentially identify children with asymptomatic bacteriuria rather than infection — may have diluted the actual benefit of antimicrobial prophylaxis, biasing results toward the null.⁶

Reports of two larger and more carefully designed investigations have been published. In a study involving 576 children in whom urinary tract infections were diagnosed with the use of stringent criteria, Craig et al. reported that in children with vesicoureteral reflux, antimicrobial prophylaxis was moderately more effective than placebo in reducing reinfections (reinfection rate, 11% vs. 17%).⁷ Although not all children underwent voiding cystourethrography, the reduction in risk was greatest among children with grade III, IV, or V reflux (–6.8%), as compared with that among children with grade I or II reflux (–5.4%) or those with no reflux (–1.8%). Brandström et al. reported on 203 children 1 to 2 years of age with grade III or IV reflux who were randomly assigned to antimicrobial prophylaxis, endoscopic surgery, or surveillance. Antimicrobial prophylaxis was the most effective — only in girls — in decreasing the likelihood of febrile urinary tract infections (19%, 23%, and 57% had infections, respectively) and renal scarring (6%, 12%, and 18% had scarring, respectively).⁸

The patient in the vignette had several episodes of high fever during which urine specimens were not cultured; accordingly, it is unknown whether she had additional infections. The most benign course of action, which avoids both additional radiation exposure and surgery, would be to observe her during 1 to 2 years of antimicrobial prophylaxis with aggressive evaluation of all febrile episodes.⁹ During this period, if she does have reinfections, surgical repair of vesicoureteral reflux would be warranted; conversely, if she does not have reinfections, antimicrobial prophylaxis could be discontinued, provided meticulous follow-up were ensured. It would also be judicious to avoid repeating voiding cystourethrography, to minimize exposure to radiation, unless the patient has a breakthrough infection.

More conclusive evidence on the benefits of antimicrobial prophylaxis is expected from the Randomized Intervention for Children with Vesicoureteral Reflux study, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, which has completed enrollment of 607 children 2 months to 6 years of age. The children have grade I through grade IV reflux that was diagnosed after urinary tract infections that were defined according to stringent criteria.¹⁰ Continuing the use of established practices derived from careful clinical observations, such as antimicro-

bial prophylaxis in children with dilating reflux, seems prudent until this more conclusive and generalizable evidence becomes available.

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TREATMENT OPTION 3

Repair of the Vesicoureteral Reflux

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The compelling reason for corrective repair in this child is the high likelihood of recurrent pyelonephritis as long as she has vesicoureteral reflux. Regardless of vesicoureteral reflux status, patients who have recurrent urinary tract infections are susceptible to infection because they have alterations in the urothelium of the bladder that enhance bacterial attachment and alter local immune response. Clinical studies in women and children show that the likelihood of future urinary tract infection correlates directly with previous urinary tract infection. Increased odds of recurrent urinary tract infections in young women are associated with an age of less than 15 years at the first urinary tract infection, as well as whether their mothers had urinary tract infection.¹¹

Whether refluxing kidneys are embryologically dysmorphic and then acquire renal scars and hypotrophy from urinary tract infections is debatable, but recurrent pyelonephritis can cause new scars, and the risk of scarring is associated with the number of urinary tract infections sustained.¹² In the patient in the vignette, the results of renal ultrasonography and scanning were normal. However, these imaging techniques cannot show subtle scars or hypotrophy,¹³ making the assessment of renal damage difficult. Markers of renal dysfunction — elevated creatinine levels, hypertension, and proteinuria — may not be evident until adulthood or pregnancy.

Antimicrobial prophylaxis has been ineffective in the prevention of recurrent urinary tract infections in this girl. Medical claims data suggest that nonadherence to prophylaxis is common, and the reasons include expense, bother, patient distaste, and caregiver concern about increasing bacterial resistance. Whether resistance results

from excessive antimicrobial usage, inappropriate dosing, or increased global and environmental usage, optimal drugs that can be used for pediatric urinary prophylaxis and that have low bacterial resistance and low serum and high urinary concentrating properties are few.

Surgical intervention turns the morbidity and costs associated with this chronic disease into a cure. Children with vesicoureteral reflux have annual or more frequent visits to their doctors, undergo imaging studies, take daily medication, and see their medical doctor when symptoms dictate. This child had a hospitalization and at least two renal ultrasound examinations, one fluoroscopic voiding cystourethrogram, three radionuclide voiding cystourethrograms, one radionuclide renal scan, and multiple urine cultures; she also has undergone multiple urinalyses, four or more urethral catheterizations, and several blood tests. Thus, she has had substantial exposure to ionizing radiation, has undergone long periods of daily medication, and has had to make multiple medical visits. These medical encounters have direct and indirect costs, such as discomfort to the child, time and dollars spent on the child, and time and dollars spent by caregivers and society.¹⁴ Extended treatment of vesicoureteral reflux makes it into a chronic disease that could adversely affect this girl's quality of life and that of her caregivers, just as asthma can. Repair decreases the frequency of febrile urinary tract infections (i.e., pyelonephritis) and eliminates the need for frequent routine follow-up visits.

The discomfort previously associated with ureteroneocystostomy or laparoscopic or robotic-assisted repair has been reduced in recent years by the supplemental use of regional and local anesthesia, avoidance of ureteral and urethral catheters, good postoperative pain management, and post-procedure hospitalizations of 1 or 2 days. Endoscopic injections of bulking agents for repair further reduce incisional pain, although the durable surgical cure rate (measured by an absence of vesicoureteral reflux on postoperative voiding cystourethrography 1 to 2 years later) for ureteroneocystostomy is 98% and for endoscopic injection (with up to three separate injection procedures) is 45 to 60%; other complications are uncommon.

Curative intervention in this 6-year-old girl should be seriously considered in order to decrease her risk of another episode of pyelonephritis, to

avoid the chronic administration of medication that has not been effective, to arrest a chronic disease, and to limit her current and future disease-related discomfort. Recent guidelines from the American Urological Association panel on vesicoureteral reflux in children recommend surgical intervention as a treatment option for children with breakthrough febrile and afebrile recurrent urinary tract infections.¹⁵

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