Received: 13 April 2018 | Revised: 9 August 2018 | Accepted: 7 September 2018

DOI: 10.1111/petr.13299

ORIGINAL ARTICLE

WILEY

When does vesicoureteral reflux in pediatric kidney transplant patients need treatment?

Hsi-Yang Wu[1] | Waldo Concepcion[2] | Paul C. Grimm[2]

[1]Division of Pediatric Urology, Lucile Packard Children's Hospital, Stanford, California

[2]Division of Kidney Transplantation, Lucile Packard Children's Hospital, Stanford, California

Correspondence
Hsi-Yang Wu, Department of Urology, Stanford Hospital and Clinics, Stanford, CA.
Email: hwu2@stanford.edu

Abstract

Purpose: The treatment of VUR in children with UTI has changed significantly, due to studies showing that antibiotic prophylaxis does not decrease renal scarring. As children with kidney transplants are at higher risk for UTI, we investigated if select patients with renal transplant VUR could be managed without surgery.

Materials and Methods: A total of 18 patients with VUR into their renal grafts were identified, and 319 patients underwent transplantation from 2006 to 2016. The cause for the detection of the VUR, treatment, and graft function was reviewed.

Results: Six boys and 12 girls were identified, 13 of whom had grade 3 or 4 VUR into the renal graft. Nine patients presented with hydronephrosis or abnormal renal biopsy: eight were successfully managed with antibiotic prophylaxis and bladder training, one developed UTI and underwent Dx/HA subureteric injection. Nine patients presented with recurrent febrile UTI, only one was successfully managed without surgery. Only 2 of 9 (22%) patients who underwent Dx/HA injection had resolution of their reflux. Of the remaining seven, five required open ureteral reimplantation (two for obstruction), one lost the graft due to rejection, and one had significant hydronephrosis. eGFR was similar between the hydronephrosis, UTI, and abnormal renal biopsy groups at all times.

Conclusion: Patients with transplant VUR and recurrent febrile UTI are more likely to require surgical therapy, but the complication and failure rate for Dx/HA injection is significant. Patients with transplant VUR without febrile UTI can be successfully managed with bladder training and temporary antibiotic prophylaxis.

KEYWORDS

dextranomer, kidney transplantation, pediatric, vesicoureteral reflux

1 | INTRODUCTION

The indications for the detection and treatment of VUR in children with UTI have changed significantly following the release of the National Institute for Health and Care Excellence and American Academy of Pediatrics guidelines.[1,2] These changes in guidelines were driven by randomized controlled trials showing that while antibiotic prophylaxis decreases the risk of UTI, prophylaxis does not prevent renal scarring, except in select populations.[3-5] As children with kidney transplants are at higher risk for UTI due to immunosuppression, pre-existing VUR, and abnormal bladder function, and there is a concern for missing initial signs of UTI on urinalysis due to immunosuppression, we reviewed our experience with children with transplant VUR to determine if management can be individualized based on their presenting symptoms. Similar to children without kidney transplants, VUR may be detected after a febrile UTI or during

Abbreviations: Dx/HA, dextranomer/hyaluronic acid; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; UTI, urinary tract infection; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

investigation of asymptomatic hydronephrosis. However, there is a 3rd group of patients that are unique to children with kidney transplants: those with "scarring" noted on routine protocol biopsies who have never had a clinically symptomatic UTI.[6] We anticipated that patients with recurrent febrile UTI would require the most aggressive treatment, patients with VUR due to hydronephrosis would only need bladder training, and the outcome of patients with asymptomatic scarring would be better than the UTI group, but worse than the hydronephrosis group. The primary outcome of this study was eGFR, the secondary outcomes were resolution of VUR and prevention of febrile UTI.

2 | MATERIALS AND METHODS

We obtained permission from our institutional review board to perform a retrospective review of patients under age 18 who underwent kidney transplantation between 2006 and 2016 with at least 6 months of follow-up. Out of 319 patients, we identified 18 patients (6%) with VUR into their kidney transplant who were volitionally voiding. We did not study patients who had persistent VUR into their native kidneys. Patients with neurogenic bladder, had a vesicostomy or augmentation cystoplasty, or who relied on intermittent catheterization prior to transplantation were excluded. The majority of the 319 patients underwent ureteral reimplantation using the Lich-2 technique[7] into the posterior and lateral wall of the bladder at the time of transplantation and had a ureteral stent placed, which was subsequently removed. For the patients with very small bladders at time of transplantation (n = 4 in this series), a Politano-Leadbetter transvesical reimplantation was used, and the ureteral stent was tied to a suprapubic tube.[8]

The VCUG was obtained to investigate (a) hydronephrosis, (b) recurrent febrile UTI, or (c) renal scarring suggestive of infection on renal allograft biopsy. The grade of VUR, initial diagnosis leading to ESRD, diagnosis (hydronephrosis, UTI, abnormal renal biopsy) that led to detection of VUR, procedures, medications, and bladder training used to treat VUR were reviewed. A febrile UTI was diagnosed based on a temperature >38.5°C, with pyuria on urinalysis, and a single organism >100 000 colonies. eGFR was reviewed at 6-month intervals, starting from the time of the detection of the VUR.

All three groups were started on bladder training, and antibiotic prophylaxis after the diagnosis of VUR was made. Antibiotics used for prophylaxis were cephalexin (10 mg/kg daily), nitrofurantoin (1-2 mg/kg daily), and trimethoprim-sulfamethoxazole (2 mg/kg of trimethoprim daily). The choice of antibiotic was based on bacterial sensitivities and patient allergies. Antibiotic prophylaxis was stopped after bladder emptying problems were corrected, if the patient had no further febrile UTI. Patients who had breakthrough febrile UTI despite bladder training and antibiotic prophylaxis underwent Dx/HA (Deflux®) injection. Patients who continued to have recurrent febrile UTI after Dx/HA injection then underwent open ureteral reimplantation. If the patient had subsequent febrile UTI, antibiotic prophylaxis was resumed, regardless of the presence or absence of VUR.

Dx/HA injection was performed in both the back wall of the ureter and circumferentially around the ureterovesical anastomosis, using the "Double HIT" technique,[9] in order to produce a mound that visually occluded the orifice. Redo ureteral reimplantation was carried out using a Cohen cross-trigonal anti-refluxing technique in four patients, one underwent an initial redo extravesical reimplantation, which later required revision with a cross-trigonal technique. eGFR was calculated using the bedside Schwartz equation of (0.41 × height in cm)/serum creatinine (mg/dL).[10] eGFR between groups was compared using a 2-tailed unpaired t test (GraphPad Prism).

3 | RESULTS

Six boys and 12 girls were identified, and kidney transplantation occurred at a median age of 6.3 years (range 1.5-16.3). Median time to

TABLE 1 Study population by presenting symptom

	Hydronephrosis (n = 5)	Recurrent UTI (n = 9)	Abnormal renal biopsy (n = 4)
Cause of ESRD	Autosomal recessive polycystic kidney disease (n = 2), Denys-Drash, hemolytic uremic syndrome, posterior urethral valves (each n = 1)	Glomerulonephritis, nephronophthisis, nephrotic syndrome, bilateral Wilms tumor, unknown (each n = 1), bilateral renal dysplasia, bilateral VUR (each n = 2)	Bilateral VUR (n = 2), methylmalonic acidemia (combined liver-kidney transplant), multicystic dysplastic kidney with glomerulosclerosis (each n = 1)
Grade of VUR	Grade 3 (n = 1) Grade 2 (n = 3) Grade 1 (n = 1)	Grade 4 (n = 1) Grade 3 (n = 8)	Grade 4 (n = 1) Grade 3 (n = 2) Grade 2 (n = 1)
Duration of anuria	5 mo-3 y, only patient with HUS maintained urine production	2 mo: glomerulonephritis. 2 y: bilateral Wilms tumor	None

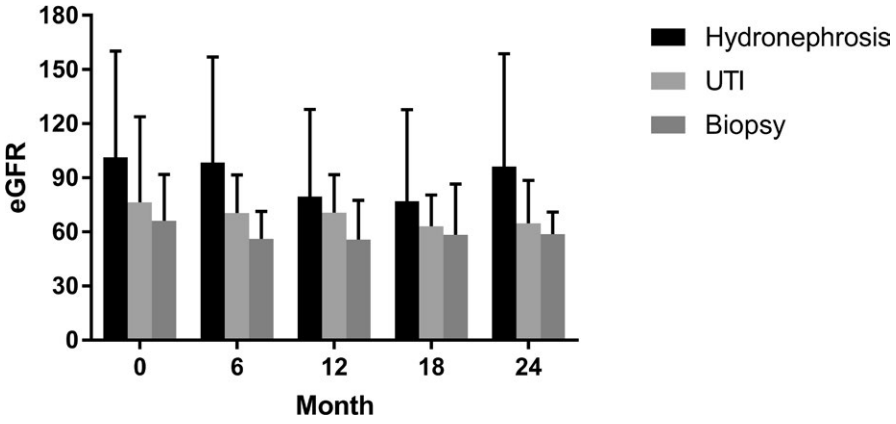

FIGURE 1 eGFR by presenting symptom at 6-mo intervals after VUR diagnosis

TABLE 2 Treatment outcome by presenting symptom

	Hydronephrosis (n = 5)	Recurrent UTI (n = 9)	Abnormal renal biopsy (n = 4)
Treatment	Bladder training, antibiotic prophylaxis.	Bladder training, antibiotic prophylaxis (n = 1). Dx/HA injection (n = 8), followed by ureteral reimplantation (4/8).	Bladder training, antibiotic prophylaxis (n = 3). Dx/HA injection followed by ureteral reimplantation (n = 1) for UTI.
VUR resolution	2 resolved 3 not assessed	2/8 Dx/HA 1/4 ureteral reimplantation 1 not assessed	1/1 ureteral reimplantation 3 not assessed
Complications	None	1/8 Dx/HA graft loss 3/8 Dx/HA obstruction	None
UTI resolution	None at baseline	2/9 (successful Dx/HA)	None at baseline
Cessation of antibiotics	3/5	2/9	3/4

detection of VUR after transplantation was 1.0 year (range 0.5-7.8), and median length of follow-up after transplantation was 5.5 years (range 1.8-10.6). Two patients had grade 4 VUR, 11 had grade 3 VUR, four had grade 2 VUR, and one had grade 1 VUR. The causes of ESRD, grade of VUR, and duration of anuria prior to transplantation for each group are listed in Table 1.

eGFR (mean ± SD, mL/min/1.73m^2) starting at the time of VUR diagnosis is shown in Figure 1. Although the hydronephrosis group continued to trend toward better graft function over 2 years, the eGFR was not better ($P > 0.05$) than the UTI or abnormal renal biopsy group at any time. The treatments and complications, rates of VUR resolution, UTI resolution, and cessation of antibiotics are listed in Table 2.

Five patients presented with hydronephrosis of the transplanted kidney. Four of five patients who presented with hydronephrosis had small bladders at the time of transplantation and underwent initial Politano-Leadbetter rather than Lich-2 ureteral reimplantation. Urodynamics were carried out prior to transplantation in the patient with posterior urethral valves, which revealed a normal capacity bladder with complete emptying. Urodynamics were carried out after transplantation in the patients with hemolytic uremic syndrome, autosomal recessive polycystic kidney disease, and Denys-Drash. The only minor urodynamic abnormality was that the patient with Denys-Drash had incomplete bladder emptying. All five patients were initially managed with timed voiding and antibiotic prophylaxis. While the hydronephrosis has not changed in any patient, subsequent urodynamic investigation for persistent hydronephrosis showed that two patients had spontaneous resolution of grade 2 VUR at 18 months and 4 years after transplantation, three patients were able to stop antibiotic prophylaxis. We are awaiting resolution of incomplete bladder emptying before stopping prophylaxis for the last two patients.

Nine patients presented with recurrent UTI, of which only two had recurrent UTI prior to transplantation. One patient with VUR underwent urodynamics prior to transplantation, this confirmed that the bladder was not emptying fully and she was started on pelvic floor biofeedback. Two patients with nephronophtisis and nephrotic syndrome underwent urodynamics after transplantation to evaluate

difficulty emptying the bladder, they were started initially on overnight catheterization or alpha blockers, and they are currently both on alpha blockers. All patients were on prophylactic antibiotics and timed voiding. One patient with recurrent UTI and grade 3 VUR was successfully managed without further febrile UTI. Eight of nine patients with recurrent UTI underwent initial Dx/HA subureteric injection for grade 4 (n = 1) or grade 3 (n = 7) VUR. Only two patients were able to stop antibiotic prophylaxis after a successful Dx/HA injection, the remainder continued on antibiotic prophylaxis after redo ureteral reimplantation due to recurrence of febrile UTI's after prophylaxis was stopped.

There were four patients in whom the initial finding triggering the search for reflux was an abnormal renal allograft biopsy. All four patients had stable creatinine and were receiving the biopsy per protocol to diagnose subclinical rejection.[11] All biopsies were performed after a negative urine culture at the immediate preoperative visit within 7 days. Two biopsies were 6 months after transplantation, two biopsies were 12 months after transplantation. One biopsy showed tubular atrophy with intra-tubular neutrophils. One biopsy showed very patchy, focal tubular inflammation. Two biopsies showed patchy tubular atrophy and inflammation. In the absence of any signs of rejection, the pathologist queried whether vesicoureteral reflux might be the cause. One patient with VUR had normal urodynamics prior to transplantation, and there were no urodynamics carried out after transplantation. All four patients were initially managed with timed voiding and antibiotic prophylaxis. One patient with an abnormal renal biopsy and grade 3 VUR subsequently developed UTI's and underwent Dx/HA subureteric injection. This was not successful, and he required a ureteral reimplantation to resolve the VUR. Three patients were able to stop antibiotic prophylaxis, and we are awaiting resolution of incomplete bladder emptying before stopping prophylaxis on the 4th patient. We were unable to determine the number of patients with "reflux nephropathy" read on biopsy who had a negative VCUG, but it is common to obtain a negative VCUG with this presentation.

The outcome of nine patients undergoing Dx/HA subureteric injection was much poorer than expected. The median total injected volume of Dx/HA was 3 mL per ureter (range 1-6 mL). Two patients had successful resolution of grade 3 VUR, both received 3 mL of Dx/HA. One underwent injection for grade 3 VUR did not have a postoperative cystogram, and eventually lost the graft due to noncompliance with her medication regimen. Of the remaining six patients (five with grade 3, one with grade 4 VUR), one had a negative cystogram but had persistent grade 3 hydronephrosis 2 years after injection, suggestive of obstruction. She was lost to follow-up before stenting, or revision could be performed.

Five patients subsequently underwent open ureteral reimplantation for persistent VUR (n = 3) and intermittent obstruction (n = 2). We were successful in resolving VUR in only 2/5 patients who underwent open ureteral reimplantation. In 1/3 cases of persistent VUR, there was no improvement in grade 3 VUR even after ureteral reimplantation, due to a short ureter. Most worrisome were two patients who presented with intermittent obstruction at the ureterovesical junction, 2 years after initial Dx/HA injection, with anuria and significant hydroureteronephrosis. They were initially treated with ureteral stenting, and then underwent open revision of the ureterovesical junction. Unfortunately, these two patients continued to have grade 4 VUR after the obstruction was resolved. Due to persistent febrile UTI, one patient underwent a second redo ureteral reimplantation using a cross-trigonal technique after the initial extravesical technique failed. Connecting the transplant ureter to a native ureter was not possible in these two patients due to prior excision of native ureters or scarring from the Dx/HA injection.

4 | DISCUSSION

Our understanding of the contribution of VUR to renal allograft dysfunction has evolved from a belief that it was a major cause for graft failure to a more nuanced view, that while it contributes to graft dysfunction, VUR may be a marker for bladder dysfunction and biological susceptibility for UTI. We no longer obtain cystograms on all children undergoing kidney transplantation, so it is likely there are some children with asymptomatic transplant VUR who are not actively being managed, if they do not have UTI. Until the routine use of the Lich-2 technique,[7,12,13] VUR was found on screening in 24%-79% of children with kidney transplants and was considered an important cause of late graft failure.[12] More recent studies show that VUR detected after symptomatic infection occurs in 4%-12% of pediatric kidney transplant patients.[14-17] Fontana et al[13] could not show a difference in graft survival or creatinine clearance when they compared their patients with VUR and without VUR at a median follow-up of 4 years. They repaired all patients with grade 4 VUR, so the implication was that grades 1-3 VUR in a kidney transplant may not as harmful as previously thought. In his editorial comment, Salvatierra pointed out that the situation is very different when there is transplant VUR in a boy with posterior urethral valves and suggested that initial antibiotic prophylaxis for grades 1-3 VUR in a child with a normal bladder is reasonable, with the option of surgical repair if there were breakthrough infections.[17]

Surprisingly, functional bladder disorders do not increase the risk for UTI or the incidence of UTI after transplant, but patients with recurrent UTI have a more rapid decrease in GFR.[18] Obstructive uropathy, pretransplant pyelonephritis, pretransplant vesicoureteral reflux, age <5 years, and congenital anomalies of the kidneys and urinary tract (mainly posterior urethral valves) have been identified as risk factors for post-transplant UTI.[19-21] However, at 2-year follow-up, no difference could be shown in eGFR between patients with febrile UTI and those without febrile UTI. This was attributed to the study being underpowered (n = 98) and the complicating factor of acute rejection.[21]

When a child is found to have persistent hydronephrosis and hydroureter after kidney transplantation, the major concern is for

obstruction at the ureterovesical anastomosis. In our population, the patients with small bladders at transplantation who presented with hydronephrosis were likely undergoing bladder cycling with an increase in bladder capacity after transplantation. If graft function is normal, the VCUG may show that the hydroureter is due to vesicoureteral reflux. In the absence of febrile UTI, we have been able to stop antibiotics in these children after correcting incomplete bladder emptying and have seen spontaneous resolution of the VUR. This population is similar to those patients who are detected as infants with VUR due to prenatal hydronephrosis. In those patients, the absence of renal scarring, recurrent UTI, and VUR less than grade 5 were predictors of successful management without surgery.[22] While transplant hydronephrosis in the absence of VUR has been correlated with worsened graft function and pyelonephritis,[23] this is due to ureteral obstruction, which poses a greater threat to the graft than VUR without UTI.

Patients with abnormal renal biopsies with inflammation suggesting vesicoureteral reflux without any clinical signs of UTI continue to pose a challenge. As we were unable to differentiate these patients from other patients with abnormal biopsies who did not have VUR, we have not been surgically aggressive unless they also have a febrile UTI. Despite the concerning biopsy findings, the clinical outcome for these patients was similar to those found to have VUR due to hydronephrosis, as we were able to stop prophylaxis after bladder training was completed.

Patients with kidney transplant VUR and recurrent febrile UTI are at the highest risk for subsequent renal injury. We were not able to predict which patients would have recurrent febrile UTI based on their pretransplant course. Eight of nine of these patients continued to have febrile UTI despite bladder training and prophylactic antibiotics. While Dx/HA subureteric injection has minimal immediate morbidity, it is less successful in pediatric transplant ureters than in native ureters, has a significant delayed morbidity of ureteral obstruction, and decreases the success rate of subsequent ureteral reimplantation. The total published experience of Dx/HA injection in 20 pediatric patients shows a success rate of 50%.[24,25] This is understandable due to the shorter submucosal tunnel and the need to inject a large amount of Dx/HA circumferentially around the ureteral orifice to resolve the VUR. The median volume of Dx/HA injected in this series of 3 mL is larger than the 1-1.5 mL reported in previous series.[24,25] The possibility that the resolution of VUR in two patients was due to spontaneous resolution rather than due to Dx/HA cannot be excluded. The rate of obstruction after Dx/HA in native ureters is low (<1%),[26] and while there are reports of obstruction after Dx/HA injection into pediatric transplant ureters, the severity of this complication is worrisome.[27] We report an alarming complication of Dx/HA injection into transplant ureters, which is delayed obstruction occurring 2 years after injection. This also occurs in native ureters, up to 5 years after injection.[28] We hypothesize that this occurs due to the placement on the transplant ureter into a relatively mobile portion of the bladder, which allows the Dx/HA to cause intermittent obstruction based on bladder filling. Alternatively, a combination of relative ischemia in the distal ureter and low-grade rejection could make the fibrotic response to Dx/HA more significant than in a native ureter.

We were also concerned that Dx/HA injection worsened our success with ureteral reimplantation, as only 2/5 patients had resolution of VUR. There are no data on ureteral reimplantation after Dx/HA in pediatric patients, but 40% is lower than the 98% success seen in native pediatric ureters after Dx/HA[29] and the expected 70%-80% for redo extravesical reimplantation of transplant pediatric ureters which have not been injected.[14,30] While anastomosing the transplant ureter into the distal native ureter is an established technique, it is sometimes not available if the child had previous high-grade VUR and prior ureteral surgery. We propose that the loss of ureteral length from the fibrotic reaction of the ureter to Dx/HA is responsible for the poor outcome in salvage ureteral reimplantation.

We excluded patients with neurogenic bladder from analysis, as they had been previously noted to be at higher risk for ureteral obstruction after Dx/HA injection.[25,26] Many of our patients with posterior urethral valves either have a vesicostomy or are on intermittent catheterization. The findings in this series apply to those patients with normal bladders or with moderate functional disorders, but not to patients with neurogenic bladders or posterior urethral valves with high voiding pressures or poor emptying.

When we consider the burden of therapy required to maintain allograft function, the traditional approach of surgically treating only high-grade transplant VUR with associated febrile UTI is supported by our finding that eGFR outcomes are similar in the hydronephrosis, febrile UTI, and abnormal renal biopsy groups. While the population in this study is small, the overall eGFR for the combined group is consistent with graft function based on historical controls.[16,31-34] As shown by Weigel et al,[21] there are multiple factors that affect graft function, and it is difficult to show that management of VUR alone will impact eGFR. Patients who are found incidentally to have VUR after investigation for hydronephrosis and abnormal renal biopsies can be treated with bladder training and temporary antibiotic prophylaxis. While 2/9 patients with VUR and recurrent febrile UTI were successfully treated with Dx/HA injection, the remaining seven patients remain on antibiotic prophylaxis, and we may have lost an opportunity to surgically correct VUR in three patients who subsequently failed ureteral reimplantation. We were unable to find clinical factors to select which patients were more likely to have a successful Dx/HA injection. Given the low success rate of Dx/HA subureteric injection in this population, the unpredictable onset and severity of ureteral obstruction, and the poor outcome of subsequent ureteral reimplantation, our preference is for primary open ureteral reimplantation in a child with a refluxing transplant ureter and recurrent UTI.

AUTHORS' CONTRIBUTION

Hsi-Yang Wu: Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics, Data

collection; Waldo Concepcion: Concept/design, Critical revision of article, Approval of article; Paul C. Grimm: Concept/design, Critical revision of article, Approval of article, Data collection.

ORCID

Hsi-Yang Wu http://orcid.org/0000-0001-5172-6387

REFERENCES

1. Urinary tract infection. Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128:595-610.
2. NICE. Urinary tract infection under 16s: diagnosis and management. 2007, revised 2017. https://nice.org.uk/guidance/cg54. Accessed April 13, 2018.
3. Craig JC, Simpson JM, Williams GJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med*. 2009;361:1748-1759.
4. Brandstrom P, Neveus T, Sixt R, et al. The Swedish Reflux Trial in children: IV. Renal damage. *J Urol*. 2010;184:292-297.
5. RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med*. 2014;370:2367-2376.
6. Akioka Y, Chikamoto H, Horita S, et al. Screening of vesicoureteral reflux in pediatric patients with kidney transplantation showing non-specific interstitial fibrosis and tubular atrophy with interstitial Tamm-Horsfall protein deposits in protocol allograft biopsy. *Clin Transplant*. 2009;23(Suppl 20):2-5.
7. Dunn SP, Vinocur CD, Hanevold C, et al. Pyelonephritis following pediatric renal transplant: Increased incidence with vesicoureteral reflux. *J Ped Surg*. 1987;22:1095-1099.
8. Alexopoulos S, Lightner A, Concepcion W, et al. Pediatric kidney recipients with small capacity, defunctionalized urinary bladders receiving adult-sized kidney without prior bladder augmentation. *Transplant*. 2011;91:452-456.
9. Cerwinka WH, Scherz HC, Kirsch AJ. Dynamic hydrodistention classification of the ureter and the double hit method to correct vesicoureteral reflux. *Arch Espan Urol*. 2008;61:882-887.
10. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20:629-637.
11. Gordillo R, Munshi R, Monroe EJ, et al. Benefits and risks of protocol biopsies in pediatric renal transplantation. *Pediatr Nephrol*. 2018. https://doi.org/10.1007/s00467-018-3959-6 [Epub ahead of print].
12. Mathew TH, Kincaid-Smith P, Vikraman P. Risks of vesicoureteral reflux in the transplanted kidney. *N Engl J Med*. 1977;297:414-418.
13. Fontana I, Ginveri F, Arcuri V, et al. Vesico-ureteral reflux in pediatric kidney transplants: clinical relevance to graft and patient outcome. *Pediatr Transplant*. 1999;3:206-209.
14. Barrero R, Fijo J, Fernandez-Hurtado M, et al. Vesicoureteral reflux after kidney transplantation in children. *Pediatr Transplant*. 2007;11:498-503.
15. Irtan S, Maisin A, Baudouin V, et al. Renal transplantation in children: critical analysis of age related surgical complications. *Pediatr Transplant*. 2010;14:512-519.
16. Torricelli F, Watanabe A, Piovesan AC, et al. Urological complications, vesicoureteral reflux, and long-term graft survival rate after pediatric kidney transplantation. *Pediatr Transplant*. 2015;19:844-848.
17. Salvatierra O. Management of vesico-ureteral reflux in renal allografts transplanted into pediatric recipients. *Pediatr Transplant*. 1999;3:171-174.
18. Herthelius M, Oborn H. Urinary tract infections and bladder dysfunction after renal transplantation in children. *J Urol*. 2007;177:1883-1886.
19. Feber J, Spatenka J, Seeman T, et al. Urinary tract infections in pediatric renal transplant recipients – a two center risk factors study. *Pediatr Transplant*. 2009;13:881-886.
20. Esezobor CI, Nourse P, Gajjar P. Urinary tract infection following kidney transplantation: frequency, risk factors and graft function. *Pediatr Nephrol*. 2012;27:651-657.
21. Weigel F, Lemke A, Tonshoff B, et al. Febrile urinary tract infection after pediatric kidney transplantation: a multicenter, prospective observational study. *Pediatr Nephrol*. 2016;31:1021-1028.
22. Martin AD, Iqbal MW, Sprague BM, et al. Most infants with dilating vesicoureteral reflux can be treated nonoperatively. *J Urol*. 2014;191:1620-1627.
23. Chu L, Bl J, Schwen Z, et al. Hydronephrosis in pediatric kidney transplant: clinical relevance to graft outcome. *J Ped Urol*. 2013;9:217-222.
24. Williams MA, Giel DW, Hastings MC. Endoscopic Deflux injection for pediatric transplant reflux: a feasible alternative to open ureteral reimplant. *J Ped Urol*. 2008;4:341-344.
25. Vemulakonda VM, Koyle MA, Lendvay TS, et al. Endoscopic treatment of symptomatic refluxing renal transplant ureteroneocystotomies in children. *Pediatr Transplant*. 2010;14:212-215.
26. Vandersteen DR, Routh JC, Kirsch AJ, et al. Postoperative ureteral obstruction after subureteral injection of Dextranomer/Hyaluronic Acid copolymer. *J Urol*. 2006;176:1593-1595.
27. Cambareri G, Carpenter C, Stock J, et al. Endoscopic antireflux surgery leading to obstruction in pediatric renal transplant patients. *Pediatr Transplant*. 2017;21:e12838.
28. Rubenwolf PC, Ebert AK, Ruemmele P, et al. Delayed-onset ureteral obstruction after endoscopic dextranomer/hyaluronic acid copolymer (Deflux) injection for treatment of vesicoureteral reflux in children: a case series. *Urol*. 2013;81:659-662.
29. Moreira-Pinto J, Osorio A, Pereira J, et al. Ureteroneocystostomy after failed dextranomer/hyaluronic acid copolymer injection for vesicoureteral reflux treatment. *J Ped Urol*. 2013;9:665-669.
30. Krishnan A, Swana H, Mathias R, et al. Redo ureteoneocystostomy using an extravesical approach in pediatric renal transplant patients with reflux: a retrospective analysis and description of technique. *J Urol*. 2006;176:1582-1587.
31. Sorof JM, Goldstein SL, Brewer ED, et al. Serial estimation of glomerular filtration rate in children after renal transplant. *Pediatr Nephrol*. 1999;13:737-741.
32. Moudgil A, Martz K, Stablein DM, et al. Variables affecting estimated glomerular filtration rate after renal transplantation in children: a NAPRTCS data analysis. *Pediatr Transplant*. 2010;14:288-294.
33. Paper L, Ahlenstiel T, Werner CD, et al. Development and validation of a new statistical model for prognosis of long-term graft function after pediatric kidney transplantation. *Pediatr Nephrol*. 2013;28:499-505.
34. De Souza VC, Rabilloud M, Cochat P, et al. Trajectories and predictors of allograft dysfunction after renal transplantation in children. *Am J Nephrol*. 2017;45:63-68.

How to cite this article: Wu H-Y, Concepcion W, Grimm PC. When does vesicoureteral reflux in pediatric kidney transplant patients need treatment?. *Pediatr Transplantation*. 2018;e13299. https://doi.org/10.1111/petr.13299