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. 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. 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.

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.
inclusion 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. 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 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.

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 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 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 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 extravascular 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). 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>
<thead>
<tr>
<th>Cause of ESRD</th>
<th>Hydronephrosis (n = 5)</th>
<th>Recurrent UTI (n = 9)</th>
<th>Abnormal renal biopsy (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal recessive polycystic kidney disease (n = 2), Denys-Drash, hemolytic uremic syndrome, posterior urethral valves (each n = 1)</td>
<td>Glomerulonephritis, nephronophthisis, nephrotic syndrome, bilateral Wilms tumor, unknown (each n = 1), bilateral renal dysplasia, bilateral VUR (each n = 2)</td>
<td>Bilateral VUR (n = 2), methylmalonic acidemia (combined liver-kidney transplant), multicystic dysplastic kidney with glomerulosclerosis (each n = 1)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade of VUR</th>
<th>Hydronephrosis (n = 5)</th>
<th>Recurrent UTI (n = 9)</th>
<th>Abnormal renal biopsy (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 (n = 1), Grade 2 (n = 3), Grade 1 (n = 1)</td>
<td>Grade 4 (n = 1), Grade 3 (n = 8)</td>
<td>Grade 4 (n = 1), Grade 3 (n = 2), Grade 2 (n = 1)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of anuria</th>
<th>Hydronephrosis (n = 5)</th>
<th>Recurrent UTI (n = 9)</th>
<th>Abnormal renal biopsy (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mo-3 y, only patient with HUS maintained urine production</td>
<td>2 mo: glomerulonephritis, 2 y: bilateral Wilms tumor</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
WU et al.

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/1.73m²) 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 nephronphthisis and nephrotic syndrome underwent urodynamics after transplantation to evaluate

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

**TABLE 2** Treatment outcome by presenting symptom

<table>
<thead>
<tr>
<th></th>
<th>Hydronephrosis (n = 5)</th>
<th>Recurrent UTI (n = 9)</th>
<th>Abnormal renal biopsy (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Bladder training, antibiotic prophylaxis.</td>
<td>Bladder training, antibiotic prophylaxis (n = 1).</td>
<td>Bladder training, antibiotic prophylaxis (n = 3).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dx/HA injection (n = 8), followed by ureteral reimplantation (4/8).</td>
<td>Dx/HA injection followed by ureteral reimplantation (n = 1) for UTI.</td>
</tr>
<tr>
<td>VUR resolution</td>
<td>2 resolved 3 not assessed</td>
<td>2/8 Dx/HA 1/4 ureteral reimplantation 1 not assessed</td>
<td>1/1 ureteral reimplantation 3 not assessed</td>
</tr>
<tr>
<td>Complications</td>
<td>None</td>
<td>1/8 Dx/HA graft loss 3/8 Dx/HA obstruction</td>
<td>None</td>
</tr>
<tr>
<td>UTI resolution</td>
<td>None at baseline</td>
<td>2/9 (successful Dx/HA)</td>
<td>None at baseline</td>
</tr>
<tr>
<td>Cessation of antibiotics</td>
<td>3/5</td>
<td>2/9</td>
<td>3/4</td>
</tr>
</tbody>
</table>
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. 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 non-compliance 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 hydrourteronephrosis. 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 extravasal 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,2,7,12,13 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 al13 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, 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/HA29 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 vescostomy 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, 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, 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, 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.

AUTHORS’ CONTRIBUTION

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


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