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# A systematic review of outcomes of Deflux® treatment for vesicoureteral reflux following pediatric renal transplantation

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## Summary

### Introduction
Vesicoureteral reflux (VUR) after renal transplant in the pediatric population may be associated with an increased incidence of urinary tract infection (UTIs) leading to increased morbidity, including graft dysfunction and graft loss. The non-orthotopic location of the transplanted ureter, and lack of submucosal tunnel may pose challenges in correcting the VUR using endoscopic injection techniques. Herein we report the results of a systematic review evaluating the outcomes of endoscopic treatment of VUR using Deflux® in this population.

### Methods
Pubmed and Embase databases were searched from October 2001 to April 2019. Full-text English articles involving patients less than 18 years old at the time of transplant, with a diagnosis of VUR post-transplantation, who underwent Deflux® treatment were included. Figure 1 outlines our PRISMA-compliant search strategy.

### Results
We found 6 eligible studies describing Deflux® treatment outcomes in 67 pediatric patients with post-transplant VUR where voiding cystourethrogram (VCUG) confirmed the diagnosis and resolution of VUR. The mean success rate was 36.8%. Ureteral obstruction occurred in 7/67 cases (10.4%). In all these 7 cases of obstruction, ureteric stenting was the initial management, but was only successful in 1 patient. Open ureteroneocystostomy (UNC) was performed in 4/7 cases, while 2/7 were managed expectantly (unknown outcomes). Persistent VUR with UTI despite Deflux® were reported in 20 out of 67 cases. Of these, 7 were managed with prophylactic antibiotics, and 13 with UNC. Success rates were consistently low for UNC after failed Deflux® in comparison to redo UNC in transplant ureters without prior injection.

### Conclusion
Low success rates are seen following injection techniques for VUR after pediatric renal transplant. Although an appealing option, Deflux® may prove counterintuitive due to the high rate of obstruction and suboptimal results if open reimplantation is required. A multi-institutional prospective study with a larger population size may further elucidate these results.

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## Introduction

Renal transplantation is the current gold standard treatment for pediatric patients with end stage renal disease. Vesicoureteral reflux into the ureteral graft is a possible cause of complicated urinary tract infections in renal transplant patients. UTI's are the most common bacterial infection following renal transplantation [1]. Sepsis in the setting of immunosuppression and renal scarring can occur as a result of acute graft pyelonephritis, leading to significant morbidity [2]. Transplant VUR in the pediatric population has been reported as high as 58% and is associated with UTI, chronic renal insufficiency, and allograft loss [3]. Literature on reflux in the pediatric kidney transplant recipients suggests that there is a higher incidence of UTI and pyelonephritis with reflux, up to 84% [4]. Given the increased morbidity and potential graft loss, correction of the transplant VUR is beneficial to the patient and may prolong graft survival.

Operative techniques vary during renal transplantation. Many renal transplants are left with a freely refluxing vesicoureteral anastomosis, which may predispose to developing graft pyelonephritis [5]. Common anti-reflux techniques during ureteroneocystostomy (UNC) in transplant include the modified Lich-Gregoir technique, which involves extravesical ureteric tunneling, where the submucosal tunnel is created superior, and the Politano-Leadbetter transvesical reimplantation, wherein the ureter is passed through a more cranial part of the bladder, through a submucosal tunnel, and then suturing it to the original mucosal insertion site [6]. Prior studies had advocated for nonrefluxing UNC in all pediatric transplant patients due to the aforementioned increased incidence of pyelonephritis with transplant VUR [4]. Although many pediatric surgeons use an anti-reflux UNC, VUR remains a risk [7].

Both open redo UNC and endoscopic approaches have been utilized in the management for patients with transplant VUR [7]. In October 2001, the Food and Drug Administration approved dextranomer/hyaluronic acid (Deflux®) for endoscopic therapy, and was subsequently began to be used widely as a treatment option for VUR. The non-anatomic location of the transplant ureter and the abnormal bladder support of the tunnel make endoscopic correction with Deflux® polymer injection potentially more challenging.

We conducted a systematic review on outcomes of Deflux® treatment for VUR in post-renal transplant pediatric patients. We hypothesize that endoscopic treatment of post-transplant VUR with Deflux® in the pediatric population has lower success rates than when used for management of primary VUR.

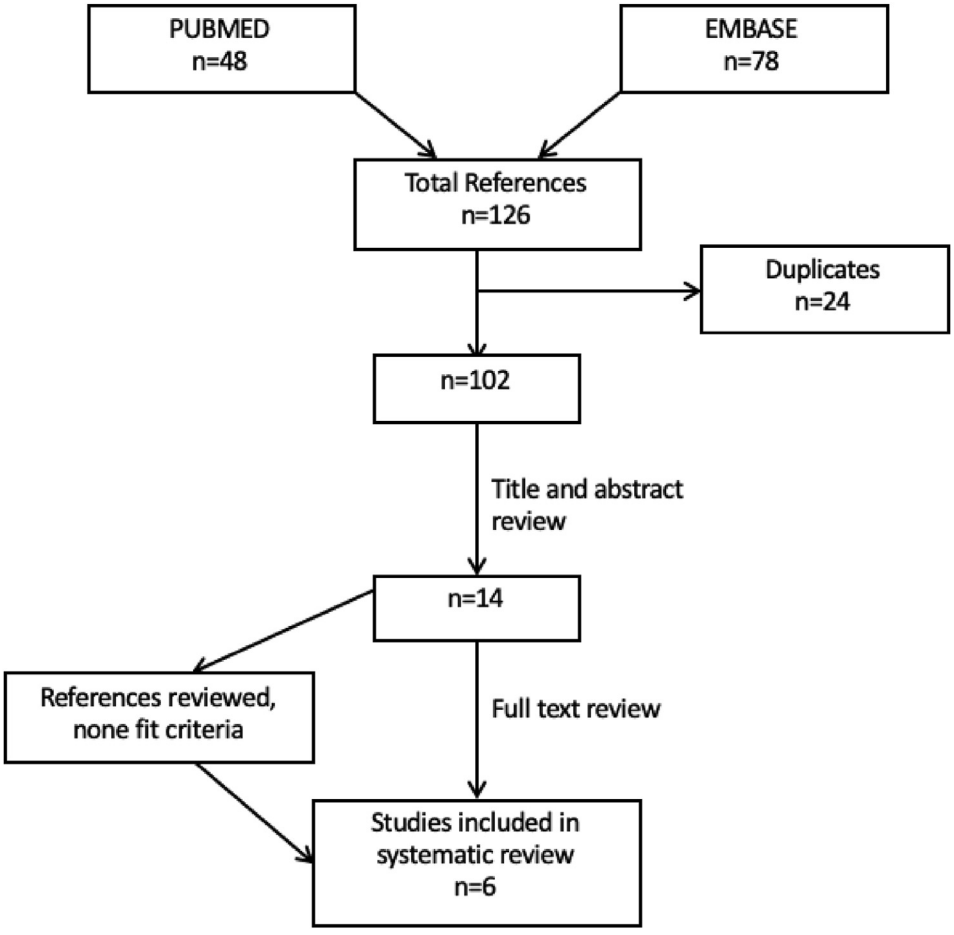


**Fig. 1** Search strategy.

**Table 1** Success and complication rates of Deflux® injections in refluxing transplanted ureters.

| Study | n | Age (years) | Cause of end-stage renal disease (ESRD) | UNC Technique | Amount injected (mL) | Deflux® Technique | Success Rate | Complication (% Obstruction) |
|---|---|---|---|---|---|---|---|---|
| Williams 2008 [24] | 8 | 11.6 (7—19) | NR | NR | 1—1.5 | NR | 43.5 | 0 |
| Vemulakonda 2010 [25] | 11 | 8 (3—16) | Upper tract 6/11<br>Lower tract 3/11<br>Both 1/11<br>Unknown 1/11 | Lich-Gregoir | 0.5—1.5 | 3.7 French needle is passed through the cystoscope and positioned within the submucosal plane of the transmural portion of the ureter. The Dx/HA is slowly injected | 54.5 | 0 |
| Castagnetti 2014 [26] | 11 | 8.3 (1.8—17.9) | Upper tract pathology 6/11<br>Lower tract pathology:<br>-Prune belly syndrome 3/11<br>-Posterior urethral valves 2/11 | Extravesical reimplantation | 0.6—2 | transplant ureteral orifice location required a dye test with i.v. injection of a vital dye in seven cases, but the orifice could be visualized and accessed using a standard pediatric cystoscope in all. Injection sites were selected according to the anatomy of each case | 63.6 | 0 |
| Cambareri 2017[a] [27] | 17 | 6—11 | Denys-Drash syndrome 1/4,<br>Bilateral multicystic dysplastic kidneys and solitary multicystic dysplastic kidney 2/4<br>unknown upper tract pathology 1/4 | NR | 1.6—3 | The injection technique was the same for all patients and included STING around the circumference of the ureteral orifice. | NR | 23.5 |
| Sheth 2018 [21] | 11 | 9.2 | Renal inflammatory process, Congenital nephrotic syndrome, | Lich-Gregoir, non-refluxing | NR | NR | 0 | 0 |

(*continued on next page*)

**Table 1** (*continued*)

| Study | n | Age (years) | Cause of end-stage renal disease (ESRD) | UNC Technique | Amount injected (mL) | Deflux® Technique | Success Rate | Complication (% Obstruction) |
|---|---|---|---|---|---|---|---|---|
| | | | Thrombotic cortical necrosis, Cystic disease, Renal dysplasia, Reflux nephropathy, Lower urinary tract, obstruction | | | | | |
| Wu 2018 [22] | 9 | 6.3 (1.5–16.3) | Glomerulonephritis, nephronophthisis, nephrotic syndrome, bilateral Wilms tumor, unknown (each n = 1), bilateral renal dysplasia, bilateral VUR (each n = 2) | Lich-Gregoir/ Politano Leadbetter | 1–6 | Injection at both the back wall of the ureter and circumferentially around the ureterovesical anastomosis, using the "Double HIT" technique | 22.2 | 33.3 |

[a] Only looked at complications, NR = not reported.

## Materials and methods

A systematic search of the English literature was performed on 1st June 2019 to identify peer-reviewed papers relating to a diagnosis of VUR post-renal transplantation, who subsequently underwent Deflux® treatment (Fig. 1). We acknowledged that the original PRISMA statement was published and disseminated in journals in 2009 [8].

An electronic search was performed using Pubmed, Scopus, and Embase databases. Boolean and MeSH search terms which included variations of "p(a)ediatric transplant" and/or "vesicoureteric reflux", and/or "Deflux", and/or "endoscopic". In addition to this, we employed the aid of a reference librarian with a masters in librarian studies to assist with all aspects of data collation including the Medline/Embase search. These were then cross-matched with the original search results. Exclusion criteria included patients >18 years old, editorials, surveys, letters to the editor, book chapters, and conference proceedings. Following identification, the records were screened by three (KR, FOK, FZ) independent reviewers based on title and abstract. Those that met inclusion criteria were screened again through a full-text review. Following full-text review, the final included records were identified. The data from included studies were summarized.

Interobserver reliability was assessed between 3 reviewers, using the kappa statistic with +1 indicating perfect agreement, and −1 indicating complete disagreement between each pair of reviewers (KR, FOK, FZ). Articles were only considered if they specifically dealt with management of vesicoureteric reflux post-renal transplantation. Any disputes were presented to a fourth author (MAK) for consensus resolution.

Univariate linear regression was performed for each variable. Inter-rater correlation was assessed by analysis of kappa scores. A p-value of $<0.05$ considered statistically significant, fragility indices were not calculated. Statistical analyses were performed on Prism statistical software (GraphPad v6.0; California).

## Results

Six eligible articles that fit our inclusion criteria were double reviewed and included in our analysis. These studies included 67 pediatric patients that had post-transplant VUR and were treated with Deflux®. Patient characteristics (age, cause of end-stage renal disease (ESRD) pre-transplantation, presence of non-refluxing transplant ureter), VUR resolution at the time of follow up, complication rate (ureteral obstruction), and rates of recurrent UTI with persistent VUR were collected. See Table 1. **Follow-up voiding cystourethrogram (VCUG) confirmed the diagnosis of VUR in all cases. Success rates, defined as VUR resolution at the time of follow up was also confirmed through VCUG in majority of the cases except in one study (Castagnetti 2014) where VUR resolution was defined as resolution of clinical symptoms and no further recurrent UTI's. In this study; however, VCUG was employed to confirm persistent VUR in those presenting with UTI symptoms.**

Five out of the six studies reported on the cause of ESRD pre-transplantation, and one study only reported the

causes but not the distribution of patients under each pathology. Upper tract and renal pathology are reported to be the cause of ESRD in at least 22 out of 67 patients. Three out of six studies reported the employment of nonrefluxing UNC technique, for a total of 31 patients; two studies did not report on their technique, and one mentioned the use of an "extravesical" approach without specifying if a nonrefluxing technique was employed.

Only one study did not report on the amount of Deflux ® injected. Volumes injected ranged from 0.5 up to 6 mL.

Subureteric injection approach or STING procedure was used in 28 patients in two studies, and the "Double HIT (Hydrodistension Implantation Technique" approach was used in 9 patients in one study. Two studies did not specify their injection techniques. One study used an intravenous dye test to determine the ureteric orifice in 7 out of 11 cases but did not specify their injection approach.

The degree of transplant VUR pre-Deflux ® was only mentioned in 4 out of the 6 studies, for a total of 21 patients (22 ureters). Grade 5 VUR was reported in 1 ureter, Grade 4 VUR in 8 ureters, and Grade 3 in 12 ureters, and Grade 2 in 1 ureter. Of these, only one of the Grade 4 and Grade 5 VUR ureters, 5 out of 12 Grade 3 VUR ureters, and zero Grade 2 ureter had complete VUR resolution.

Mean success rate, defined as VUR resolution at the time of follow up was 36.8% (0%—63.6%). Ureteral obstruction occurred in 7 out of 67 cases (10.4%), higher when compared to rates of primary, non-transplant reflux (0.6%—5.7%) [9,10]. Ureteric stenting was the initial management in all seven cases of obstruction but was only successful in 1 patient (14%). Open ureteral reimplantation was performed in 4 out of 7 cases (57%), while 2 out of 7 were managed expectantly (29%, unknown outcomes).

Persistent VUR with UTI despite Deflux® were reported in 20 cases. Of these, 7 were managed with instituting prophylactic antibiotics, 12 with open ureteroneocystostomy (UNC), and 1 unreported management.

## Discussion

Renal transplantation is commonly used for the treatment of ESRD in children. The younger recipients have higher incidence of UTI, which can result in recurrent graft pyelonephritis and ultimately graft loss [11]. UTI in renal transplant recipients is associated with several risk factors including VUR, female gender, immunosuppression, stents or other manipulation, and underlying urological abnormalities pretransplantation [12]. Given the significant consequences, management of UTI and VUR in this population is warranted.

Successful redo UNC has been reported in transplant patients with symptomatic VUR [7,11]. Factors such as prior abdominal surgeries, previous peritoneal dialysis, obesity, and other comorbidities may, however, make an open UNC a less desirable option. Endoscopic injection of Deflux® for non-transplant VUR has gained popularity over the recent years, with high success rates [13].

This systematic review demonstrates that reflux resolution in transplant ureters after endoscopic correction with Deflux® is consistently low. In comparison to the success rates of Deflux® in adult transplant VUR, the series included in this review had poorer results. **Five studies in the adult renal transplant population who underwent subureteric Deflux® injection had VUR resolution rates ranging from 53.8% to 100% [14—18]. In these adult studies, there appears to be higher success rates for lower grade VUR. Injection technique did not seem to significantly affect success rate [17]. One study reports 100% resolution of VUR in 4 patients, but after a second Deflux ® treatment in 2 of these patients** [16]. Similarly, in comparison to the resolution rates of up to 90% in primary VUR in pediatric cases that underwent endoscopic correction with Deflux® [19], the success rates in this series is much lower. There are technical differences in the endoscopic treatment of non-transplant, native VUR versus that of transplant VUR. We believe that scarring from the ureteral anastomosis site may make needle placement challenging, leading to poor Deflux® bulking effect. Identifying the transplant orifice may also be difficult and may necessitate additional procedures such as use of intravenous dye. **Additionally, the use of refluxing versus anti-refluxing anastomosis during the transplantation may influence the bulking effect of Deflux®. Deflux® injection into the submucosal tunnel in anti-refluxing UNC allows for an increased tissue bulk and better coaptation of the distal ureter**. Lastly, the location of the transplant ureter itself may make needle access and proper injection particularly challenging. In addition to the challenging anatomy, it was reported that inadequately treated bladder dysfunction can also influence success rates of endoscopic therapy [20].

Complication rates, which correspond to ureteral obstruction in this review, are also higher compared to those reported for non-transplant VUR [9,10]. **Although no definite conclusions can be made, we observe that reported ureteral obstruction occurred in patients with circumferential injection of the ureteric orifice with Deflux® instead of injection only into the back wall.**

This review also highlights that obstruction after Deflux® injection is not an insignificant complication, and that options for management vary. A particularly concerning finding from one of the studies is the lower success rates of open UNC as a salvage technique for post-Deflux® obstruction compared to redo reimplantation of transplant ureters which have not had any prior injection [21,22]. Two series (Wu 2018, Sheth 2018) reported consistently lower success rates for UNC after failed Deflux® (40—50%) [21,22] in comparison to redo reimplantation in transplant ureters without prior injection (70—80%) [7,23]. Wu et al. (2018) proposed that the loss of ureteral length from the fibrotic reaction of the ureter to Deflux® might be causing this poor outcome [7].

While there is value in our presented data, the present systematic review is not without its limitations, including the small number of studies included, with lack of data regarding Deflux® technique and/or amount injected in some. In addition, not all included studies commented on the grade of reflux pre- and post- Deflux® treatment. The goal of this review was to demonstrate the success rate of Deflux® treatment for VUR in post-renal transplant pediatric patients. We recommend that in order to improve the study power and standardization of post renal transplant complications reporting, it may be beneficial to create an inter-institutional transplant patient registry that would

allow access to multicentered individual patient data and could easily be coordinated by pediatric urology professional associations.

## Conclusions

There appears to be a trend towards lower VUR resolution rates and higher complication/obstruction rates with Deflux® treatment in post-transplant VUR in the pediatric population compared to Deflux® treatments in pediatric non-transplant VUR, and in adult post-transplant VUR. This review also suggests poorer performance of endoscopic treatment with Deflux® in this population in comparison to open UNC. We believe that the poor results following Deflux® treatment in this cohort is due to combination of altered ureteral tunnel anatomy, altered bladder pathophysiology, recipient immunosuppression. **Deflux® should still be considered; however, in select cases such as in low grade reflux with favourable orifice configuration.** No firm conclusions can be made however with such small numbers and the lack of information in some of the studies included. A multi-institutional prospective study with a larger population size (study power) may further elucidate these results.

## Sources of funding

Nil.

## Ethical approval

None required.

## Conflicts of interest

Nil.

## References

[1] Kamath NS, John GT, Neelakantan N, Kirubakaran MG, Jacob CK. Acute graft pyelonephritis following renal transplantation. Transpl Infect Dis 2006;8:140—7.
[2] Giral M, Pascuariello G, Karam G, Hourmant M, Cantarovich D, Dantal J, et al. Acute graft pyelonephritis and long-term kidney allograft outcome. Kidney Int 2002;61:1880—6.
[3] Ranchin B, Chapuis F, Dawhara M, Canterino I, Hadj-Aissa A, Said MH, et al. Vesicoureteral reflux after kidney transplantation in children. Nephrol Dial Transplant 2000;15:1852—8.
[4] Dunn S, Vinocur C, Hanevold C, Wagner C, Weintraub W. Pyelonephritis following pediatric renal transplant: increased incidence with vesicoureteral reflux. J Pediatr Surg 1987;22:1095—9.
[5] Salvatierra O. Management of vesicoureteral reflux in renal allografts transplanted into pediatric recipients. Pediatr Transplant 1999;3:171—4.
[6] Dewan PA. Ureteric reimplantation: a history of the development of surgical techniques. BJU Int 2000;85:1000—6.
[7] Krishnan A, Swana H, Mathias R, Baskin LS. Redo ureteroneocystostomy using an extravesical approach in pediatric renal transplant patients with reflux: a retrospective analysis and description of technique. J Urol 2006;176:1582—7.
[8] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
[9] Vandersteen DR, Routh JC, Kirsch AJ, Scherz HC, Ritchley ML, Shapiro E, et al. Postoperative ureteral obstruction after subureteral injection of dextranomer/hyaluronic acid copolymer. J Urol 2006;176:1593—5.
[10] Mazzone L, Gobet R, González R, Zweifel N, Weber DM. Ureteral obstruction following injection of dextranomer/hyaluronic acid copolymer: an infrequent but relevant complication. J Pediatr Urol 2012;8:514—9.
[11] Neuhaus TJ, Schwobel M, Schlumpf R, Offner G, Leumann E, Willi U. Pyelonephritis and vesicoureteral reflux after renal transplantation in young children. J Urol 1997;157:1400—3.
[12] John U, Kemper MJ. Urinary tract infections in children after renal transplantation. Pediatr Nephrol 2009;24(6):1129—36. https://doi.org/10.1007/s00467-007-0690-0.
[13] Capozza N, Caione P. Dextranomer/hyaluronic acid copolymer implantation for vesicoureteral reflux: a randomized comparison with antibiotic prophylaxis. J Pediatr 2002;140:230—4.
[14] Pichler R, Buttazzoni A, Rehder P, Bartsch G, Steiner H, Oswald J. Endoscopic application of dextranomer/hyaluronic acid copolymer in the treatment of vesico-ureteric reflux after renal transplantation. BJU Int 2011;107:1967—72.
[15] Romero NP, Romo MI, Vegas AG, Izquierdo JB, Varela JC, Arteche AH, et al. Deflux® injections for vesicoureteral reflux in transplanted kidneys. Transplant Proc 2010;42:2892—5.
[16] Seifert HH, Ruszat R, Muller A, Steiger J, Bachmann A, et al. Transurethral injection therapy with dextranomer/hyaluronic acid copolymer (Deflux®) for treatment of secondary vesicoureteral reflux after renal transplantation. J Endourol 2007;21:1357—60.
[17] Yucel S, Akin Y, Celik O, Erdogru T, Baykara M. Endoscopic vesicoureteral reflux correction in transplanted kidneys: does injection technique matter? J Endourol 2010;24:1661—4.
[18] Akiki A, Boissier R, Delaporte V, Maurin C, Gaillet S, Karsenty G, et al. Endoscopic treatment of symptomatic vesicoureteral reflux after renal transplantation. J Urol 2015;193:225—9.
[19] Kirsch AJ, Perez-Bayfield M, Smith EA, Scherz HC. The modified sting procedure to correct vesicoureteral reflux: improved results with submucosal implantation within the intramural ureter. J Urol 2004;171(6 Pt 1):2413—26.
[20] Traxel E, DeFoor W, Reddy P, Sheldon C, Minevich E. Risk factors for urinary tract infection after dextranomer/hyaluronic acid endoscopic injection. J Urol 2009:182.
[21] Sheth KR, White JT, Stanasel I, Janzen N, Mittal A, Koh CJ, et al. Comparing treatment modalities for transplant kidney vesicoureteral reflux in the pediatric population. J Pediatr Urol 2018;14:554.e1—6.
[22] Wu HY, Concepcion W, Grimm PC. When does vesicoureteral reflux in pediatric kidney transplant patients need treatment? Pediatr Transplant 2018;22(8).
[23] Barrero R, Fijo J, Fernandez-Hurtado M, García-Merino F, León E, Torrubia F. Vesicoureteral reflux after kidney transplantation in children. Pediatr Transplant 2007;11:498—503.
[24] Williams MA, Giel DW. Colleen Hastings M. Endoscopic Deflux injection for pediatric transplant reflux: a feasible alternative to open ureteral reimplant. J Pediatr Urol 2008;4:341—4.
[25] Vemulakonda VM, Koyle MA, Lendvay TS, Risk MC, Kirsch AJ, Cheng EY, et al. Endoscopic treatment of symptomatic refluxing renal transplant ureteroneocystostomies in children. Pediatr Transplant 2010;14:212—5.
[26] Castagnetti M, Angelini L, Ghirardo G, Zucchetta P, Gamba P, Zanon G, et al. Ureteral complications after renal transplant in children: timing of presentation, and their open and endoscopic management. Pediatr Transplant 2014;18:150—4.
[27] Cambareri G, Carpenter C, Stock J, Lewis J, Marietti S. Endoscopic antireflux surgery leading to obstruction in pediatric renal transplant patients. Pediatr Transplant 2017:21.