Title page

Factors influencing success in endoscopic treatment of Grade 4-5 primary vesicoureteric reflux (VUR) in infancy and childhood

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Keywords
Vesicoureteric reflux; vesicoureteral reflux; endoscopic treatment; endoscopic injection; subureteric injection; hydrodistension; dextranomer hyaluronic acid; deflux injection; renal scarring; urinary tract infection; VUR children

Structured Abstract

Introduction: There is equipoise among pediatric urologists regarding endoscopic versus surgical intervention for symptomatic Grade 4-5 Vesicoureteric Reflux (VUR), particularly in infancy. Our aim was to assess outcomes of first-line endoscopic treatment in all cases of symptomatic Grade 4-5 VUR **and we hypothesised that using endoscopic Dx/HA as first line management for primary VUR would obviate the need for ureteric reimplantation in the majority of cases.**
Methods: Retrospective single-surgeon analysis of consecutive patients with primary Grade 4-5 VUR over 15 years. Indication for intervention was breakthrough UTI on prophylaxis. Endoscopic dextranomer/ hyaluronic acid co-polymer (Dx/HA; Deflux®) injection was first-line procedure. Primary outcomes were both post-procedure febrile culture positive urinary tract infection (UTI) and VUR recurrence on post-operative VCUG requiring further surgical intervention**.** We **postulated that risk factors** influencing outcome are: age under 1 year, female gender, postnatal versus antenatal presentation, duplex anatomy, circumcision status and presence of congenital uptake defects on DMSA. Data analysed using Fisher's Exact Test/ Multivariate Analysis.
Results: 77 patients with Grade 4-5 VUR were identified, of whom 49 (11 bilateral) underwent a Dx/HA injection at median 12 (3-84) months. Median follow-up post-injection was 32 (2–145) months. There were no reported complications or ureteral obstruction. Sixteen (33%) patients suffered a febrile UTI at follow-up; on further investigation, half (8/16) of these were found to have recurrent VUR. Therefore 67% were symptom free and 84% did not require further intervention after one injection (41/49), and 98% after further injections (48/49). Duplex systems had a similar outcome of 80% not requiring further intervention. On multivariate analysis, males were found to have a significantly better outcome than females ($p<0.015$) irrespective of circumcision status. Forty-one percent of the children in our cohort had uptake defects on DMSA prior to intervention, but this did not have any difference on outcome.
Conclusion: Endoscopic Dx/HA injection is a safe first-line, day-case treatment for Grade 4-5 VUR in children of any age, with a low complication rate. Two-thirds of patients are asymptomatic after one injection; 84% do not require further procedures after one injection, and 98% after 2 injections.

Introduction

Vesicoureteric reflux (VUR) has a prevalence of 1–2%. The incidence is higher in babies with prenatally diagnosed urinary tract dilation (UTD) (up to 20%) and in those presenting with febrile urinary tract infection (UTI) (25%)[1,2]. Most children do not need treatment, but it is important to identify those at risk of renal injury, in particular patients suffering recurrent

febrile UTI's, which can increase the risk of renal scarring [3,4]. VUR is commonly associated with congenital renal dysplasia, and uptake defects on dimercapto-succinic acid (DMSA) renal scan may be an additional risk factor for breakthrough UTI's[5]. Where indicated, ureteric reimplantation has been the main surgical treatment in cases of Grade 4-5 VUR; however the number of open ureteric re-implantations has been declining since the turn of the century [6]. Despite evidence that endoscopic injection (albeit with two injections in some cases) can be as effective as ureteral re-implantation [7], there still exists reluctance to intervene endoscopically in severe VUR. However, faced with the choice and appropriate counselling, parents would normally prefer an endoscopic option and a day-case procedure.

Our aim was to assess our outcomes of endoscopic treatment in infants and children with primary Grade 4-5 VUR. Our primary outcome was recurrence of febrile culture positive urinary tract infections (UTI) and our secondary outcome was VUR recurrence requiring further surgical intervention. **We hypothesised that using endoscopic Dx/HA as first line management for primary VUR would obviate the need for ureteric reimplantation in the majority of cases.**

Materials & Methods

We carried out a retrospective analysis of consecutive patients with primary Grade 4-5 VUR, identified from a prospectively kept departmental database of all patients with VUR. The database was approved by our Trust audit & research committee (registration WLC3). This was a single surgeon experience spanning a 15 year period from 2008 to 2023. VUR was diagnosed either on voiding cystourethrogram (VCUG) or indirect MAG-3 cystogram depending on age and toileting status. On MAG-3, "high-grade" was defined as reflux up to the pelvicalyceal system associated with a dilated collecting system along with a dilated and tortuous ureter (= severe). We excluded patients with VUR secondary to bladder outlet obstruction or neuropathy as well as any patients with **established** bladder bowel dysfunction. **Bladder emptying was specifically checked for and reported on initial cystogram and at each follow-up on ultrasound scan**.

Our VUR cohort came from 2 main patient groups:

1. The antenatal asymptomatic group that were diagnosed following investigation of UTD identified on fetal ultrasound. Indication for VCUG was presence of a dilated ureter (defined as >4mm); bilateral hydronephrosis >10mm on the postnatal ultrasound scan; or a dilated duplex system +_ ureterocoele
2. The postnatal symptomatic group, diagnosed following febrile, culture-positive, UTI's

Indication for intervention was breakthrough UTI on prophylaxis or presentation with severe urosepsis in infancy. Endoscopic dextranomer/ hyaluronic acid co-polymer (Dx/HA;Deflux®) injection was our first-line procedure in all cases. Absolute contraindications to Dx/HA were a poorly functioning kidney/moiety of <10% on DMSA **(the premise is that polyuria secondary to poor function may precipitate obstruction, hence a nephroureterectomy is preferable in symptomatic patients)**; obstructing and refluxing megaureters (suspected with severe upper tract dilatation on USS with beaking and poor post-void drainage on VCUG) or ectopic ureters. Relative contraindications were a close proximity to a large ureterocoele or para-ureteric diverticulum. **Patients with duplex systems did not undergo**

any prior surgery for associated ureterocoeles. One patient had an upper pole heminephrectomy prior to Dx/HA treatment to the lower pole ureter.

Injection techniques were sub-ureteric injection (STING)[8,9] (as demonstrated in Figure 1) and/or hydrodistension implantation technique (HIT) (as demonstrated in Figure 2), determined by an assessment of the pre-injection ureteric orifice using the hydrodistension score (HD)[10,11]. Dx/HA was administered until good coaption was achieved (aiming for HD 0 or 1).

All procedures were planned as day-cases, and patients were discharged on prophylaxis until the first follow-up ultrasound scan 4-6 weeks post-operatively. Prophylaxis was then stopped, and patients followed up with ultrasound only, every 6 months for at least 2 years. Patients with pre-intervention uptake defects on DMSA were offered long-term follow-up by a paediatric nephrologist. A post-procedure cystogram was only obtained if the patient suffered a febrile culture-positive UTI after cessation of prophylaxis, in order to look for recurrent or persistent VUR.

We gathered data from the patient notes on demographics, disease characteristics and treatment outcomes. We defined symptomatic success as being free of febrile UTI post-procedure and overall treatment success as no requirement for further surgical intervention. We hypothesised that factors influencing outcome might be: age under 1 year at procedure, female sex, postnatal versus antenatal presentation, duplex anatomy, circumcision status and presence of congenital uptake defects on DMSA. Data were analysed using Fisher's Exact Test with a significance level of $p<0.05$. Given that many factors may be coincidental in the same infant, we performed a Multivariable Logistic Regression Analysis for both outcomes of treatment success using pre-defined variables of: Sex, Antenatal Diagnosis, Duplex System, Presence/Absence of Scarring on DMSA, and Timing of intervention (before or after 1 year of age).

Results

Patients Demographics and Procedural Details

There were 77 patients (44 male, 57%) with primary high-grade VUR. **72 patients (94%) were diagnosed with G4-5 VUR on VCUG. 5 patients were diagnosed on MAG 3 cystogram with high grade VUR as well as a dilated collecting system and dilated tortuous ureter.** 16 patients (21%) had bilateral G4-5 VUR. There were a total of 93 G4-5 refluxing units.

Twenty-four (31%) patients had successful conservative management without break-through UTI's. Of this group, the majority (17 patients (71%)) were male and VUR was bilateral in 4 patients (17%).

Fifty-three (69%) patients required an anti-reflux procedure. Of these, 2 patients underwent ureteric reimplantation, 1 had a nephrectomy and 1 a hemi-nephrectomy for non-functioning kidneys or moieties. The remaining 49 patients (24 males) underwent a Dx/HA injection; of

these, 11 (22%) had bilateral G4-5 VUR therefore 60 refluxing units underwent Dx/HA injections. A median of 1ml Dx/HA was injected per ureter (range 0.1 – 2mls/ureter).

Outcomes and follow-up

Median age at first intervention was 12 (3-94) months. Median follow up was 32 (2–145) months. There were no complications or 30 day re-admissions. No obstruction was noted on the first post-operative ultrasound at 4-6 weeks, nor on later follow up scans. Of the 49 patients who underwent an endoscopic procedure, 16 (33%) went on to have a post-procedure febrile, culture positive UTI at a median time of 9 (3-60) months post-op, giving a 67% symptom-free success rate.

On further investigation, only half (8/16) of these patients were found to have recurrent VUR requiring further intervention. One boy with bilateral duplex systems and ureterocele proceeded to a lower moiety ureteric reimplantation (having had a previous upper moiety heminephrectomy). We did not encounter technical difficulty performing the re-implantation following an endoscopic injection. Four patients had unilateral G4-5 VUR which persisted/recurred post first Dx/HA injection. There were 2 patients with bilateral G4-5 VUR which persisted post-endoscopic treatment, one of these was in bilateral duplex systems. One patient with unilateral VUR initially went on to have both recurrent and contralateral VUR.

Six patients underwent a successful 2nd Dx/HA injection, and 1 patient (with bilateral duplex systems) required a 3rd intervention. Therefore, 84% of patients (41/49) did not require further intervention after a single endoscopic procedure, and 98% (48/49) after further injections.

Ten (20% of the injection cohort) patients had VUR into a duplex system. Of these, 4 suffered a post-procedure febrile UTI, but only 2 patients were then found to have recurrent VUR (20% of duplex group), needing further surgery. Therefore 80% of patients with VUR in a duplex system did not require further intervention. Of note, only 2 patients had a ureterocoele and both required further surgery.

Factors influencing outcomes

Males had significantly better outcomes than females with 96% vs 72% ($p<0.05$) requiring no further intervention. We routinely offer circumcision at time of Dx/HA injection. Of our cohort, 19/24 (79%) males were circumcised, 18 at the time of their Dx/HA procedure. 5 parents declined circumcision for their son, and of these, two had a post-procedure UTI. Incidence of UTI was no different between the circumcised and uncircumcised males, but may be due to small numbers. 41% of the children in our cohort had uptake defects on DMSA prior to intervention, but this did not have any difference on outcome ($p>0.7$ for both UTI and requirement for re-intervention).

Table 1A & 1B summarise the success rates of endoscopic injection for the prevention of future UTI (analysed per patient, n=49) and the overall treatment success (not requiring a further procedure; analysed per ureter, n =60). On univariate analysis, for either outcome,

the only variable associated with a favourable outcome was male sex (p<0.01 for both). Antenatal presentation, duplex anatomy, DMSA cortical defects or the age at intervention did not have an association. As per intention, multivariable analysis was performed (Figure 3 or Table 2). Male sex was significantly less likely to require a second intervention (15.8 [1.71-145]; p=0.015), although association with post-procedure UTI was not significant (7.55 [0.70-81.5]; p=0.096).

Discussion

Within the limitation of patient numbers and limited follow-up, our study **revealed** that endoscopic Dx/HA injection is a safe, day-case procedure even in infants under one year. Our results suggest that **in our experience,** parents can be counselled that there is a 67% chance that patients will be symptom-free after one procedure, and that we would only need to repeat a cystogram in the event of a post-operative febrile UTI. In those cases, only half the patients would have a VUR recurrence meriting a second endoscopic injection or re-implantation surgery. Therefore 84% of patients will not require a second procedure, whereas 98% will be symptom-free after two injections. Sub-analysis showed that 80% of patients with duplex system VUR do not require further procedures. Although we would also consent for the risks of bleeding and obstruction, we have not experienced those complications to date. The procedure can be safely performed as a day-case, including in infants. Boys appear to have a better success rate, irrespective of circumcision status, whereas age, mode of presentation and presence of cortical defects do not seem to influence outcome. On further analyses, it appears that males are more likely to have a successful outcome after just one procedure.

The majority of our patients were diagnosed on VCUG. We elected to also include the 5 patients diagnosed on MAG3 cystogram as these were all patients that had recurrent febrile urinary tract infections from infancy and had not been investigated at the time. It is most likely that they had primary VUR that was missed. Once a child is 1 year of age it is not usual practice in the UK to perform an MCUG. The majority of these children (4/5, 80%) did not have a further UTI following their Dx/HA treatment with a good follow up time of 2.3 years (median, range 1.4-4.2yrs) which also points against any pre-operative undiagnosed BBD being a factor. The one girl diagnosed on MAG3 who did develop a UTI (at just 4 months following her Dx/HA treatment) had a repeat MAG3 which showed resolution of her previous unilateral VUR and no reflux on the contralateral side. All 5 patients diagnosed with VUR on MAG 3 cystogram were noted to have VUR into a dilated system.

Although we accept our limitation of patient numbers and extent of follow-up, our results compare with a much larger single-centre study reporting radiological and symptom-free success rates of 87% after one injection and 98% after a second injection[12]. In this study, univariate and multivariate analyses revealed that younger age, Grade 4-5 VUR and DMSA uptake defects, were significant variables for the failure of endoscopic treatment after the first injection. Although our numbers are much smaller, our study did not show any difference in outcome in these patient groups[12]. Our duplex system outcomes are even more positive than those reported by Hunziker et al in a larger study of 123 patients[13]. The study reported overall VUR resolution after the first endoscopic injection in 68% (93 of 136

ureters). Sub-analysis revealed success rates of 67% in Grade 4 and 45% in Grade 5 VUR, on repeat cystogram at 3 months[13]. Our experience revealed that although a ureterocoele is not an absolute contra-indication to endoscopic treatment, success rates are lower in those cases.

A further limitation of our study is that we do not routinely repeat a VCUG post-procedure, and we therefore do not know our actual VUR resolution rates. The reasons for this are multiple. Firstly, VCUG is an invasive investigation with a significant radiation burden. Secondly, we would not intervene on asymptomatic residual VUR, hence we would only repeat the study following a post-operative febrile UTI. Lastly, usual practice in the UK is to avoid VCUG in children over one year due to the anxiety caused by catheterisation. Kaye et al. questioned the definition of "success" based on clinical and radiographic results of endoscopic injection[14]. Although post-operative cystograms were routinely requested, further management was dictated by the patient's symptoms – with UTI's also manifesting after "radiographic success". Based on a 94% overall clinical success rate, the authors recommended cessation of routine VCUG following endoscopic treatment, instead reserving this test for instances of recurrent pyelonephritis or other clinical indications[14]

Within our follow-up of 2-84 months, we have not come across ureteral obstruction secondary to endoscopic injection, although we are aware that obstruction could occur further down the line. It is possible that endoscopic treatment is avoided in infants due to the fear of ureteral obstruction. Friedmacher and Puri reviewed the literature for clues on risk factors for iatrogenic obstruction. The authors suggested that the variance in the rate of obstruction (on average, less than 1%) in these studies is most likely related to the number of associated anatomical variants (e.g. refluxing megaureter with distal aperistaltic segment) or functional risk factors (e.g. bladder and bowel dysfunction or neurogenic bladder) rather than the type or volume of implant injected[15]. Careful patient selection and attention pre-operative imaging are therefore key in avoiding obstructive complications.

Our study supports previous publications reporting that the procedure is safe in infants. Al Hindi et al. prospectively studied 30 infants who underwent Dx/HA injections for Grade 4-5 VUR; success rate was based on resolution of symptoms as well as VUR on repeat cystogram at 1 year follow-up[16]. Success rate after one injection was 90%; one procedure was complicated by obstruction but authors report managing this conservatively[16].

We noted that boys appear to have better outcomes after Dx/HA injection. Analysis of the effect of circumcision showed that the incidence of UTI was no different between the circumcised and uncircumcised males but this may be due to small numbers. Although circumcision is frequently offered in boys with VUR, the influence of circumcision on UTI risk is variable between studies[17,18,19,20,21]. The caveat is that a retractable foreskin has also been shown to reduce UTI risk[22,23]. It is difficult to reconcile why some studies show a benefit of circumcision whereas others do not – this may be because the retractability in the non-circumcised group is often not documented[24].

We are aware of the association between bladder bowel dysfunction (BBD) and high grade VUR. A long-term follow-up study by Hunziker et al.[25] looking at the incidence of febrile UTIs in 1,271 consecutive children after successful endoscopic

correction of intermediate and high-grade VUR revealed that female sex, history of preoperative BBD and BBD after endoscopic correction were the most important independent risk factors for a febrile UTI after successful endoscopic correction of VUR. We were careful to exclude children with BBD from the initial cohort as this is a study focused on primary VUR. We continued to carefully assess for any development of BBD and specifically looked at bladder capacity and post void residuals on ultrasound. Out of the 16 patients who had a post Dx/HA febrile UTI, 3/16 (19%) developed BBD. Our findings concur with the Swedish reflux trial in children which showed a 20% association between HG VUR and BBD [26]. There was no evidence of BBD pre-operatively in these patients and there was a significant time lag between Dx/HA treatment and symptoms of BBD occurring (3-5yrs). Out of the 3 patients who did develop BBD we were able to address this successfully and avoid further surgical intervention in 2 of the patients. The 3rd patient who developed BBD initially had unilateral G4 VUR diagnosed on MCUG after an antenatal presentation. Over 3 years post Dx/HA she had a febrile UTI, and repeat imaging showed bilateral HG VUR. Around this time she had also developed bladder and bowel symptoms with poor drinking and constipation. After discussion her parents were very keen for a dual approach to avoid further UTIs and so she had repeat endoscopic Dx/HA whilst concurrently addressing the bladder and bowel dysfunction. She has remained asymptomatic with 4 years of follow up post repeat Dx/HA.

We had a 33% rate of febrile UTI post Dx/HA (16/49) but after careful assessment 50% (8/16 patients) did not require further surgical intervention. 2/8 had BBD which was treated successfully with solely conservative measures. 1 patient had an E. Coli UTI associated with a severe diarrhoea episode. This was an isolated event occurring 2 years after Dx/HA treatment. With such a clear precipitator she was not re-imaged and has remained asymptomatic since. 1 patient returned to theatre for management of her ureterocele which was not performed at the first sitting. She had no further UTIs following this. 1 boy had a UTI 10 months post Dx/HA but parents had declined a circumcision at initial sitting. He had no recurrent VUR on imaging and has now had a circumcision performed. The final 3 patients had no clear cause of the UTI but repeat imaging with MAG3 showed no evidence of VUR recurrence and therefore further surgery was not indicated. BBD was carefully excluded for each using clinical history, examination and investigations.

It is occasionally necessary to perform a ureteric reimplantation following one or two endoscopic injections. Previous studies have shown that prior Dx/HA injection does not make a subsequent ureteric reimplantation more difficult[27,28]. In our experience, given the choice, parents are happy to opt for the less invasive procedure as long as success rates are reasonable, and that it does not preclude reimplantation surgery if required. Lee et al. compared the outcomes of 17 patients who underwent a ureteric reimplantation, having had a previous endoscopic injection, with those of 64 patients following a primary reimplant [27]. There was no significant difference between each group in sex, mean operative time, postoperative transfusion, complication rate, and success rate. A telephone survey of the reimplanted group suggested that responders preferred endoscopic treatment as primary treatment of VUR because it was a simple method and no hospitalization[27].

Conclusion

Within the **limitation of numbers and limited follow-up, our experience suggests** that endoscopic Dx/HA injection **can be** a safe first-line treatment for Grade 4- 5 VUR in children of any age, provided pre-operative imaging has excluded the presence of a refluxing obstructive megaureter or a non/ poorly-functioning kidney or moiety. The procedure can be performed as a day case and carries success rates of 84% after one injection, and 98% after 2 injections.

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Figure 1. A: Hydrodistension grade 2 orifice. B: STING (subureteral) procedure. C: Dx/HA mound

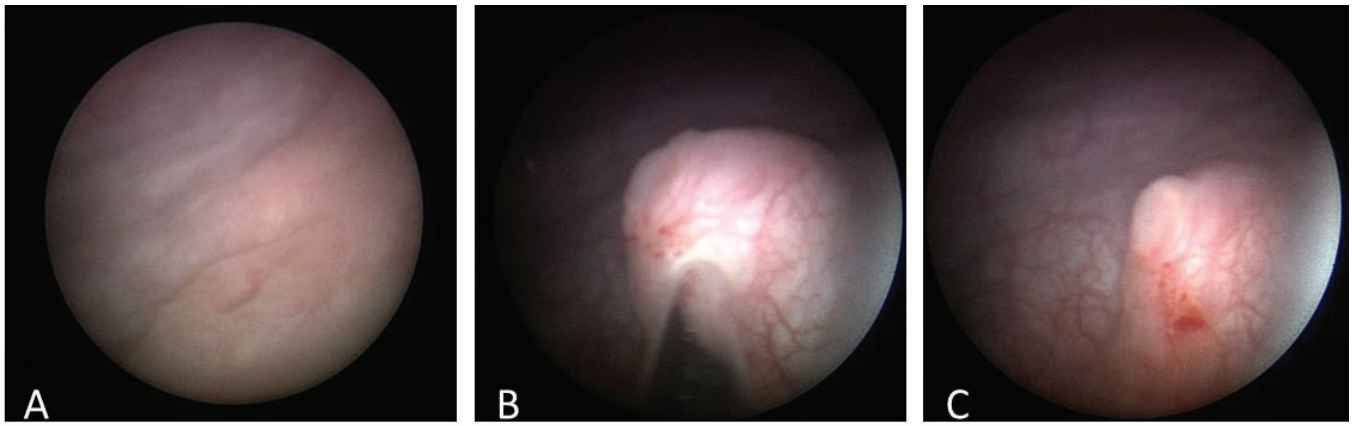

Figure 2. A: Hydrodistension grade 3 orifice. B: first HIT procedure. C: second HIT to reduce hydrodistension grade to 0-1 (double HIT)

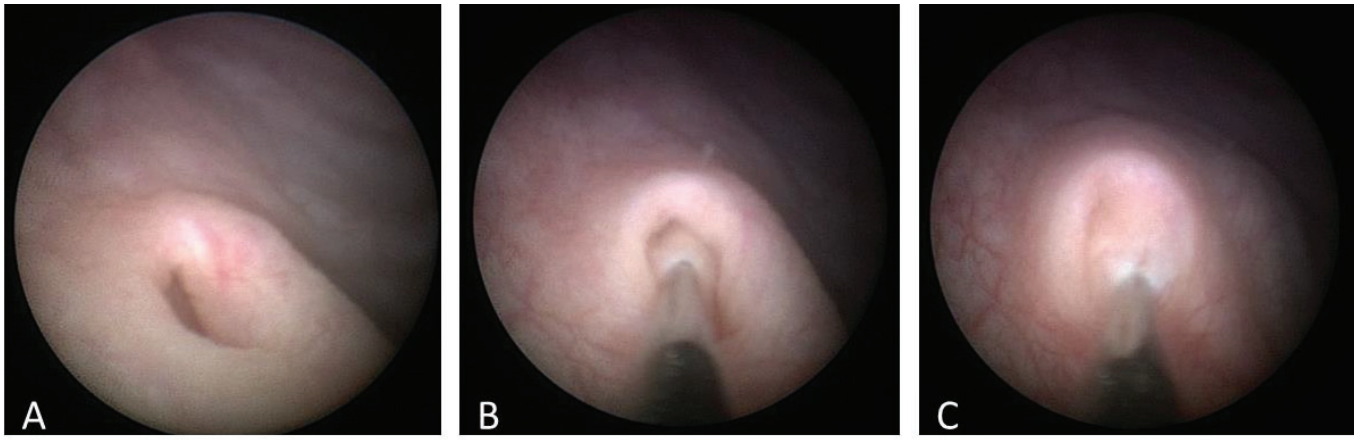

Figure 3 - Multivariable Logistic Regression Analysis for treatment success using all analysed variables. Variables presented with Odds Ratio with 95% Confidence Interval.

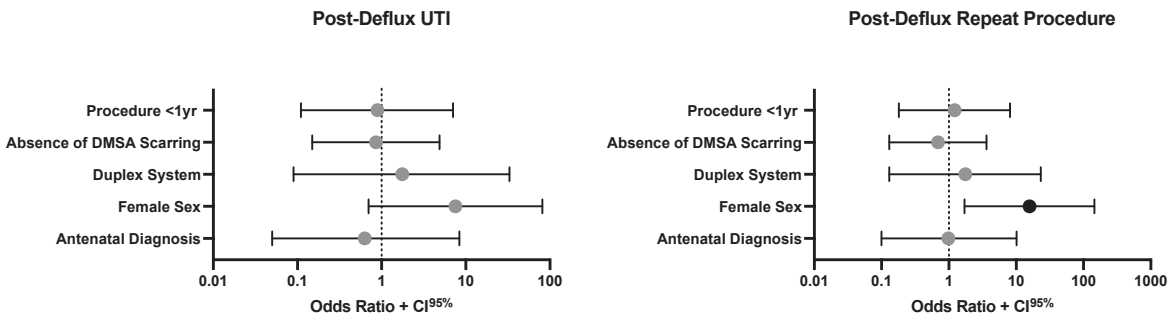

TABLE 1A: Comparison of Symptomatic Success Rates / UTI free post-procedure (Fisher's Exact Test)

	UTI-free post-procedure N (%)	
Overall VUR cohort, patients (n=49)	33 (67%)	
Timing of Presentation		
Antenatal (n=17)	12 (71%)	
Postnatal (n=32)	21 (66%)	p= 0.761
Duplex Anatomy		
Yes (n=10)	6 (60%)	
No (n=39)	27 (69%)	p= 0.709
Patient Sex		
Female (n=25)	12 (48%)	
Male (n=24)	21 (88%)	*p=0.005*
Circumcision Status (Male only)		
Circumcised (n=19)	18 (95%)	
No Circumcision (n=5)	3 (60%)	*p=0.100*
Age at Intervention		
<1 year of age (n=24)	17 (71%)	
>1 year of age (n=25)	16 (64%)	*p=0.762*
Absence of DMSA scarring		
Yes (n=29)	19 (66%)	
No (n=20)	14 (70%)	p= 0.769

TABLE 1B: Comparison of Overall Success Rate / no requirement for further surgery post-intervention (Fisher's Exact Test)

	No requirement for further surgery N (%)	
Overall VUR cohort, refluxing ureters (n=60)	51 (85%)	
Timing of Presentation		
Antenatal (n=20)	18 (90%)	
Postnatal (n=40)	33 (83%)	p= 0.704
Duplex Anatomy		
Yes (n=11)	9 (82%)	
No (n=49)	42 (86%)	p= 1.00
Absence of DMSA Scarring		
Yes (n=38)	32 (84%)	
No (n=22)	19 (86%)	p= 1.00
Patient Sex		
Female (n=28)	20 (71%)	
Male (n=32)	31 (97%)	*p= 0.009*
Circumcision Status (Male only)		
Circumcised (n=26)	26 (100%)	
No Circumcision (n=6)	5 (83%)	*p= 0.161*
Age at Intervention		
<1 year of age (n=24)	20 (83%)	
>1 year of age (n=36)	31 (86%)	*p= 1.00*

TABLE 2: Multivariable Logistic Regression Analysis for treatment success using all analysed variables.

	UTI-free post-procedure		**No requirement for further surgery**	
Variable	***OR [95% CI]***	***P-value***	***OR [95% CI]***	***P-value***
Antenatal Dx	0.63 [0.05-8.41]	0.723	0.98 [0.1-10.1]	0.989
Duplex system	1.76 [0.09-33.1]	0.705	1.76 [0.13-23.1]	0.668
Absence of DMSA-Scarring	0.86 [0.15-4.88]	0.865	0.69 [0.13-3.64]	0.658
Female Sex	7.55 [0.70-81.5]	0.096	15.8 [1.71-145]	0.015
Procedure <1yr	0.89 [0.11-7.06]	0.915	1.22 [0.18-8.07]	0.839