Journal of Pediatric Urology (2019) 15, 73.e1–73.e6

Surgical outcome of patients with vesicoureteral reflux from a single institution in reference to the ESPU guidelines: a retrospective analysis

B. Çitamak *, A.C. Bozaci, M. Altan, H.B. Haberal, O. Kahraman, T. Ceylan, H.S. Doğan, S. Tekgül

Department of Urology, Hacettepe University School of Medicine, Ankara, Turkey

* Corresponding author. B Floor Urology Department, Hacettepe University Hospital, Altındağ, Ankara, Turkey. Tel.: +903123051969; Fax: +903123112262.
burakcitamak@gmail.com (B. Çitamak)

Keywords
Vesicoureteral reflux; EAU/ESPU guidelines; Ureteroneocystostomy; Subureteric injection

Received 9 October 2017
Accepted 20 October 2018
Available online 27 October 2018

Extended Summary

Introduction
Vesicoureteral reflux (VUR) is an anatomic or functional disorder, and it is a condition associated with renal scarring, hypertension, and end-stage renal disease. Renal damage can be prevented by appropriate medical and surgical intervention for selected patients.

Objectives
The objective of this study was to retrospectively analyze the surgically treated patient group of this study in reference to the risk analysis criteria used in European Association of Urology (EAU), European Society for Paediatric Urology (ESPU) guidelines to see the outcome of the study management protocol within the last 15 years in respect to this risk analysis.

Study design
A total of 686 patients who were operated upon in a single institution for VUR between 1997 and 2016 were retrospectively analyzed. According to the criteria in EAU/ESPU guidelines, the patients were classified into three groups: low, medium, and high risk. Risk factors were compared between the groups.

Results
The patient numbers for low, medium, and high risk were 92 (13.4%), 485 (70.7%), and 109 (15.9%), respectively. In the high-risk group, surgeons tended to do more ureteroneocystostomy (UNC) (82.6%), whereas in the low-risk group, surgeons tended to do more subureteric injection (STING) (76.1%). The success rates for STING and UNC were found to be 75% and 93%, respectively. Although there was a difference in success rates among patients treated with STING or UNC, this difference was not statistically significant in success rates regarding risk groups for patients treated with STING or UNC.

Discussion
The most recent guideline was that which was published by the EAU/ESPU organization in 2012. This guideline is established based on the risk analysis. The analysis revealed that patients in the low-risk group tended to undergo endoscopic surgery treatment method, whereas patients in the high-risk group tended to undergo open surgery. Therefore, the study management over the last 10 years has been mainly in line with the current recommendations.

Conclusion
The analysis shows that when the patients are classified according to the EAU/ESPU risk classification, surgeons tended to perform more endoscopic and more open surgery for the low- and high-risk groups, respectively. Although each surgical modality had similar success rates in each group, open surgical results were overall much higher than those of endoscopic surgery in each group. This was a specifically important finding in high-risk group where the endoscopically treated group of patients was small in number, and the need for a definitive correction is essential in this group because of increased risk of renal injury.

Table Comparison of surgical procedures according to risk groups.

Parameters		Low risk	Medium risk	High risk	p
Operation	STING	70 (76.1%)	203 (41.9%)	19 (17.4%)	**<0.0001**
	UNC	22 (23.9%)	282 (58.1%)	90 (82.6%)	
All patients	Successful	71 (77.2%)	417 (86%)	97 (89%)	**0.045**
	Unsuccessful	21 (22.8%)	68 (14%)	12 (11%)	
STING	Successful	52 (74.3%)	153 (75.4%)	14 (73.7%)	0.975
	Unsuccessful	18 (25.7%)	50 (24.6%)	5 (26.3%)	
UNC	Successful	19 (86.4%)	264 (93.6%)	83 (92.2%)	0.426
	Unsuccessful	3 (13.6%)	18 (6.4%)	7 (7.8%)	

STING, subureteric injection; UNC, ureteroneocystostomy.
Bold values are statistically significant.

https://doi.org/10.1016/j.jpurol.2018.10.017

Introduction

Vesicoureteral reflux (VUR) is an anatomic or functional disorder, and it is a condition associated with renal scarring, hypertension, and end-stage renal disease. Patients with VUR may present with symptoms of recurrent febrile urinary tract infections (UTIs) and pyelonephritis. Renal damage can be prevented by appropriate medical and surgical intervention for selected patients. The aim of the present study is to retrospectively analyze the surgically treated patient group of this study in reference to the risk analysis criteria used in EAU/ESPU guidelines to see the outcome of the study management protocol within the last 15 years in respect to this risk analysis [1].

Patients and methods

A retrospective analysis of 686 patients who were operated upon in a single institution for VUR between 1997 and 2016 was carried out using the SPSS 17.0 software. The patients were identified and reviewed from the antireflux operation records database. Two surgeons (S.T. and H.S.D.) performed the surgeries or supervised them in similar proportions. According to the criteria in EAU/ESPU guidelines which are based on the gender, laterality, age at presentation, presenting symptoms, VUR grade, renal scar, and presence of voiding dysfunction, the patients were classified into three groups: low, medium, and high risk (Table 1). Low-risk group included all asymptomatic or symptomatic patients with normal kidneys with reflux and no lower urinary tract dysfunction (LUTD). High-risk group included symptomatic male or female patients after toilet training, with high-grade reflux (grade IV/V) and abnormal kidneys with/without LUTD. Patients outside these two groups were defined as medium risk. The grade of reflux with a grading system developed by the International Reflux Study Committee and based on most recent voiding cystourethrogram (VCUG) was determined because there was no cutoff time between VCUG and the surgery [2]. Reflux was classified as low (grade 1–2), moderate (grade 3), and high (grade 4–5). Lower urinary tract dysfunction was defined as the presence of lower urinary tract symptoms including urgency, urge incontinence, weak urinary stream, hesitancy, frequency, and UTIs in children older than 5 years. Behavioral modification and/or medical treatment were appropriately administered before any intervention. Behavioral modification includes awareness of bladder cycling and timely emptying to improve voiding habits, life style, and relaxation of pelvic floor muscles. Medical treatment includes anticholinergic medications and treatment of constipation.

The surgical indications included one febrile breakthrough infection (BTI) although this was often more than one due to long waiting lists. Renal scarring on a dimercaptosuccinic acid (DMSA) scan was not a sole indication for surgery, although patients with severe scars were considered for earlier correction.

Various ureteroneocystostomy (UNC) techniques (Cohen, Glenn–Anderson, Lich–Gregoir, and extravesical) and an endoscopic correction with a classical subureteric injection (STING) method were used. A dextranomer–hyaluronic acid copolymer agent was used as a bulking agent in all of the cases.

The patients were maintained on prophylaxis for 3 months after the intervention. After then, any patient presenting with recurrent symptoms or a febrile infection was regarded as a candidate for further evaluation with a VCUG. In a regular clinical practice, a VCUG was not regularly performed after open antireflux operations, considering the fact that they are highly successful. Performing a VCUG would be considered only if there are clinical symptoms and infection. No clinical symptoms or positive findings of a postoperative VCUG were regarded as a success. Multiple BTI, postoperative VCUG reflux, and UTI with fever were regarded as a failure.

Pre-operative DMSA scanning was used to detect renal scarring for all of the patients, but a postoperative DMSA scan was not routinely performed.

Gender, age, laterality of reflux, urinary BTI, renal scarring, the degree of VUR, and LUTD were compared between the groups.

The Mann–Whitney, Kruskal–Wallis, chi-squared, and *t*-tests were used where appropriate, and a logistic regression analysis was used for a multivariate analysis. A p value

Table 1 Distribution of patients according to risk groups and comparison with risk factors.

Parameters		Low risk	Medium risk	High risk	p
Gender	Male	28 (30.4%)	171 (35.3%)	37 (33.9%)	0.667
	Female	64 (69.6%)	314 (64.7%)	72 (66.1%)	
Postoperative UTI	(−)	76 (83.5%)	372 (78.8%)	79 (73.1%)	0.200
	(+)	15 (16.5%)	100 (21.2%)	29 (26.9%)	
Laterality	Unilateral	50 (54.3%)	208 (42.9%)	37 (33.9%)	**0.014**
	Bilateral	42 (45.7%)	277 (57.1%)	72 (66.1%)	
Grade	1–3	92 (100%)	277 (52.4%)	0 (0%)	**<0.0001**
	4–5	0 (0%)	252 (47.6%)	109 (100%)	
BTI	(+)	41 (48.8%)	179 (40.6%)	42 (40%)	0.351
	(−)	43 (51.2%)	262 (59.4%)	63 (60%)	
Scar	(+)	0 (0%)	313 (66.7%)	102 (100%)	**<0.0001**
	(−)	92 (100%)	156 (33.3%)	0 (%0)	
LUTD	(+)	0 (0%)	101 (38%)	17 (39.5%)	**<0.0001**
	(−)	52 (100%)	165 (62%)	26 (60.5%)	

BTI, breakthrough infection; LUTD, lower urinary tract dysfunction; UTI, urinary tract infection.
Bold values are statistically significant.

of <0.05 was considered to be statistically significant. This study was approved by the local ethical committee (GO-17/106).

Results

The mean age was 69.6 ± 44 months (3—204), and the male-to-female ratio was 250:436. Subureteric injection was performed in 42% of the patients, and a UNC was performed in 58% of the patients. The mean follow-up period was 26 ± 1.3 months.

The patient numbers in the low-, medium-, and high-risk groups were 92 (13.4%), 485 (70.7%), and 109 (15.9%), respectively. In the high-risk group, surgeons tended to perform UNC (82.6%), whereas in the low-risk group, surgeons tended to perform STING (76.1%). No statistically significant differences in the success rates were found regarding the risk groups for the patients treated with any intervention (Table 2). Although the overall success rate was slightly lower in the low-risk group than in the high-risk group (77.2% vs 89%), this was not statistically significant.

The overall success rate was found to be 85.3%. The success rates of STING and UNC were 75% and 93% ($p < 0.0001$), respectively. Open re-implantation (UNC) was more successful than STING in especially the moderate- and high-risk groups ($p < 0.001$ and $p = 0.02$, respectively).

The success rates of various UNC techniques were as follows: Lich—Gregoir, 100% (5); Glenn—Anderson, 100% (7); Cohen, 93.7% (365); extravesical, 94.2% (17) in different UNC subsets. The patients with a history of STING had a lower success rate for both consequent STING and UNC (63% vs 77%, $p = 0.025$; 87% vs 94%, $p = 0.024$, respectively) groups (Table 3). In the STING group, the success rate was 78.7% in children older than 54 months (determined by an receiver operating characteristic (ROC) curve) and 68.7% in children younger than 54 months ($p = 0.047$).

The LUTD and VUR grades did not affect the success rate of the surgery groups. The patients with LUTD had a higher percentage of low-grade VUR, and endoscopic treatment was preferable for these patients.

Postoperatively, the VUR grade and bilateral disease were found to be predictors for the presence of renal scarring. In a multivariate analysis, the VUR grade was found to be the most significant factor for the presence of renal scarring ($p < 0.0001$). The female gender was found to be the only factor for predicting pre-operative BTI ($p < 0.0001$) (Table 4). Patients with pre-operative BTI had a higher postoperative UTI rate (34.9% vs 12.6%, the chi-squared test, $p < 0.001$). The LUTD grade in the female patients was significantly higher than that in the male patients.

Table 3 Previous endoscopic treatment effects on following intervention.

Operation	Previous STING history	Success	Failure	p
STING	No	189 (77%)	54	**0.025**
	Yes	30 (63%)	18	
UNC	No	296 (94%)	18	**0.024**
	Yes	66 (87%)	10	

STING, subureteric injection; UNC, ureteroneocystostomy.
Bold values are statistically significant.

The VCUG was performed in 124 of 394 (31.4%) patients who had undergone UNC and in 221 of 292 (75.7%) patients who had undergone STING. There were 345 of 686 (66.5%) patients who had postoperative VCUG. Reflux was shown to be 9.7% (12/124) in the re-implantation group, and 71 of 221 (32.1%) patients had VUR in the STING group. Fifty-six (16%) patients had postprocedure UTI with a negative VCUG. Twelve of 28 patients who failed at UNC were diagnosed with VCUG, and 71 of 73 patients who failed at STING were diagnosed with VCUG. In STING group, two patients were described as unsuccessful with clinical symptoms and in UNC group, 17 patients were described as unsuccessful with clinical symptoms.

Discussion

VUR is a multifactorial disease and shows diversity in its presentation and prognosis; hence, a single type of approach is not appropriate for all patients. Therefore, in 1997 and 2010, the American Urological Association (AUA) guidelines were published to provide a systematic approach for both diagnosis and management [3]. The most recent guideline was that which was published by the EAU/ESPU organizations in 2012 [1]. This guideline is established based on the risk analysis. A total of nine groups were defined (2 high-, 5 moderate-, and 2 low-risk groups) depending on the mode of presentation, laterality, age at presentation, VUR grade, gender, anatomic abnormalities, the presence of renal scarring, and LUTD. Most of the study patients were operated on before the formation of this

Table 2 Comparison of surgical procedures according to risk groups.

Parameters		Low risk	Medium risk	High risk	p
Operation	STING	70 (76.1%)	203 (41.9%)	19 (17.4%)	**<0.0001**
	UNC	22 (23.9%)	282 (58.1%)	90 (82.6%)	
All patients	Successful	71 (77.2%)	417 (86%)	97 (89%)	**0.045**
	Unsuccessful	21 (22.8%)	68 (14%)	12 (11%)	
STING	Successful	52 (74.3%)	153 (75.4%)	14 (73.7%)	0.975
	Unsuccessful	18 (25.7%)	50 (24.6%)	5 (26.3%)	
UNC	Successful	19 (86.4%)	264 (93.6%)	83 (92.2%)	0.426
	Unsuccessful	3 (13.6%)	18 (6.4%)	7 (7.8%)	

STING, subureteric injection; UNC, ureteroneocystostomy.
Bold values are statistically significant.

Table 4 Comparison of BTI and scar with risk factors.

Parameters	Scar			BTI		
	Scar (−)	Scar (+)	p	BTI (−)	BTI (+)	p
Successful	204	361	0.064	320	221	0.355
Failure	45	53		48	41	
Postoperative UTI (+)	195	314	0.614	318	166	**<0.0001**
Postoperative UTI (−)	50	89		46	89	
Male	77	153	0.114	152	62 (29%)	**<0.0001**
Female	172	261		216	200 (48%)	
Grade 1−3	153	151 (49%)	**<0.0001**	163	129	0.233
Grade 4−5	95	258 (73%)		201	131	
BTI (−)	127	230	0.284	–	–	–
BTI (+)	100	151		–	–	
History of STING (−)	198	339	0.280	311	201(39%)	**0.035**
History of STING (+)	51	70		57	57 (50%)	
STING	137	138	**<0.0001**	159	110	0.760
UNC	112	276		209	152	
Low risk	92	0	**<0.0001**	43	41	0.351
Medium risk	156	313		262	179	
High risk	0	102		63	42	
LUTD (−)	93	147	0.255	124	92	0.113
LUTD (+)	51	62		54	58	
Unilateral	120	161 (57%)	**0.019**	150	117	0.329
Bilateral	129	253 (66%)		218	145	

BTI, breakthrough infection; LUTD, lower urinary tract dysfunction; STING, subureteric injection; UNC, ureteroneocystostomy; UTI, urinary tract infection.
Bold values are statistically significant.

guideline, yet this is a report of a large cohort of patients. A retrospective analysis was to be performed, and EAU/ESPU VUR guidelines were used as the reference to classify patients according to their risks. First of all, the operated patients mostly (70%) fall under the moderate-risk group. The analysis revealed that patients in the low-risk group were treated more by endoscopic surgery, whereas patients in the high-risk group were treated more by open surgery. When groups were specifically looked at, success rates were much better for all risk groups with open surgery, and this was statistically significant for moderate- and high-risk groups. For endoscopic treatment, the success rates were comparable in all risk groups and changed from 73.7% to 75.4%. For open surgery, success rates were also comparable in all risk groups that had success rated changed from 86.4% to 92.2%.

Open surgery, which has a higher success rate, has been the treatment of choice for the high-risk group in practice. The risk classification seems consistent with the daily practice, especially in the way treatment modality is selected. The guidelines also recommend a more aggressive follow-up and gives priority to interventional treatments for high-risk group. In particular, in the moderate-risk group also, high success rates can be achieved with open surgery. Therefore, management over the last 10 years has been mainly in line with the current recommendations.

The endoscopic STING technique is a minimally invasive modality and has become popular with its short learning curve, low complication rate, and considerable success rate [4]. Previous studies have reported a success rate of about 70% [4,5]. In a meta-analysis, the success rates of the second and third treatments were reported as 68% and 34%, respectively [4]. In the study institution, the overall patient-based STING success rate is around 75%. Although the success rates seem similar in all risk groups, it is important to see that the number of patients who had STING in the high-risk group was very small. It is not clear what made the surgeon choose endoscopic surgery for some patients in this group, but use of endoscopic surgery has not been the primary practice in this group. The finding that success rates are much higher with open surgery in this group also supports this approach.

Apparently UNC gives much higher success rate than STING in any group. Because STING was rarely used in the high-risk group, this statement is specifically true for the low- and medium-risk group. The main advantage that STING offers is minimal invasiveness. It is the surgeon's choice to outweigh the advantages versus lower success and consider if STING is a good alternative for medium- and low-risk groups. UNC would definitely be considered as the primary treatment option when the risk is high as also stated in the guidelines. By definition, this group has a higher risk of scar formation, and one should consider the most definite antireflux surgical modality.

Patients with a history of STING had a lower success rate for both consecutive STING and UNC (63% vs 77%; 87% vs 94%) operations. As mentioned earlier, the success rate of STING was reported to be decreasing with repetitive injections [4]. The study findings are consistent with these literature data. On the other hand, for open surgery, the success rate of UNC was shown to be not affected by previous STING [6−8]. However, it was detected that the success rate of UNC was lower in patients with a history of STING procedure than in those without the history.

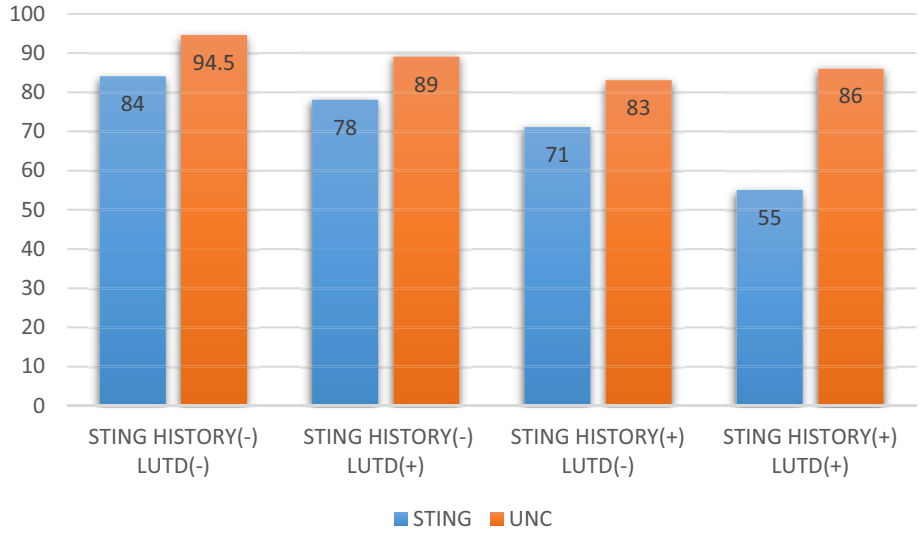

Fig. 1 Relation to success rates of 2 parameters (presence of previous STING history and lower urinary tract dysfunction [>5 years age]; in %) in STING and UNC procedures. STING, subureteric injection; UNC, ureteroneocystostomy.

Several analyses, including all of the aforementioned parameters (gender, age at diagnosis and operation, laterality and grade of reflux, mode of presentation, BTI, the presence of LUTD and renal scarring, and operation technique), have been carried out to discover the reason for this finding. The only two differences were the higher BTI rate (50% vs 39%) and the older patient age (79.1 $\pm$ 47.7 vs. 69.2 $\pm$ 47.2 months, the Mann—Whitney test, $p = 0.032$) in patients with the history of STING procedure, and this may simply be attributed to the time delay from the injection date to the decision date to perform UNC.

Another point is the effect of LUTD on the surgical outcomes. It would be expected that the surgical outcome may be related to the presence of LUTD, but this is mainly for the patients who have LUTD during surgery. There is a strict protocol to use LUTD therapy aggressively before surgery. Surgery is considered to be performed only if the reflux persists despite LUTD treatment; therefore, this is mainly the group who has already been treated for LUTD and is left with an anatomical deficiency which needs to be treated surgically. Behavioral modification and/or medical treatment were appropriately administered before any intervention. Thus, similar success rates were found among the groups. Although the effect is not significant in the UNC group, the success rate was decreasing dramatically in the STING group by the presence of both the history of STING and LUTD (Fig. 1).

Grade, scar, laterality, and LUTD are the main parameters in creating EUA risk classification. These parameters are separate from each other low- and high-risk groups. Gender distribution was similar between groups. From low-risk to high-risk patients, postoperative UTI increases and BTI decreases. However, postoperative UTI and BTI rates were not significant between EUA/ESPU risk groups.

This study has some limitations. In this study, only the patients who underwent surgical treatment were included, and the applicability and outcome of EAU guidelines could not be evaluated for the follow-up of patients without an intervention. Because most patients are referrals, the number of patients under observation is limited, and this is already a selected group. The retrospective nature of this study is another limitation as patients in different risk groups were not randomized to STING or UNC, and this fact carries the risk of an operator-dependent bias in the patient selection. Moreover, the results of patients could not be compared according to the severity or nature (congenital or acquired) of scintigraphic cortical abnormalities in the high-grade reflux group because it was not possible to distinguish these scars properly. When congenitally scarred kidneys could be diagnosed, it was made more from the surgical perspective as the congenitally scarred kidneys have lower resolution rates, and the anatomic deficiency is more severe [9]. All of these shortcomings may be corrected or minimized by multi-institutional prospective controlled studies in larger patient groups. Besides these limitations, the present study is important as it reflects 20 years of experience in a considerably large group that offers an opportunity to evaluate the guideline recommendations within the daily practice.

Conclusion

The results of the present study which reflect a 20-year experience showed that the daily practice on VUR is compatible with the guidelines and that the guidelines validate the management. The analysis shows that when the patients are classified according to the EAU/ESPU risk classification, the surgeons tended to perform more endoscopic and more open surgery for the low- and high-risk groups, respectively. Although each surgical modality had similar success rates in each group, open surgical results were overall much higher than the endoscopic surgery results in each group. This was a specifically important finding in the high-risk group where the endoscopically treated group of patients was small in number, and the need for a definitive correction is essential in this group because of increased risk of renal injury.

Author statements

Ethical approval

This study was approved by the local ethical committee (GO-17/106).

Funding

None declared.

Competing interests

None declared.

References

[1] Tekgül S, Riedmiller H, Hoebeke P, Kocvara R, Nijman RJ, Radmayr C, et al. EAU guidelines on vesicoureteral reflux in children. Eur Urol 2012;62:534—42.
[2] Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International Reflux Study in Children: international system of radiographic grading of vesicoureteric reflux. Pediatr Radiol 1985;15:105—9.
[3] Peters CA, Skoog SJ, Arant Jr BS, Copp HL, Elder JS, Hudson RG, et al. Summary of the AUA guideline on management of primary vesicoureteral reflux in children. J Urol 2010; 184:1134—44.
[4] Lackgren G, Stenberg A. Endoscopic treatment of vesicoureteral reflux: current practice and the need for multifactorial assessment. Ther Adv Urol 2009;1:131—41.
[5] Elder JS, Diaz M, Caldamone AA, Cendron M, Greenfield S, Hurwitz R, et al. Endoscopic therapy for vesicoureteral reflux: a meta-analysis, I: reflux resolution and urinary tract infection. J Urol 2006;175:716—22.
[6] Chertin B, Prosolovich K, Aharon S, Nativ O, Halachmi S. Surgical reimplantation for the correction of vesicoureteral reflux following failed endoscopic injection. Adv Urol 2011;352716: 1—5.
[7] Moreira-Pinto J, Osório A, Pereira J, Sousa C, de Castro JL, Réis A. Ureteroneocystostomy after failed dextranomer/hyaluronic acid copolymer injection for vesicoureteral reflux treatment. J Pediatr Urol 2013;9:665—9.
[8] Sencan A, Yıldırım H, Ozkan KU, Uçan B, Hoşgör M. Open ureteroneocystostomy after failed endoscopic injection with three different bulking agents for the treatment of vesicoureteral reflux. J Pediatr Surg 2014;49:1652—5.
[9] Godley ML, Desai D, Yeung CK, Dhillon HK, Duffy PG, Ransley PG. The relationship between early renal status, and the resolution of vesico-ureteric reflux and bladder function at 16 months. BJU Int 2001 Apr;87(6):457—62.