

*VESICICO-URETERAL REFLUX: ENDOSCOPIC TREATMENT,
MANAGEMENT AND LONG-TERM FOLLOW-UP.*

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Introduction. Vesicoureteral reflux (VUR) is a dynamic event in which there is a retrograde passage of urine from the bladder to the ureters. It is the most common urological disease in the childhood and it manifests with recurrent urinary tract infections (UTI). The therapeutic strategy provides an antibiotic prophylaxis, invasive surgery (Cohen reimplantation) and minimally invasive surgery (endoscopic subureteral injection). Recently, Endoscopic Subureteral Injection with Deflux became the treatment of choice. The purpose of this work was to conduce a retrospective study of our patients with VUR to evaluate the role of endoscopic technique (Deflux and Macroplastique) in the treatment.

Materials and Methods. Forty two patients with VUR were treated by us in 65 refluxing units. Twenty were males (47.6%) and 22 (52.4%) females. Sex, age of infiltration, presence of associated diseases, unilaterality and bilaterality, side of presentation of VUR and substance used for injection were considered. The follow-up study included urine cultures and periodic renal ultrasound. The micturitional cystourethrography was performed after 12 months. The results were statistically evaluated with the "Wilcoxon test", comparing data of patients treated with Deflux and Macroplastique.

Results. Refluxing ureters underwent endoscopic treatment by submeatal injection were 65, 4.6% with VUR grade I, 12.3% grade II, 43% grade III, 29.23% grade IV and 10.87% grade V. In 19 patients, amounting to 45.2%, this was a unilateral VUR (84.2% left, 15.78% right) and in 23 patients, equal to 54.76%, a bilateral VUR. Thirty eight per cent of these patients had associated diseases. At the first follow-up, the cure rate was 81.53%. At the second follow-up, the cure rate, including the 9 children re-infiltrated, was 89.23%. Four patients underwent a further infiltration, so as at the third follow-up, the overall cure rate was 93.84%. In only one patient with bilateral VUR grade IV, it was necessary to perform Cohen ureteral reimplantation due to the persistence of VUR after 2 endoscopic infiltration. In another one, due to the clinical severity and the persisting of VUR after two endoscopic infiltration, we decided to plan the bilateral reimplant according to Cohen. We have not been demonstrated significant differences based on gender, age of infiltration and the substance used, were not observed.

Conclusions. At the moment, our patients have a regular weight-height growth and they don't have urinary tract infection or vesicoureteral reflux. The sub-meatal infiltration is a simple, repeatable and reliable technique whereby results are immediate and safe in most cases. For this reason, we conclude that the submeatal infiltration represents the first-line treatment in patients with vesicoureteral reflux.

key words: Vesicoureteral reflux (VUR)

INTRODUCTION

Vesicoureteral reflux (VUR) is a dynamic event in which there is a retrograde passage of urine from the bladder to the ureters. It is the most common urological disease in childhood and it occurs with recurrent urinary tract infections (UTI).

Management of VUR in children is debated. Since 1970 many studies were elaborated about VUR (1). In particular techniques provide bladder opening and ureters mobilization.

Politano-Leadbetter and Cohen's strategies are most followed surgical techniques. They allowed to augment the length of intra-vesical ureter and to create a strong support by compression exercised by detrusor muscle.

Patients submitted to these invasive surgery had good

results but a longer stay in hospital and an higher rate of complications.

In 1984 O'Donnel and Puri first reported the systematic use of injection treatment for reflux in children. The original procedure consisted of endoscopic injection of polytetrafluoroethylene (PTFE) paste suspended in glycerine. Injection was made into the lamina propria just behind the ureteric opening and it was shown to be very effective in a number of clinical studies. Since then many substances were used for sub-ureteral injection like Teflon, bovine collagen, Macroplastique and Deflux .

In particular Deflux and Macroplastique have been used in several studies to correct vesico-ureteric reflux with excellent success rates, but again some concerns

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about the duration of the treatment success has been raised (2).

MATERIALS AND METHODS

A retrospective study was carried out to value the role of endoscopic treatment in patients with VUR.

Since 1° January 2002 to 31 may 2010 42 patients with VUR were treated corresponding to 65 ureters. Male were 20 (47,6%) and female 22 (52,4%).

These data were analyzed:

1. Demographic factors: ratio male/female (M/F), age at the moment of endoscopic injection;
2. Risk factors: associated pathology like duplex system, posterior urethral valves, renal ectopia in patient with malformative syndrome and reflux nephropathy;
3. Unilateral and bilateral VUR, side of VUR presentation (left or right) and grade;
4. mode of presentation and diagnosis of UTI with positive urine exam, urine culture, renal ultrasound and retrograde cystourethrography;
5. Surgical therapy: endoscopic injection with Deflux and Macroplastique; ureteral reimplantation according to Cohen if the previous treatment failed.
6. Complications: VUR relapse, wound dehiscence, hemorrhage and fistula;
7. Mean duration of endoscopic treatment and hospitalization of patients.

For the endoscopic injection the patient was placed in the dorsal lithotomy position and an accurate inspection of two ureters was performed by cystoscopy. Classical technique for STING injection was applied and after introduction of injection needle into subureteral space, infiltration was performed with Macroplastique or Deflux. We excluded all patients spontaneously healed or that were submitted to open surgery. Diagnostic exams showed ureteral dilatation, presence of renal scars and VUR grade on the basis of International Reflux Study classification (IRS) of 1981, before the treatment.

Urino-culture, renal ultrasound and retrograde cystourethrography were performed on annual follow-up. Data were expressed by standard deviation and range.

Wilcoxon signed test was used for statistical survey. We considered significant p values <0.05.

RESULTS

Patients with VUR were 42 corresponding to 65 refluent ureters. In 4.6% they showed VUR grade I°, in 12.3% grade II°, in 43 % grade III°, in 29.23% grade IV° and in 10.87% grade V (Tab. I).

Table I- VUR grade

VUR grade	n° ureters	% ureters
VUR I°	3	4.6%
VUR II°	8	12.3%
VUR III°	28	43%
VUR IV°	19	29.23%
VUR V°	7	10.87%

Mean age of injection was 5,3 years in male (range 9m-18y) and 5,8 years in female (range 1-18y). The ratio M:F was 1:1.

In 13 cases equal to 38%, there were associated diseases, as show in Table II.

Table II- Associated diseases in patients with VUR

ASSOCIATED DISEASES	PATIENTS	%
Double ureters	2	4,76%
Neurogenic bladder	4	9,52%
Myelomenigoncel	2	4,76%
Reflux nephropaty	5	11,9%
Plurimalformative syndrome	2 (1 with renal ectopia)	4,76%
Posterior Urethral valves	1	2,3%

Nineteen patients (45,2%) out of the 42 analyzed presented unilateral VUR: 16 to the left (84,2%) and 3

	UNILATERAL LEFT	UNILATERAL RIGHT	BILATERAL LEFT	BILATERAL RIGHT
I grade	0	0	0	3
II grade	2	0	2	4
III grade	9	2	12	5
IV grade	3	1	7	8
V grade	2	0	2	3
TOTAL	16	3	23	23

Table III- Ureteral distinction on the basis of grade in patients with unilateral and bilateral VUR

(15,78%) to the right.

Patients with bilateral VUR were 23 (54,76%) corresponding to 46 ureters. Table III shows VUR grades. All patients come to our observation because of UTI (100%). In fact they had urine exam and urine culture positive.

In all patients with VUR III, IV, V (81,5%) grade renal ultrasound showed an average pelvic dilatation of 19,6 mms. Retrograde cystourethrography revealed the grade of VUR. Thirteen patients (31%) were treated with Macroplastique since 2002 to 2005; 29 patients (69%) were treated with Deflux since 2006.

The total cure rates at the first follow-up, after urine exam, urine culture and retrograde cystourethrography at 12 months, was 81.53% corresponding to 33 patients. Figure 1 shows the comparison between successes and failures on the basis of VUR grade to the first follow-up.

Nine patients (21.5%) presented UTI and retrograde cystourethrography revealed the persistence of VUR. For this reason it was necessary a second injection. At the II follow-up after 12 months, the cure percentage was 89.23%. Five patients were recovered after the II injection. Two showed unilateral VUR (1 III left and 1 V left) and 3 bilateral (IV left and I right, the first recovered at the I follow-up; IV bilateral, one of which recovered at the I follow-up; V right and II left the second of which recovered at the I follow-up).

Figure 2 shows the comparison between successes and failures on the basis of VUR grade at the second follow-up.

In 4 patients (11,91%) was necessary to carry out a third injection. They presented bilateral VUR:

- 1 patient with grade V right and III left (VUR grade III was recovered at the I follow-up)
- 1 patient with bilateral grade III (one of which recovered at the I follow-up)
- 1 patient with left grade III and right grade I (VUR grade I recovered at the I follow-up)
- 1 patient with bilateral VUR with grade IV

In the first 3 patient a third injection was performed and this strategy was resolutive. In 4 patients with bilateral VUR with grade IV it was necessary to perform the bilateral ureteral reimplantation according to Cohen after failure of the third injection.

In one patient because of the gravity of VUR and for persisted symptoms, we decided to program Bilateral reimplantation according to Cohen.

At the III follow-up the cure percentage was 93.84%, equal to 40 patients.

Figure 3 shows the comparison between successes and failures on the basis of VUR grade the third follow-up. Mean duration of endoscopic treatment was 20 minutes.

The hospitalization of patient was 3 days.

Finally we applied Wilcoxon's test comparing results obtained with two substances (Deflux and Macroplastique).

This test did not reveal any difference between the substances used (P was inferior to 0,05).

DISCUSSION

Many Autors, in agreement to the International Literature, propose antibiotic prophylaxis (up to 1 year) in patient with VUR. This strategy represents the first therapeutic approach to allow the spontaneous resolution or the reduction of VUR grade. In fact in this period it's possible the development of the vesico-ureteral junction (GUV) (4, 5).

The purpose of antibiotic prophylaxis is to make urine sterile to avoid the onset of UTI and possible evolution in renal insufficiency (2, 3). This strategy presents some difficulties: therapeutic compliance, continue monitoring, possibility to develop bacterial resistances and finally reflux nephropaty (6). American Urological Association Education and Research in 2010 also confirmed the value of prophylaxis in the first year of life (7). In fact the meta-analysis of 21 studies recommended that:

- The continue antibiotic prophylaxis (CAP) is indicated in all children with VUR and symptoms.
- If there are not UTI the continue antibiotic prophylaxis (CAP) is also recommended in all children with high grade (III-V) VUR.
- If there are not UTI in children with VUR low grade (I-II), CAP may be given on the basis of preferences of doctor.
- Male children with VUR and UTI may be subjected to circumcision.

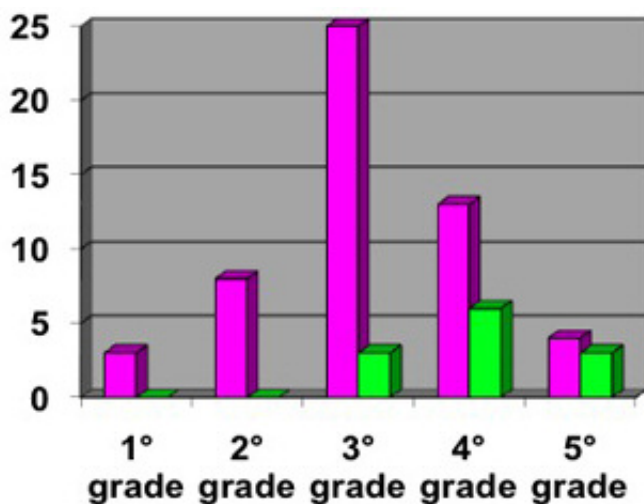
There are also 84 studies that analyzed children above one year of life.

CAP may be given to children with asymptomatic UTI, VUR and without bladder/gut disorders.

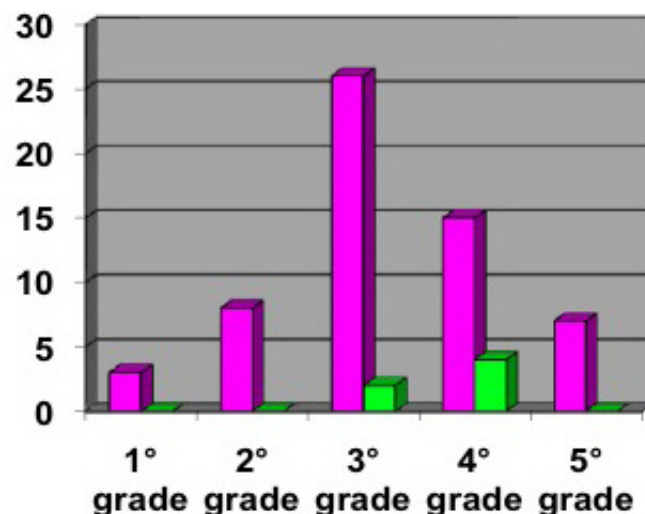
A recent article published on Seminars in Nephrology, showed the role of antibiotic prophylaxis in patients (age 0-24 months) with UTI and VUR. On urine culture the most frequent pathogens were Escherichia coli (54-67%), Klebsiella (6-17%), Proteus (5-12%), Enterococcus (3-9%) and Pseudomonas (2-6%). In patients with age below 3 months and with UTI the antibiotic prophylaxis is recommended. Patients older than 3 months were treated with cefixim or amoxicillin / clavulanic acid. In conclusion the Autors argue that the therapeutic management should include antibiotic prophylaxis in the first year of life (8).

American Urology Association recommends endoscopic injection in children with VUR (10). Recommendations for Endoscopic treatment in patients with VUR are:

1. Prevention of reflux nephropathy;
2. VUR grade III-V;
3. Age older than one year;
4. No controindications;



■ Successes
■ Failures



■ Successes
■ Failures

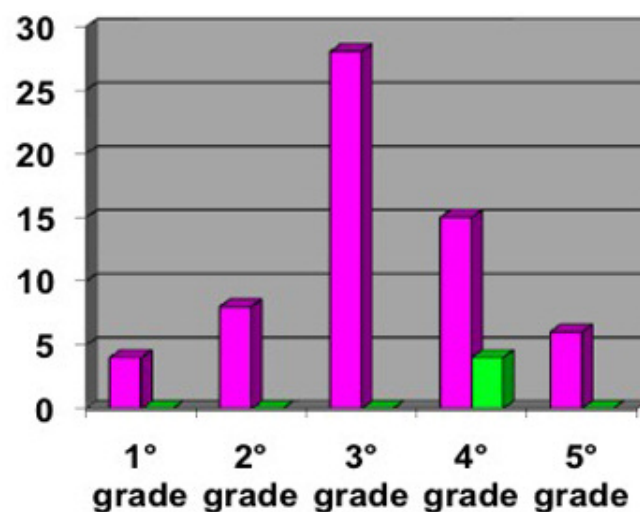
Figures (clockwise):

Figure 1(above):

The comparison between successes and failures on the basis of VUR grade to the first follow-up.

Figure 2:

The comparison between successes and failures on the basis of VUR grade to the second follow-up.



■ Successes
■ Failures

Figure 3:

The comparison between successes and failures on the basis of VUR grade to the second follow-up.

5. Poor compliance of parents who choose the endoscopic injection instead of prolonged antibiotic prophylaxis also for VUR low grade (9).

The substance actually utilized for endoscopic injection is Deflux, that was introduced in 2001. Before 2001 the silicone (Macroplastique) was utilized. The Macroplastique is constituted by solid particles of polimetilsilossano and no-iodized povidone gel; it is not toxic, biocompatible, no migrant, no antigenic. It causes a local flogistic reaction; moreover it is possibile to utilize a small quantity of the substance. Numerous studies demonstred that Macroplastique isn't effective for possibile migration in the bladder side.

Food and Drug Administration (FDA) in 2001 establish that Deflux is the only substance that can be used

for the treatment of VUR. Deflux is dextranomer/hyaluronic acid copolymer and it consists of microspheres in 1% hight-molecular-weight sodium hyaluronan solution. Each milliliter of Deflux contains 0.5 ml sodium hyaluronam and 0.5 ml dextranomer. The molecule is non-toxic and non-immunogenic, and its pseudoplastic properties facilitate the injection. No risk of implant migration and adverse reactions were reported. The repetition of the implant is possible and there were no problem if the expected results are not reached after the first endoscopic injection.

Its effectiveness has been demonstrated for over 7 years. In addition, endoscopic infiltration with Deflux is a minimally invasive procedure without long-term complications and does not require hospitalization. The endoscopic technique, as we can verify from the

literature and our experience, does not preclude the possibility to open surgery in cases of endoscopic treatment failure.

A "review" of the current International Literature shows that, despite the treatment options proposed by various authors, the sub-meatal endoscopic infiltration is now the treatment of "first -line. "

A single centre retrospective performed in Sweden, published in 2006 in the Journal of Pediatrics Urology Company, assessed the long-term follow-up of patients with III-V grade of VUR. Seventy two per cent of these patients received one infiltration, 20,1% and 3,9% two and three infiltrations. In conclusion, this study demonstrates that endoscopic infiltration offers significant advantages over antibiotic prophylaxis and ureteral reimplantation. Therefore the endoscopic treatment can be considered the treatment of choice in patients with VUR (10).

Another multicentric study performed in America with the participation of two centers, published in 2006 in Pediatric Urology Company, has reviewed the main option for treatment of VUR, with particular attention to the endoscopic technique. The conclusion of this review was that endoscopic infiltration is the first-line treatment of patients with VUR (11).

According to the International Literature since 2005 the treatment of choice is endoscopic injection of Deflux.

Our cure rate was 93.84%. Only one patient (bilateral VUR with grade IV) was submitted to ureteral reimplantation according to Cohen. We will program the ureteral reimplantation for VUR high grade for the other patient.

"Open surgery" must be the last choice. In fact complications like urinary disease, wound deiscence, hemorrhage and long hospitalization are more frequent with this technique.

The parents are satisfied too for this treatment.

CONCLUSION

In agreement with International Literature our results are good in patients with VUR treated by endoscopic injection. We may observe that our patients present a good growth, no UTI and no VUR. The results reveal that the sub-meatal infiltration is a simple, repeatable and reliable technique and the results are immediate and safe in most cases. It is a mini-invasive technique, and it is characterized by a short surgical time and reduced hospitalization. The results are immediate and safe in most cases. According with International Literature, since 2005, we utilized Deflux for all endoscopic injection. For this reason, we conclude that the sub-meatal infiltration represents the first-line treatment in patients with vesicoureteral reflux.

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