VESICOURETERIC REFLUX (VUR) IN CHILDREN: WHERE ARE WE NOW?

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Summary.- In 1960 Hodson and Edwards published their landmark paper about the association between chronic pyelonephritis and vesicoureteric reflux (VUR). Since then, the approach for VUR became more important (1).

In the last 30 years there have been multiple publications on vesicoureteric reflux (VUR) and discussions at Pediatric Urology meetings with the purpose to give answers to the questions what the best treatment is for VUR, at what age the treatment is advocated, does it prevent for febrile urinary tract infections (UTI's) and does it stop of decreases the risk for reflux nefropathy and renal scars.

Well known are the International Reflux Study (1981) with a European and an American arm in which the researchers compared medical approaches with surgical approaches to reflux, and the Birmingham Reflux study (1987) which was a prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children with five years observation (2).

In 2009 the group from John Hopkins (Baltimore, USA) published their interim results from a randomized placebo-controlled study of children with VUR (the RIVUR Study) (3). The most recent randomized controlled trial (RCT) is the Swedish Reflux Trial published in the Journal of Urology 2010, July. This was set up as a RCT to compare 3 treatment alternatives, including antibiotic prophylaxis, endoscopic therapy and surveillance as the control group, in regard to recurrent febrile UTIs, renal damage and VUR status after 2 years (4).

Since these new data are available, we want to give an update in this specific and interesting field in Pediatric Urology.

Keywords: Vesico-ureteric reflux. Pyelonephritis. Kidney. Urinary tract infection. Renal damage.

Resumen.- En 1960 Hodson y Edwards publicaron su memorable trabajo sobre la asociación entre la pieлонefritis crónica y el reflujo vesicoureteral (RVU). Desde entonces, el abordaje del RVU se ha vuelto cada vez más importante (1).

En los últimos 30 años ha habido múltiples publicaciones sobre el reflujo vesicoureteral (RVU) y discusiones en reuniones de Urología Pediátrica con el propósito de dar respuesta a las preguntas ¿cuál es el mejor tratamiento para el RVU?, ¿a qué edad se aconseja el tratamiento?, ¿previene las infecciones febriles del tracto urinario?, y si el tratamiento consigue detener o disminuir el riesgo de nefropatía por refluo y de cicatriz renal.
INTRODUCTION

The non-physiologic retrograde flow of urine from the bladder to the kidneys in children can lead to pyelonephritis and secondary renal injury due to renal scarring.

Sterile reflux does not cause scarring, but acute pyelonephritis can cause damage to the kidney(s) in children with and without reflux (5). However in the seventies and eighties Rolleston and Bailey suggested that sterile reflux alone might be sufficient to cause renal scarring (6,7).

About 1-2% of all children have VUR and in some cases there is a genetic predisposition. Demographic studies and statistical analysis have shown that VUR is 10 times as common in white children as in black children.

VUR is frequently diagnosed after a urinary tract infection (UTI) in children but nowadays the widespread use of antenatal ultrasonography has allowed identification of fetuses with urinary tract abnormalities in a very early stage, which can result in diagnosis of reflux prior to the development of UTIs. About 3-5% of girls and 1-2% of boys develop a urinary tract infection before puberty. When the UTI has been proved there is a 30-40% chance the child has VUR. In siblings with known VUR the risk is about 30%. Reflux is a birth defect but also may be acquired e.g. in bladder outlet obstruction, neurogenic bladder or detrusor instability.

An acute pyelonephritis in children requires a diagnostic work-up with micturition cystourethrography and only in 25-40% VUR is present. In follow-up studies 10-20% of all children with refluxnepropathy develop hypertension or end-stage renal disease (8). The incidence of VUR in children and young adults with end-stage renal failure (chronic renal insufficiency (CRI)) that necessitates therapy (dialysis or transplantation) is about 6%. VUR is the fifth-most-common cause of CRI in children, after structural malformations, glomerunolephritis, hereditary nephropathies and systemic diseases.

The optimal management of VUR is controversial and has been discussed over more than thirty years several times in the literature. The aim of the treatment is to prevent or reduce (further) renal scarring. Although medical therapy with antibiotics and surgical correction are both recommended to treat VUR, until now it is not clear which type of treatment is superior because there are contradictory studies.

It seems that the newer data can give a more specific advice depending on age, sex, the presence of a renal scar, the grade of VUR, unilateral or bilateral, the presence of bladder dysfunction and toilet trained or not.

The Swedish Reflux Study tries to give definitive answers. They compared 3 treatment alternatives: antibiotic prophylaxis, endoscopic therapy and surveillance as the control group. End point was to look at the results after 2 years in regard to recurrent febrile UTIs, renal damage and VUR status (4).

The RIVUR-study started in 2009 and is a multi-institutional randomized study to determine if antibiotic prophylaxis is beneficial for the prevention of UTIs in children with VUR identified following a UTI. They will try to recruit 600 children to answer the fundamental question in the management of VUR: does antibiotic prophylaxis lead to prevention of UTIs and secondarily renal scarring? (9).
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junction in 1903. This valve mechanism is created by the oblique course of the ureter within the intramural portion of the bladder wall.

In the mid-to-late 1950s, Hutch postulated the causal relationship between VUR and chronic pyelonephritis in a group of patients with spinal cord injury.

A few years later, in 1959, Hodson demonstrated that renal parenchymal scarring is more common in children with VUR and urinary tract infections (UTIs).

In a study by Tanagho in 1975 and confirmed later in a study by Ransley and Ridson, both groups demonstrated that reflux could be experimentally created in animals by modifying the ureterovesical junction. They were also able to show the correlation between reflux, renal papilla anatomy, pyelonephritis, and renal injury.

At the same time, Smellie and Normand performed long-term studies of patients with reflux. They documented the natural history of patients treated medically (10).

At that time, Paquin, Hutch, Lich and Gregoir (11), Daines and Hudson, Politano and Leadbetter (12), Glenn and Anderson, and Cohen (13) developed and popularized various surgical techniques for treating VUR. The International Reflux Grading System was adopted in the early 1980s, and the International Reflux Study compared medical approaches with surgical approaches to reflux. Finally, endoscopic treatment for reflux was introduced in the late 1980s.

In 1982, Noe and colleagues showed a genetic predisposition for reflux (14). In addition, the widespread use of antenatal ultrasonography has allowed identification of fetuses with urinary tract abnormalities, which can result in diagnosis of reflux prior to the development of UTIs.

Predisposition, development of reflux and refluxnephropathy

Anatomy

Vesicoureteric reflux is a developmental anomaly of the vesicoureteric junctions. The ureters are displaced more laterally and they enter the bladder more directly instead of entering the bladder at an angle resulting in an absent or too short intramural course. Normal intravesical pressure at rest and during voiding should compress the intramural and submucosal parts of the ureter against the backing of the detrusor muscle.

Primary vesicoureteric reflux

Primary VUR is attributed to a congenital abnormality of the ureteric orifice and vesicoureteric junction. It is hereditary with a 30-50% chance of occurring in first-degree relatives, thus it is important

<table>
<thead>
<tr>
<th>Grade I</th>
<th>Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation</th>
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<tbody>
<tr>
<td>Grade II</td>
<td>Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices</td>
</tr>
<tr>
<td>Grade III</td>
<td>Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible</td>
</tr>
<tr>
<td>Grade V</td>
<td>Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux</td>
</tr>
</tbody>
</table>
to check the familial history in the diagnostic work-up (14).

**Secondary vesicoureteric reflux**

Secondary VUR occurs in bladder pathology in which abnormally elevated bladder pressure exists e.g. bladder outlet obstruction problems, posterior urethral valves and neurogenic bladder dysfunction (15). Appropriate management of voiding dysfunction will often result in the resolution of reflux (15). A typical example of a combination of low grade VUR and voiding dysfunction are girls presenting with diurnal wetting and urinary infection.

**Spontaneous resolution**

The severity of VUR varies from reflux into the lower end of an undilated ureter during micturition to the severest form with reflux during bladder filling and voiding, with a distended ureter, renal pelvis and clubbed calyces. Mild reflux is in most cases not significant, has a high chance of spontaneous resolution - VUR resolves in 10% each year during growth - and mostly needs no treatment.

In low grade VUR the spontaneous resolution rate can go up to 80% at the age of 10.

On the other hand the more severe degrees of VUR are associated with intraparenchymal reflux, the backflow of urine from the renal pelvis into the papillary collecting ducts. This is associated with a high risk of renal scarring if urinary infection occurs.

The explanation for this reaction is that infection may destroy renal tissue resulting in a scar, which leads to a shrunken poorly functioning segment of the kidney (reflux nephropathy).

In case of severe or repeated infection there is a higher risk of damaging renal tissue resulting in severe, chronic renal failure with a risk of hypertension. The possibility of spontaneous resolution is around 40% for grade 4 or 5 of VUR patients at the age of 10. These numbers only counts for primary reflux patients with ureterotrigonal defect. In secondary VUR the underlying problem should first be managed to reach these numbers.

**Clinical presentation**

An acute pyelonephritis in children requires a diagnostic work-up with micturition cysto-urethrography and only in 25-40% VUR is present. About 3-5% of girls and 1-2% of boys develop a urinary tract infection before puberty. With the enormous technical evolution resulting in the development of ultrasound and nowadays the widespread use of antenatal ultrasonography, this has allowed identification of fetuses with urinary tract abnormalities (e.g. antenatal hydronephrosis), which can result in diagnosis of reflux prior to the development of UTIs.

**Bacteria**

The most common organisms which cause urinary infections are E. coli, Proteus and Pseudomonas. In boys there is a higher incidence to diagnose a Proteus infection compared to girls because of its presence under the foreskin (16).

**Classification**

More than twenty-five years ago the International Reflux Study Committee introduced a uniform system for the classification of VUR (1985). This was derived from two earlier classifications and was based upon the extent of filling and dilatation of the ureter, the renal pelvis and the calyces on a VCUG (voiding cystourethrogram). The Committee also standardized the technique of VCUG to make comparison possible (5,8,17).

**Diagnostic work-up**

We advise to first start with a detailed medical and family history, physical examination,
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Urine-analysis including proteinuria and bacteriuria, and urine culture. The renal function can be determined by serum creatinine level or nuclear renal scan (Cr-EDTA-scan) if necessary. A DMSA-scan (dimercaptosuccinic acid) is the best method to visualize cortical tissue, evaluating renal parenchyma and to determine the presence of renal scars. A micturition cystourethrography (MCUG) remains the ‘gold standard’ investigation for the diagnosis and evaluation of VUR and it permits to grade the severity of VUR, anatomical variants and abnormalities like duplex systems, bladder trabeculation, para-ureteric diverticula, posterior urethral valves etc.

Which is the best treatment?

Early diagnosis and vigilant monitoring are the cornerstones of the treatment. The goal of the treatment is to allow normal renal growth and to prevent permanent renal parenchymal damage and its late complications. Until now there is no single therapeutic solution for all grades and clinical settings of VUR.

There are two therapeutic strategies: a conservative (medical) management with antibiotic prophylaxis and surgery: a minimal invasive approach consisting of endoscopic intra and/or subureteral injection or a ureteral reimplantation either open or laparoscopic. The medical management of VUR is based upon the observation that there is a natural evolution to improvement of the grade of reflux or disappearance of the VUR (18).

When a kidney is grossly scarred and the renal function in the affected kidney is less than 10%, there is a risk of hyperfiltration damage to this kidney which can lead to hypertension. In such cases a nephroureterectomy should be considered (19).

An overview of the landmark studies

Because there were widely divergent opinions in the optimal management of high grade reflux in children in the 1970s and eighties, the International Reflux Study Committee decided in 1980 to start a prospective international study with a European and an American arm in which the researchers will compare medical approaches with surgical approaches to reflux (20). 438 children under 11 years of age with grade III or IV reflux (only grade IV for infants under 1 year of age), with or without renal scarring were recruited during January 1980 to February 1985. Follow up was planned for 5 years, but extended follow up was proposed in the 306 patients of the European limb and was possible in 252 patients. 5-year and 10-year results have been published, but in 2006 Jodal and Smellie presented their overall results of the study and the results of the 252 patients who completed the 10-year clinical follow up (21).

In the European arm were 306 patients included: 155 were treated medically (low dose cotrimoxazole, trimethoprim or nitrofurantoin) until the VUR had resolved or improved to grade I, and 151 surgically (ureteral reimplantation with the Politano-Leadbetter or Cohen technique). The 5-year results in these 306 children showed no statistical difference in outcome between both treatment regimens: there were no statistical differences in acquisition of urographic new scars (22), no changes in images or differential function on DMSA studies (23), renal growth or function (24), or rate of recurrence of UTI (25). But the medical treated group had a higher incidence (21%) in febrile UTIs compared to the surgical group (11%). There was again no statistical difference in the development of new scars. The medical treatment had some side effects (allergic reactions, stomach upset, diarrhea, yeast infections and the risk to having resistant bacteria) as had the surgical treatment.

<table>
<thead>
<tr>
<th></th>
<th># febrile UTI</th>
<th>Kidney damage</th>
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<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td>8/43 (19%)</td>
<td>2/26 (8%)</td>
</tr>
<tr>
<td>Endoscopic treatment</td>
<td>10/43 (23%)</td>
<td>4/23 (17%)</td>
</tr>
<tr>
<td>Surveillance</td>
<td>24/42 (57%)</td>
<td>1/26 (4%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>0/43 (0%)</td>
<td>0/26 (0%)</td>
</tr>
<tr>
<td></td>
<td>5/43 (12%)</td>
<td>1/23 (4%)</td>
</tr>
<tr>
<td></td>
<td>8/42 (19%)</td>
<td>1/26 (4%)</td>
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The first two years of observation.

The 10-year results showed again no statistical difference between the treatment groups concerning the development of urographic renal scars (the main end point), no difference in renal growth or function, nor in recurrence of symptomatic UTI. The only difference noticed was that there was a higher incidence in a febrile recurrence of UTI in the medically treated group, but there was no influence in kidney growth or renal function.

Another important trial was the Birmingham Reflux study (1987) which was a prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children with five years observation (26).

In the Birmingham Reflux Study Group 161 children were observed: 57 children were followed up for two years and the majority (104 children) were observed for 5 years. The main objectives in the treatment of VUR was to prevent or at least limit renal damage. At that time there were 2 treatment options: open surgical correction and long term antibiotics prophylaxis. In the group who were operatively treated (The Leadbetter-Politano method or the Cohen technique) reflux disappeared in 98%, but more than half of the patients treated with antibiotics prophylaxis (trimethoprim or nitrofurantoin, both in a single nightly dose of 1-2 mg/kg body weight) continued to show severe reflux at five years follow up. Two patients progressed to end stage renal failure (CRI) and four other patients with extensive bilateral renal scarring developed hypertension. But there were no significant differences between treatment groups when compared in the incidence of breakthrough urinary infection, renal excretory function and concentrating ability, renal growth, progression of existing renal scars, or new scar formation. They concluded that neither treatment can claim superiority or fully protect the kidneys from further damage. The Birmingham Reflux Study Group already published results earlier but with a smaller number of patients included and with a shorter follow-up period. Essentially there was no difference between treatment groups. One remark was that the relation between bacteriuria and new scar formation needs further attention, while four out of ten new scars developed in patients in whom they did not show breakthrough infection and three of these had undergone operative correction of their reflux. A further scar occurred in an unallocated, contralateral kidney drained by a non-refluxing ureter and all of the ten new scars developed during the first two years of observation.

Two other important trials are the Swedish Reflux trial which published their results in 2010 in the Journal of Urology and the RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux)-study which is a multicenter, randomized, double-blind, placebo-controlled trial designed to determine whether daily antimicrobial prophylaxis is superior to placebo in preventing recurrent UTI and renal scarring in children with grade I-IV VUR. The RIVUR-study subjects are also evaluated for bacterial resistance, constipation, voiding dysfunction, changes in renal function, quality of life, medication compliance, and the utilization of health resources. To test the study hypotheses, a total of 600 children will be randomly assigned to daily antimicrobial prophylaxis (trimethoprim-sulfamethoxazole) or placebo (300 in each group) and followed for a 2-year period. The recruitment for the study started in May 2007 and in November 6, 2009, 373 (62%) patients have been randomized. We hope they will have their results ready in 2013.

In the Swedish Reflux Study (2010) 203 children were included in this prospective randomized controlled multicenter study: 128 girls and 75 boys (4). They all were 1 to younger than 2 years old during recruitment and had a grade III-IV VUR. They were randomized to prophylaxis, endoscopic treatment or surveillance. Follow-up was 2 years and the main study end points were recurrent febrile urinary tract infection, renal status on dimercaptosuccinic acid scintigraphy and reflux status.

In the prophylaxis group the children received 0.5 to 1 mg/kg trimethoprim once daily as the first choice. Alternatives were 1 mg/kg nitrofurantoin and 5 mg/kg cefadroxil, each given once daily. We know that trimethoprim is associated with increased bacterial resistance and nitrofurantoin can cause gastrointestinal intolerance. In the group that received endoscopic injection, dextranomer/hyaluronic acid copolymer was used (Deflux).

There were febrile recurrences in 19% of girls on prophylaxis, in 23% in the endoscopic therapy group and in 57% of the surveillance group, so there was no difference between the prophylaxis and endoscopic groups (Table II). In girls the recurrence rate was associated with persistent reflux after 2 years. The recurrence rate in boys was very low – which is already well-known in boys older than 1 year (27) and showed no differences between treatment groups. We can conclude that neither prophylaxis nor endoscopic treatment is of value to decrease recurrence after age 1 year.
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Which treatment?

a) Conservative management

The conservative medical therapy is based upon the observation that reflux of sterile urine does not cause damage to the kidney and that there’s a certain chance that reflux will resolve spontaneously with time, mostly in young patients with low-grade reflux.

It was the work of Smellie and others who demonstrated a relatively high spontaneous resolution rate of reflux on low-dose antibiotic prophylaxis (28). This explains that long-term prophylactic antibiotics were recommended as initial approach for children with any degree of VUR. The surgical approach was reserved for children on prophylactic antibiotics with persistent VUR and breakthrough febrile urinary tract infections. In the meantime evidence has grown that prophylactic antibiotics does not significantly decrease the risk of recurrent infections and may increase the risk of resistant bacteria (29-31).

There are two randomized controlled trials, one from Garin et al. and one from Pennesi et al., demonstrating that prophylactic use of antibiotics does not prevent for acute pyelonephritis and thus not the incidence of renal damage (29,30). Even more, Garin suggested that prophylactic antibiotics increased the risk of acute pyelonephritis and contribute to antibiotic resistance of the infecting bacteria. Immediate recognition and treatment of urinary tract infections is probably the most important factor to prevent renal scarring.

In children without any urinary tract infection during the last 12 months, who are old enough to communicate symptoms of urinary tract infections, who are potty trained and in absence of risk factors for urinary tract infections such as constipation, discontinuing the prophylactic antibiotics is a good alternative and should be considered as a management option (31).

In 2007 the RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux) study started and will try to answer the question whether no antibiotic prophylaxis in children with VUR is a safe option. They want to perform a risk assessment which will take a lot of variables into account, like the age of the child at the time of infection, character of the infection (cystitis or pyelonephritis), status of the renal parenchyma, the voiding pattern of the child, the grade of reflux at presentation... Once all the variables are known, a risk analysis can be generated. If the assigned risk is high, the option for aggressive treatment is advised. If the calculated risk is low, the option of observation without antibiotic prophylaxis can be proposed (32).

b) Endoscopic correction and ureteric reimplantation

Curative surgical interventions are reserved for children in whom conservative measures fail. Indications are recurrent episodes of pyelonephritis during antibiotic prophylaxis, medical noncompliance, breakthrough infections by resistant organisms and persistent reflux during puberty, certainly in females.

The success rates of a surgical approach are very high with about 99% success and a complication rate of less than 2%. In the open technique there is an intravesical approach with ureteral reimplantation (Cohen and Politano-Leadbetter) or an extravesical ureteral reimplantation technique (Lich-Gregor procedure). Ureteral reimplantation has been shown to decrease risk for febrile urinary tract infections. (33). The endoscopic treatment of VUR with injectable polymers (like Deflux®) has been approved in the USA in 2001 and is effective, even in duplex ureter systems (34). Wadie et al. showed that the mean incidence of urinary tract infections decreased fivefold after endoscopic treatment (35).

The chance of being VUR-free after endoscopic treatment is 78.5% in VUR grade I-II, 72% in grade III, 63% in grade IV and 51% in grade V. If the first injection was unsuccessful, the second treatment had a successrate of 68%, and the third treatment 34%. The total success of endoscopic injection with one or more injections was 85% (36).

According to the guidelines of the European Association of Urology in 2009, children under the age of one year should be treated conservatively. Low grade VUR between 1-5 year can be treated conservative, but the high grade VUR group (grade IV-V) will be advised for surgical correction. Boys with VUR after 5 years of age mostly don’t need any surgical treatment, and prophylactic antibiotics can be stopped. If VUR persists after the age of 5 year in girls, a surgical correction will be advised, certainly in the high grade group.

CONCLUSIONS

Vesico-ureteric reflux is a frequent diagnosis in children and until now the optimal treatment is not always clear. We know that the chance of spontaneous resolution of reflux is high in the low grade VUR-group, and that in high grade reflux after the age of one year the chance of spontaneous resolution is diminished.
This means that surgical intervention will be advised in the high risk groups after the age of 1 year and in girls older than five years.

The endoscopic approach is an excellent alternative for conservative treatment with a higher success rate. It is very important to explain the therapeutic options to the parents and let them decide.

REFERENCES AND RECOMMENDED READINGS
(∗of special interest, ∗∗of outstanding interest)

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