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Vesicoureteral Reflux

Diagnostic tools

&

Challenges
INTRODUCTION

- Vesicoureteral reflux (VUR) is the retrograde passage of urine from the bladder into the upper urinary tract.

- The most common urologic finding in children

- Occurring in approximately 1 percent of newborns

- 30 to 45 percent of young children with a urinary tract infection (UTI)
The resulting infection may lead to loss of renal parenchyma (renal scarring). Extensive scarring may progress to CKD (eg, hypertension, decreased renal function, proteinuria, and ESRD).

However, this long-held belief that reflux in most instances may lead to progressive CKD and potentially ESRD has been increasingly questioned.

The clinical impact of VUR and its management remain uncertain and controversial.
The risk for primary VUR varies based on

- **Ethnicity**
  - White children are *three times more* likely to have VUR than black children. The maximal grade of reflux was significantly lower in black children.
Gender – Girls are twice as likely to have reflux as boys. However, the gender difference is smaller in countries where circumcision is not routinely performed. In contrast, there is a male predominance in patients who present with antenatal hydronephrosis.

Age – Young children and infants (<2 years of age) were more likely to have VUR than older children based on the natural course of spontaneous resolution of VUR with growth in most affected patients.
There is a **genetic predisposition** for primary vesicoureteral reflux (VUR).

The genetic loci underlying these associations as well as the mode(s) of inheritance are **unknown**.

There is speculation that the length of the intravesical ureter may be genetically dictated, but genome linkage studies in 320 families with at least two affected siblings **failed to detect** any association with six candidate genes (AGTR2, HNF1B, PAX2, RET, ROBO2, and UPKA3).
Research studies have also suggested a genetic susceptibility of individuals to renal scarring, which may explain the variability in scarring in many children with VUR and recurrent UTI.
DIAGNOSIS

- The diagnosis of vesicoureteral reflux (VUR) is based upon: the demonstration of reflux of urine from the bladder to the upper urinary tract.

- Contrast voiding cystourethrogram (VCUG)
- Radionuclide cystogram (RNC).

- In many centers RNC is not used as the initial study, but is used to monitor for persistent reflux.
Other imaging techniques have been proposed that either eliminate the need for catheterization and/or radiation exposure. These include:

- Sonographic contrast agents
- Color Doppler ultrasound
- Indirect radionuclide
- Magnetic resonance imaging (MRI) cystography
- Thermal imaging after heating bladder urine with external devices.

However, these are all experimental modalities, which need to be confirmed as an effective but not too costly alternative to VCUG.
● Indirect urinary and serum markers
   ➢ Procalcitonin
   ➢ Cystatin C
   ➢ Urinary mrna
   ➢ C-reactive protein
   ➢ Matrix metalloproteinase 9
   ➢ Interleukin 6 & 8
   ➢ Urinary proteome analysis

● None of these methodologies are as accurate as cystography in making the diagnosis of VUR
Likelihood of resolution

- In the majority of cases with primary VUR, especially those with low-grade reflux, there is spontaneous resolution.

- Rates of spontaneous resolution were 72, 61, 49, and 32 percent for grades I, II, III, and IV/V, respectively.
Grades I and II – By five years of age, spontaneous resolution occurred in **80 percent** of patients. The likelihood of resolution was **not dependent upon age** at presentation or whether the reflux was unilateral or bilateral (laterality of reflux).

Grade III – Age at presentation and **laterality** of reflux had major effects on resolution of reflux.

- The oldest group of children (5 to 10 years of age) with bilateral reflux had less than **20 percent** resolution over five years.
- In contrast, there was a **70 percent** resolution rate in the youngest group of children (one to two years) with unilateral disease.
Grade IV – There was a 60 percent resolution rate for unilateral disease and a less than 10 percent resolution rate for bilateral reflux over five years, regardless of age at presentation.

Grade V – Spontaneous resolution is rare except for in male infants who have a resolution rate of about 30 percent in the first year of life.
THERAPEUTIC INTERVENTIONS

- Identification of children with VUR
- Prevention of recurrent UTI
- Prevention of further renal damage resulting from infection and inflammation
- Minimization of morbidity of treatment and follow-up
- Identifying and managing children with bladder and bowel dysfunction (BBD)
Interventions include

- Medical therapy
- Treatment of comorbid conditions (such as BBD)
- Surgical correction.
Medical treatment

- **Daily prophylactic administration** of an antibiotic agent.

- It is based on the assumptions that use of continuous antibiotics results in sterile urine and the continued reflux of sterile urine does not cause renal damage, and the observation that reflux spontaneously resolves in most cases.
Antimicrobial agents most commonly used for prophylaxis include:

- **Trimethoprim-sulfamethoxazole** (TMP-SMX) or TMP alone – Dosing is based on TMP at 2 mg/kg
- **Nitrofurantoin** – 1 to 2 mg/kg
- **Cephalexin** – 10 mg/kg
- **Ampicillin** – 20 mg/kg
- **Amoxicillin** – 10 mg/kg

One daily dose is administered at bedtime. The dose is one-half to one-quarter the usual therapeutic dose for treating an acute infection.
Complications

- Nausea and vomiting
- Abdominal pain
- Increased antibiotic resistance
- Marrow suppression
- Stevens-Johnson syndrome (rare)
- Breakthrough infection because of antibiotic resistance or lack of compliance.
However, **no serious side effects** were noted in the Randomized Intervention for Vesicoureteral Reflux (RIVUR) study.

The need for **periodic monitoring** of VUR either by contrast voiding cystourethrogram (VCUG) or radionuclide cystogram (RNC).
CHOICE OF THERAPY
There has been heightened interest in whether there is a need for **therapeutic intervention** versus a regimen of surveillance and prompt treatment of intercurrent episodes of urinary tract infection (UTI), referred to as "**watchful waiting**".

Data are contradictory on whether or not medical intervention improves long-term renal outcome compared with "**watchful waiting**".
Antibiotic prophylaxis versus surveillance/placebo trials

- Systematic reviews of the literature reported that medical therapy compared with no treatment or placebo did not reduce the risk of UTI or renal scarring.

- A subsequently published high-quality clinical trial has shown that prophylactic antibiotic reduces the risk of recurrent UTI in young children with VUR.
Discontinuation of medical therapy

- Indications of when to discontinue medical therapy are uncertain.
  - Some experts will only discontinue therapy when the VCUG is negative.
  - Older children or adolescents with grade I reflux who have been infection free for a year.
  - Early adolescence in patients with persistent grade I reflux.

- Girls should be made aware that the presence of reflux increases the risk of UTI during pregnancy and that they should be carefully monitored at that time.
Medical versus surgical therapy

- Data from clinical trials and a systematic review have demonstrated

- Comparable long-term renal outcome (recurrent UTI and scarring) in patients treated with either prophylactic antibiotics or surgical correction.

- The choice of therapy does not impact the long-term renal outcome in children with severe bilateral disease who are at increased risk for CKD and in some, ESRD.
Medical versus surgical therapy

- Based upon the lack of evidence suggesting a difference between medical and surgical therapies

- The clinician should provide parents with information regarding the benefits and limitations of the different therapeutic options.
However, surgical correction should be considered in patients who fail to comply with antibiotic prophylaxis, who have episodes of febrile UTIs while on medical therapy, or who are unlikely to have spontaneous VUR resolution.
Bladder bowel dysfunction (BBD) is a common finding in patients with VUR.

Patients with both BBD and VUR have a

- Higher incidence of breakthrough UTI
- Longer time for VUR resolution
- Increased failure rate of surgical correction than patients with only VUR.
Interventions for BBD

- Use of laxatives
- Timed frequent voiding
- Pelvic floor exercises
- Behavioral modification
  (both improving bladder function and leading to VUR resolution.)

- All patients with VUR be screened for BBD
All children with grades III through V reflux be treated

Initially place all patients on prophylactic antibiotic therapy.

Surgical correction is indicated if there is persistent grade IV or V reflux in patients at two or three years of age, or if there is breakthrough UTI.

consider parental preference regarding continuation of antibiotic prophylactic therapy versus surgical correction.
Children with grade I to II reflux are at the lowest risk for renal scarring, but remain at risk for recurrent UTI.

Surgical correction is not recommend in patients with low-grade reflux (unless there is breakthrough UTI on medical therapy as there is a high likelihood of spontaneous resolution).
Patients who are treated medically or by "watchful waiting" require

- Mandatory **urine cultures** whenever there are symptoms suggestive of UTI or unexplained fever
- Monitoring by **repeat cystogram** for the continued presence of VUR.
- **DMSA renal scan** is performed initially in all children and is repeated in select patients at risk for renal scarring.
Long-term follow-up

- Annual assessment of linear growth
- Measurement of blood pressure
- Urinalysis

- Families should be aware of the association of VUR with increased risk of chronic kidney disease (CKD) (eg, hypertension, renal impairment, or proteinuria).
Conclusions

- VUR remains a **clinical challenge**
- There is **no definitive algorithm** to manage reflux
- Risk assessment of renal injury/scarring
It is necessary to look at the total patient with special attention on

- Voiding function
- Age
- Grade of reflux
- History of UTI
- Presence of renal abnormalities and scarring
- Parental preferences
THANK YOU