Management options in vesico-ureteric reflux

Sivaprakasam
• **Presentation scope**
  – medical management
    • continuous antibiotic prophylaxis (CAP)
      – role and controversies
      – subgroups who benefit
      – *Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR)* study
  – surgical management
    • endoscopic treatment
      – *Elders et al metaanalysis*
    • open surgical treatment
      – techniques
      – pros and cons
      – outcomes
VUR management

• rational for intervention in paediatric VUR
  – prevention of febrile UTI
  – preservation of renal parenchyma
  – prevent childhood hypertension secondary to renal failure

• grading of reflux (International Reflux Study Grading)
Conservative treatment

- rational
  - most VUR can resolve spontaneously
    - potential for 5-year resolution of VUR varies from 25% to 50% between prospective studies[1]
    - favourable factors young age & low grade reflux [2]

- negative predictors; lower bladder volume or pressure at onset of reflux, older age, female sex, bilateral VUR, ureteral duplication, abnormal or scarred kidneys, and bladder dysfunction

• online VUR resolution calculators available for parent/patient counselling: [http://www.childrenshospital.org/vurcalculator/](http://www.childrenshospital.org/vurcalculator/)
  – kidney damage doesn’t occur in the absence of UTI and LUTD
  – no evidence that small renal scars leads hypertension, renal insufficiency, or problems during pregnancy

• conservative approach
  – watchful waiting with lab and imaging investigations
  – IAP or CAP; reduce UTI reduce renal scarring
  – bladder rehabilitation in presence of LUTD
  – circumcision
• at follow up:
  • UFEME & C+S
  • BUSE
    • imaging with; US KUB, VCUG, nuclear cystography, or DMSA scanning

  – to monitor spontaneous resolution and kidney status
  – frequency and intensity of follow up; has no consensus
  – when febrile UTI occurs despite conservative management, intervention recommended

  – common CAP regimen (at bedtime)[1]
    • amoxicillin and trimethoprim at 1/3 dose given nocturnally (<2 months)
    • trimethoprim-sulfamethoxazole or nitrofurantoin (older infants)

• controversies surrounding CAP make it difficult to make definitive recommendations
  – current clinical evidence derived from suboptimal studies:
    • underpowered studies
    • lack of randomization
    • methodological shortcoming
  – evidence that CAP may not be required in all cases of VUR[1-4]
  – CAP may prevent renal damage in higher grades of reflux (3&4) [5-9]

– factors influencing initiation of CAP
  • young age
  • high-grade VUR
  • status of toilet training/LUTD
  • female sex
  • circumcision status

– no reliable information about the ideal duration of CAP in reflux patients
**EAU 2012 VUR recommendations:**

Table 3 – Recommendations for management of vesicoureteral reflux in childhood

Regardless of the grade of reflux or the presence of renal scars or symptoms, all patients diagnosed within the first year of life should be treated initially with CAP. During early childhood, the kidneys are at higher risk of developing new scars. Immediate antibiotic treatment should be initiated for febrile breakthrough infections; treatment may be parenteral in children who are not capable of taking oral medications. Definitive surgical or endoscopic correction is the preferred treatment in patients with frequent breakthrough infections [77].

Surgical correction should be considered in patients with persistent high-grade reflux (grade IV/V). There is no consensus about the timing or type of surgical correction. The outcome of open surgical correction is better than endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved by endoscopic injection in lower grades.

There is no evidence that correction of persistent low-grade reflux (grade I-III) in patients with no febrile UTI and normal kidneys offers a significant benefit. These patients may be candidates for endoscopic treatment.

In all children presenting at age 1–5 yr with dilating reflux (grade III–V), CAP is the preferred option for initial therapy. For patients with high-grade reflux or abnormal renal parenchyma, surgical repair is a reasonable alternative. In patients with lower grades of reflux and no symptoms, close surveillance without antibiotic prophylaxis may be an option.

A detailed investigation for the presence of LUTD should be performed in all children after toilet training. If LUTD is detected, the initial treatment should be directed toward LUTD.

If parents prefer definitive therapy to conservative management, surgical correction may be considered. Endoscopic treatment is an option for all children with low grades of reflux.

The traditional approach of offering initial medical treatment after diagnosis and shifting to interventional treatment in case of breakthrough infections and new scar formation must be challenged, because the treatment should be tailored to the risk group.

The choice of management depends on the presence of renal scars, the clinical course, the grade of reflux, ipsilateral renal function, bilaterality, bladder function, associated anomalies of the urinary tract, age, compliance, and parental preference [83]. Febrile UTI, high-grade reflux, bilaterality, and cortical abnormalities are considered to be risk factors for possible renal damage. The presence of LUTD is an additional risk factor for new scars. In high-risk patients who already have renal impairment, a more aggressive, multidisciplinary approach is needed.

CAP = continuous antibiotic prophylaxis; UTI = urinary tract infection; LUTD = lower urinary tract dysfunction.
- EAU risk based approach:

<table>
<thead>
<tr>
<th>Risk groups</th>
<th>Presentation</th>
<th>Initial treatment</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>High</td>
<td>Symptomatic male or female patients after toilet training, with high-grade reflux (grade IV/V), abnormal kidneys, and LUTD</td>
<td>Initial treatment is always for LUTD; intervention may be considered in cases of recurrent febrile infections or persistent reflux</td>
<td>Greater possibility of earlier intervention; More aggressive follow-up for UTI and LUTD; full reevaluation after 6 mo</td>
</tr>
<tr>
<td>High</td>
<td>Symptomatic male or female patients after toilet training, with high-grade reflux (grade IV/V), abnormal kidneys, and no LUTD</td>
<td>Intervention should be considered</td>
<td>Open surgery has better results than endoscopic surgery; Postoperative VCUG on indication only; follow-up of kidney status until after puberty</td>
</tr>
<tr>
<td>Moderate</td>
<td>Symptomatic male or female patients before toilet training, with high-grade reflux and abnormal kidneys</td>
<td>CAP is the initial treatment; intervention may be considered in cases of BT infections or persistent reflux</td>
<td>Spontaneous resolution is higher in males; Follow-up for UTI/ hydronephrosis; full reevaluation after 12-24 mo</td>
</tr>
<tr>
<td>Moderate</td>
<td>Asymptomatic patients (PNH or sibling), with high-grade reflux and abnormal kidneys</td>
<td>CAP is the initial treatment; intervention may be considered in cases of BT infections or persistent reflux</td>
<td>Follow-up for UTI/ hydronephrosis; full reevaluation after 12-24 mo</td>
</tr>
<tr>
<td>Moderate</td>
<td>Symptomatic male or female patients after toilet training, with high-grade reflux and normal kidneys with LUTD</td>
<td>Initial treatment is always for LUTD; intervention may be considered in cases of BT infections or persistent reflux</td>
<td>In case of persistent LUTD despite urotherapy, intervention should be considered; the choice of intervention is controversial; Follow-up for UTI, LUTD, and kidney status; full reevaluation after successful urotherapy</td>
</tr>
<tr>
<td>Moderate</td>
<td>Symptomatic male or female patients after toilet training, with low-grade reflux and abnormal kidneys with or without LUTD</td>
<td>Choice of treatment is controversial; endoscopic treatment may be an option; LUTD treatment should be given if needed</td>
<td>Follow-up for UTI, LUTD, and kidney status until after puberty</td>
</tr>
<tr>
<td>Moderate</td>
<td>All asymptomatic patients with normal kidneys, with low-grade reflux and without LUTD</td>
<td>Initial treatment is always for LUTD</td>
<td>Follow-up for UTI and LUTD</td>
</tr>
<tr>
<td>Low</td>
<td>All asymptomatic patients with normal kidneys, with low-grade reflux with no LUTD</td>
<td>Either no treatment or CAP</td>
<td>If no treatment is given, parents should be informed about risk of infection; Follow-up for UTI</td>
</tr>
<tr>
<td>Low</td>
<td>All asymptomatic patients with normal kidneys and low-grade reflux</td>
<td>Either no treatment or CAP in infants</td>
<td>If no treatment is given, parents should be informed about risk of infection; Follow-up for UTI</td>
</tr>
</tbody>
</table>

LUTD = lower urinary tract dysfunction; UTI = urinary tract infection; VCUG = voiding cystourethrography; CAP = continuous antibiotic prophylaxis; BT = breakthrough; PNH = prenatally diagnosed hydronephrosis.

A symptomatic patient is a patient with febrile UTI (upper tract involvement) or with marked findings of afebrile UTI confined to the bladder (i.e., malodorous or discolored urine with or without voiding difficulties). An asymptomatic patient is a patient with none of these findings.
• AUA 2010 VUR recommendation:
  – CAP is recommended in
    • symptomatic child > 1 yr with VUR and history of febrile UTI
    • asymptomatic child < 1 yr with a VUR G3-5 identified through screening
    • optional symptomatic child < 1yr with VUR G1-2
    • child with both bladder bowel dysfunction (BBD) and VUR

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>Observation</th>
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<tbody>
<tr>
<td><strong>No BBD, recurrent febrile UTI, renal cortical abnormalities</strong></td>
<td>option</td>
<td>option</td>
</tr>
<tr>
<td><strong>BBD, recurrent febrile UTI, OR renal cortical abnormalities</strong></td>
<td>recommended</td>
<td>not recommended</td>
</tr>
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</table>
• Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR)

  – multicenter, randomized, double-blind, placebo-controlled trial

  – primary end point

    • recurrent febrile or symptomatic urinary tract infection during 2-year follow-up

  – secondary end points

    • renal scarring based on DMSA scan performed 1 and 2 years after enrolment
    • severe renal scarring on outcome scan
    • treatment failure composite based on multiple recurrent UTIs or, in children with baseline scarring of grade 3 or higher, new renal scarring at 12-months or further scarring at any time following recurrent febrile UTI
    • presence of E coli resistant to TMP/SMZ
    • recurrent febrile or symptomatic UTI caused by TMP/SMZ-resistant organism
• RIVUR study flow diagram:

- Recruitment target:
  - 300 placebo arm
  - 300 treatment arm
Endoscopic management

- first described in 1981 by Matouschek[1] using PTFE
- Kirsch modified the technique – intraureteric Deflux injection [3]; hydrodistension implantation technique (HIT) and the (double HIT)

• post procedure (Campbell Urology)
  – antibiotics for 3 months
  – KUB US and VCUG to reassess VUR at 3 months
  – if still refluxing, repeat injection after 6 month interval
  – there is a significant learning curve associated with procedure [1,2]
  – agents used in endoscopic injection divided into
    • non-autologous
      – Polytetrafluoroethylene (PTFE), Cross-linked bovine collagen,
        Polydimethylsiloxane, Dextranomer hyaluronic copolymer (Deflux),
        Coaptite
    • autologous
      – chondrocytes, fat, collagen, muscle
  – concerns with injectibles; particulate migration & durability
  – migration occurs through:
    • intravascular dissemination at the site of injection
    • phagocytosis

Elders et al performed a metaanalysis on all studies using the endoscopic treatment in VUR [1]

- shortlisted & analysed 63 studies
  - 7 prospective
  - 52 retrospective
  - 3 randomised prospective
  - 1 unknown

- each study was analysed by 2 paediatric urologist and data extracted from a standardised data retrieval sheet

Reflux resolution after 2\textsuperscript{nd} course of treatment

Reflux resolution after 3\textsuperscript{rd} course of treatment
Fig. 6. Resolution is significantly lower for duplicate than for non-duplicate ureters (single treatment).

Fig. 7. Resolution is significantly lower in neuropathic than in nonneuropathic bladders.
• longterm recurrence following endoscopic treatment
  ➢ 5% recurrence with PTFE after 17 year follow up [1]
  ➢ 13% recurrence with Deflux after 2-5 year follow up [2]
  ➢ preinjection history of multiple febrile UTIs, BBD, and renal scarring carry higher risk of recurrent infection and late recurrence [3]

Open surgical management

- open surgery carries 98.1% success rate [1]
- intravesical approach
  - supravesical tunnels
    - Pollitano Leadbetter technique
    - Paquin technique
  - infravesical tunnels
    - Glen-Anderson technique
    - Cohen Cross Trigonal Technique

- extravesical approach
  - Modified Lich-Gregoir/detrusorrhaphy technique

Pollitano Leadbetter technique
Paquin technique

• combined extravesical and intravesical approach
• ureteric mobilisation is done extravesical (see later section)
• existing VUJ divided extravesically
• bladder opened in midline to create new ureteric hiatus
• mucosa around new hiatus mobilised
• submucosal ureteric tunnel created at a ratio 5:1 (tunnel length:diameter or ureter)
• psoas hitch can be used for longer tunnel length
• suited for dilated ureters, complex and previously failed ureteric implants
Glenn Anderson technique

Figure 122-18. Glenn-Anderson technique. The ureter is mobilized and advanced beneath a new submucosal tunnel. (From Glenn JF, Anderson EE. Distal tunnel ureteral reimplantation. J Urol 1967;97:623.)
Cohen Cross Trigonal technique

- particularly suited for small bladders or thick-walled bladders (PUV or neuropathic) because the ureteral advancement across the back wall of the bladder rarely results in kinks or obstruction
- procedure of choice in conjunction with bladder neck reconstructive procedures because the superior displacement of the ureters provides room for adequate elongation of the bladder neck
- disadvantage: the difficulty of retrograde catheterization of the superolaterally positioned ureteral orifice for radiographic studies, insertion of stents and management of ureterolithiasis as significant
Modified Lich-Gregoir/detrusorrhaphy technique
## Pros and Cons of various techniques

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<th>Procedure</th>
<th>Illustration</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td><strong>Extravesical</strong></td>
<td></td>
<td></td>
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<tr>
<td>Lich-Gregoir</td>
<td><img src="image1" alt="Illustration" /></td>
<td>Bladder is not opened Decreased postoperative hematuria/bladder spasm</td>
<td>Increased risk of urinary retention due to damage to pelvic nerves in bilateral repairs</td>
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<td></td>
<td>(24)</td>
<td></td>
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<tr>
<td><strong>Intravesical</strong></td>
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<tr>
<td>Polliaro-Leadbatter</td>
<td><img src="image2" alt="Illustration" /></td>
<td>Creation of longer tunnel</td>
<td>Ureteral kinking/obstruction</td>
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<td>1958</td>
<td>(26)</td>
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<tr>
<td>Glenn-Anderson</td>
<td><img src="image3" alt="Illustration" /></td>
<td>Avoids ureteral kinking</td>
<td>Limited tunnel length</td>
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<td>1967</td>
<td>(27)</td>
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<tr>
<td>Cohen</td>
<td><img src="image4" alt="Illustration" /></td>
<td>Avoids ureteral kinking Longer tunnel length</td>
<td>Difficult retrograde catheterization</td>
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<td>1975</td>
<td>(30)</td>
<td></td>
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</table>
Complications

• early complications
  – persistent reflux
    • common at upto 1 year post op
    • resolves spontaneously
    • more common in high grade VUR[1]
  – contralateral reflux
    • higher risk with correction of high grade VURs and in duplex systems [2]
    • could represent missed contralateral VUR
    • expectant management recommended, intervene in complications such as pyelonephritis
    • prophylactic reimplantation not advised
  – obstruction
    • early obstruction common and resolve spontaneously
    • symptomatic, progressive obstruction within 2 weeks, can be managed by retrograde stenting or nephrostomy + antegrade stenting

• **late complications**
  – **obstruction**
    • supr ahialtal – twisting or poor handling of ureter with resultant ischaemia during implantation
    • hiatal - positioned too lateral or anterior results in obstruction when bladder fills – stenting or redo
    • tunnel – inadequate submucosal tunnel resulting in compression – dilatation, stenting or redo
    • orifice – treated with dilatation, stenting or endoscopic deroofing
The End
• Management options in VUR
• Discuss about the role/controversies of CAP
• Groups of pts who may need CAP (refer to AUA VUR guidelines)
• Role of circumcision to be covered by speaker on circ and UTI (Azhan)
• RIVUR study (describe the basis of this study)
• Endoscopic injections and outcome (refer to metaanalysis by Elder et al)
• Open surgery-describe common intra and extravesical techniques-pros and cons and outcome