Treatment of Vesicoureteral Reflux (VUR) Using a Minimally Invasive Endoscopic Procedure
Today’s talk

• What is vesicoureteral reflux (VUR)?
  – Prevalence
  – Symptoms
  – Grades

• The clinical consequences of VUR
  – Febrile UTIs
  – Renal scarring

• Treatment goals
  – Definition of success

• Overview of Deflux
  – Minimally invasive endoscopic injection
    • Materials and techniques
  – Efficacy
  – Safety

• Parent preference

• Summary

• References
What is VUR?

- VUR is a bladder valve defect that allows urine to reflux from the bladder through one or both ureters and up to the kidneys\(^1\)

- Febrile urinary tract infection (UTI) is the defining symptom\(^1,2\)

\(^1\) Hensle 2007; \(^2\) Wadie 2007
VUR prevalence

- 75%–80% of children diagnosed with VUR are girls
- Caucasians are 3x as likely to get VUR than African Americans
- Most children diagnosed with VUR are <4 years of age
- Affects approximately 1% of all children
  - May be present in 14%-35% of children with asymptomatic UTIs
- Recurrent febrile UTIs trigger screening and diagnosis
- Found in 30%–40% of children with recurrent UTIs
- Some congenital anomalies of the upper urinary tract are associated with increased risk of VUR

VUR and febrile UTI: A common clinical presentation

- Unexplained fever\(^1\)
- Frequent or urgent urination\(^2\)
- Urine dribbling between urinating\(^2\)
- Dysuria (pain on urination) \(^2\)
- Strong-smelling, cloudy, or bloody urine\(^1\)
- Abdominal, back, or side pain\(^2\)

\(^1\) AAP 1999; \(^2\) AUA Guidelines 1997
Clinical consequences of VUR

- Infected urine traveling back up to the kidneys increases the likelihood of having a febrile UTI\(^1\)
- There is a 70% overall incidence of upper UTI (acute pyelonephritis or kidney infection) in children with first febrile UTI\(^2\)
- More than half (57%) of these children developed renal scars

\(^1\)Panaretto 1999; \(^2\)Lin 2003
VUR grades

- The severity of VUR is based upon a grading system, reflecting the extent of reflux and ureter abnormality\(^1\)

\[\text{Grade I} \quad \text{Grade II} \quad \text{Grade III} \quad \text{Grade IV} \quad \text{Grade V}\]

- More severe VUR is associated with more severe renal scarring and increased complications\(^2,3\)

\(^1\)AUA Guidelines 1997; \(^2\)Gonzalez 2005; \(^3\)Caione 2004
VUR and renal scarring

- Renal damage usually occurs within the first 3-5 years of life\(^1,2\)
  - In some cases renal damage can occur prenatally

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1. Sherbotie 1991; 2. AAP 1999
Consequences of renal scarring and damage

These data are a graphic representation of the data within these studies.

1Smellie 1998; 2McNiece 2007; 3Kiberd 2002
Importance of effectively treating VUR

- Reduce febrile UTI-associated morbidity\(^1\)
- Eliminate ongoing health problems\(^2\)
- Fewer voiding cysto-urethrogram (VCUG) examinations\(^1\)
- Without treatment, reflux persists for at least 4–5 years in at least half of all cases\(^2\)
- Early management is recommended to reduce the incidence and severity of renal scarring\(^3-5\)

\(^1\)Thompson 2005; \(^2\)Wheeler 2003; \(^3\)Smellie 1994; \(^4\)AAP 1999, \(^5\)Smellie 1998
Definition of success in VUR treatment

Aim of treatment
• Protect against febrile UTIs
• Prevent renal scarring

Definition of success
• The successful, durable prevention of febrile UTIs that could lead to renal scarring
Rate of febrile UTIs higher with antibiotic prophylaxis than with no treatment at all

A 1-year, follow-up, randomized, urinary antibiotic prophylaxis-controlled study of 218 patients aged 3 months to 18 years with documented acute pyelonephritis to determine antibiotic efficacy of febrile UTI management.¹

¹Garin et al. 2006
Rate of renal scarring higher with antibiotic prophylaxis

- Incidence of renal scarring increased approximately 3 fold in patients on antibiotic prophylaxis

\[\text{Garin et al. 2006}\]
Additional risks of antibiotic prophylaxis

- **Noncompliance**
  - Only 17% of patients were greater than 80% compliant and only 10% were 100% compliant based on Medication Possession Ratio (MPR) values\(^1\)

- **Susceptibility of resistance**
  - According to the World Health Organization (WHO), patient noncompliance is a factor that encourages the spread of resistance\(^2\)

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\(^1\) Hensle 2007b; \(^2\) WHO Antibiotic Fact Sheet
Deflux—Effective in low-to-moderate VUR

- Nearly 4x better reduction in VUR-associated UTIs than antibiotics
- Febrile UTI protection comparable to surgery
- Durable protection against febrile UTIs
- Excellent safety profile

AUA Board of Directors 2007: *Deflux must be considered an option in the care of the pediatric patient with VUR.*

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A minimally invasive endoscopic injection

- Deflux is injected in or around the ureteral opening to create a valve function and stop urine from flowing back up the ureter\textsuperscript{1}

\textsuperscript{1}Deflux PI
A minimally invasive endoscopic injection

- Deflux is injected in or around the ureteral opening to create a valve function and stop urine from flowing back up the ureter\(^1\)

\(^1\text{Deflux PI}\)
Nearly 4x fewer VUR-associated UTIs vs antibiotic prophylaxis

A 4-year retrospective analysis of 152 patients who had 2 diagnoses of VUR to determine Deflux as a feasible alternative to antibiotic prophylaxis.¹

¹Elder 2007
Overall febrile UTI protection comparable to surgery

- The incidence of febrile UTIs with Deflux was lower than surgery in a single head-to-head, retrospective study.

A study reviewing the charts of children treated with either surgery or Deflux in 2003 to compare the incidence of febrile and afebrile UTI occurrence postoperatively.

Elmore 2008
Efficacy proven in multiple studies

- Combined results from 4 other independent studies show febrile UTI rates with Deflux compare favorably to surgery
  - Stenberg and Traxel report low incidence of febrile UTI recurrence following Deflux treatment vs surgery (3.4% and 3.5%, respectively)\(^1,2\)
  - The US and European arms of the International Reflux Study observed similar rates following surgery (8% and 10%, respectively)\(^3,4\)

\(^1\)Stenberg 2007, \(^2\)Traxel 2009, \(^3\)US Arm of International Reflux Study 1992, \(^4\)European Arm of the International Reflux Study 1992
Durable protection—up to 3 years\(^1\)

- Dramatic and durable reduction of febrile UTIs
  - Deflux provided a >6-fold post-treatment reduction in the incidence of febrile UTI infections per year\(^1\)
  - Additionally, the incidences of both febrile and afebrile UTIs were similar to those reported after surgery\(^1\)
  - Long-term efficacy studies found Deflux delivered protection against febrile UTIs for up to 12 years\(^2\)

\(^1\)Chi, 2008; \(^2\)Stenberg 2007
Durable protection—up to 12 years$^1$

- Of 179 patients initially treated successfully* with Deflux, only 3.4% experienced a febrile UTI 7-12 years after treatment
  - 96.6% of patients did not have a febrile UTI 7-12 years after treatment

* In Europe, grades I-II are considered positive outcomes.

$^1$Stenberg 2007
Proven safety

- Treat grade II-IV with more confidence

Low incidence of adverse events

<table>
<thead>
<tr>
<th>Adverse event category</th>
<th>Randomized study (n=39)</th>
<th>Nonrandomized studies (n=170)</th>
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<tbody>
<tr>
<td>Urinary tract infection (UTI)</td>
<td>6 (15.4%)</td>
<td>13 (7.6%)</td>
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<td>Ureteral dilatation</td>
<td>1 (2.6%)</td>
<td>6 (3.5%)</td>
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<tr>
<td>Nausea/Vomiting/Abdominal pain</td>
<td>0 (0%)</td>
<td>2 (1.2%)</td>
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</table>

1 Data from clinical trials.
Parent preferred\textsuperscript{1}

\begin{itemize}
  \item Endoscopic injection 80%
  \item Antibiotics 5%
  \item Open surgery 2%
  \item Undecided 13%
\end{itemize}

\textsuperscript{1}Capozza 2003
Summary

- VUR is an uncommon, but dangerous condition
- Goal of therapy is the prevention of febrile UTIs and improving QOL
- Antibiotics are of limited use in low-to-moderate VUR and require regular VCUGs, which parents and children consider the most stressful and unpleasant part of VUR treatment
- Deflux is a safe, highly effective treatment for VUR
  - Extensively studied
  - Professional group endorsed
  - Nearly 4x better reduction in VUR-associated UTIs than antibiotics and comparable to surgery
  - Parent preferred
Additional Deflux Information
Deflux gel—A minimally invasive endoscopic procedure

- Outpatient procedure takes approximately 15 minutes\(^1\)
- Requires short-acting general anesthesia\(^2\)
- Made from materials that have been in medical use for over a decade\(^3\)
- More than 50,000 children have been treated\(^3\)
- Dextranomer microspheres stay at the implant site\(^1,4,5\)
- Does not migrate from the injection site\(^1,4,5\)

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\(^1\) Cerwinka 2008; \(^2\) DEFLUX Package Insert 2009; \(^3\) Data on file; \(^4\) Stenberg 1997; \(^5\) Stenberg 2003
Made from biocompatible material

- Easily injectable, viscous gel made from 2 polysaccharides\(^1,2\)
  - Non-animal stabilized hyaluronic acid (NASHA\(^{TM}\))
  - Dextranomer microspheres (80–250 μm)

- Implant is stable, long term, remains in position, and does not disappear over time\(^2,3\)

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\(^1\)Cerwinka 2008; \(^2\)DEFLUX Package Insert 2009; \(^3\)Stenberg 2003
Some physicians report that using the HIT/double-HIT technique (sites 1 & 2) has improved success rates over the STING technique (site 3).\(^1\)

The standard STING procedure was used in clinical studies with Deflux treatment for VUR that were pivotal to approval of Deflux by the FDA. The success rates seen with this approach are approximately 70%.\(^1\)

\(^1\text{Kirsch 2004}\)
Intended Use/Indications
Deflux® is indicated for treatment of children with vesicoureteral reflux (VUR) grades II-IV.

Contraindications
Deflux is contraindicated in patients with any of the following conditions:
- Non-functional kidney(s)
- Hutch diverticuli
- Ureterocele
- Active voiding dysfunction
- Ongoing urinary tract infection

Warnings
- Do not inject Deflux intravascularly. Injection of Deflux into blood vessels may cause vascular occlusion.

Precautions
- Deflux should only be administered by qualified physicians experienced in the use of a cystoscope and trained in subureteral injection procedures.
- Treatment of duplex systems has not been prospectively studied.
- Ureters with grossly dilated orifices may render the patient unsuitable for treatment.
- The risks of infection and bleeding are associated with the cystoscopic procedure used to inject Deflux.
- The usual precautions associated with cystoscopy (e.g. sterile technique, proper dilation, etc.) should be followed.
- The safety and effectiveness of the use of more than 6 ml of Deflux (3 ml at each ureteral orifice) at the same treatment session have not been established.
- The safety and effectiveness of Deflux in the treatment of children under 1 year of age have not been established.
Adverse Events

List of treatment-related adverse events for 39 patients from a randomized study and 170 patients from nonrandomized studies. (Follow-up for studies was 12 months.)

<table>
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<tr>
<th>Adverse Event</th>
<th>Randomized (n=39 Deflux)</th>
<th>Nonrandomized (n=170)</th>
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<tr>
<td>Urinary tract infection (UTI) (i)</td>
<td>6 (15.4%) (ii, iii)</td>
<td>13 (7.6%) (ii, iii)</td>
</tr>
<tr>
<td>Ureteral dilatation (iv)</td>
<td>1 (2.6%)</td>
<td>6 (3.5%)</td>
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<tr>
<td>Nausea/Vomiting/Abdominal pain (v)</td>
<td>0 (0%)</td>
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(i) Cases of UTI typically occurred in patients with persistent reflux.
(ii) Patients in the nonrandomized studies received antibiotic prophylaxis until the 3-month VCUG. After that only those patients whose treatment had failed received further antibiotic prophylaxis. The patients in the randomized study received antibiotic prophylaxis 1 month post-treatment.
(iii) All UTI cases were successfully treated with antibiotics.
(iv) No case of ureteral dilation required intervention and most cases resolved spontaneously.
(v) Both cases of nausea/vomiting/abdominal pain were resolved.
Adverse Events (Continued)

Although vascular occlusion, ureteral obstruction, dysuria, hematuria/bleeding, urgency and urinary frequency have not been observed in any of the clinical studies, they are potential adverse events associated with subureteral injection procedures. Following approval, rare cases of postoperative dilation of the upper urinary tract with or without hydronephrosis leading to temporary placement of a ureteric stent have been reported.
References


• Data on file. Oceana Therapeutics (US), Inc.

• DEFLUX® [Package Insert]. Edison, NJ: Oceana Therapeutics (US), Inc; 2009.

References


References

References


Deflux® is a registered trademark and NASHA™ is a trademark of Q-Med AB.

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