

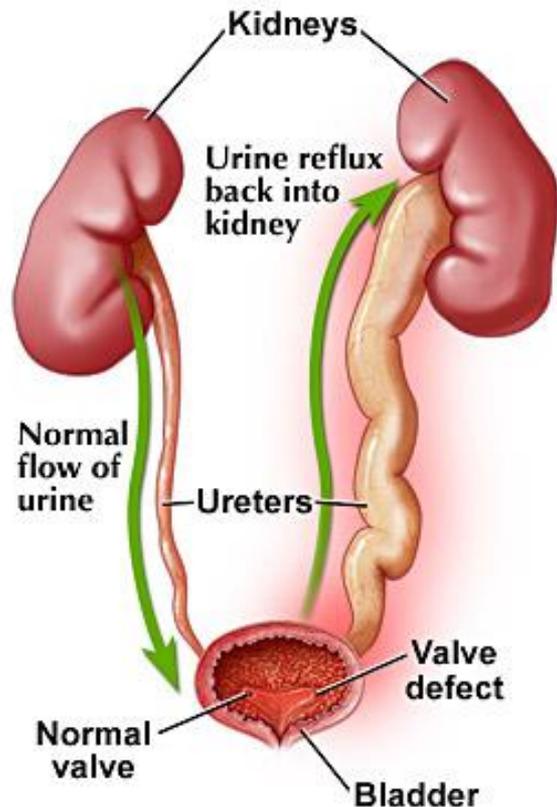
Deflux[®]

**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 kidneys¹
- Febrile urinary tract infection (UTI) is the defining symptom^{1,2}

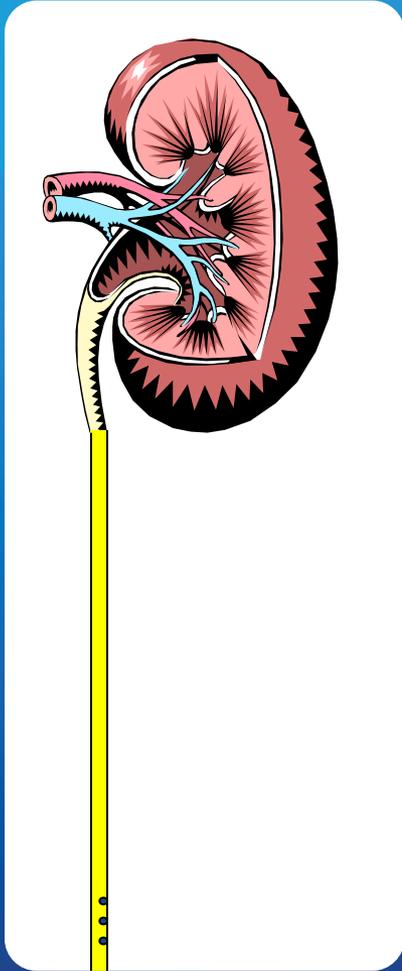
VUR prevalence

- 75%–80% of children diagnosed with VUR are girls¹
- Caucasians are 3x as likely to get VUR than African Americans²
- Most children diagnosed with VUR are <4 years of age³
- Affects approximately 1% of all children⁴
 - May be present in 14%-35% of children with asymptomatic UTIs³
- Recurrent febrile UTIs trigger screening and diagnosis⁴
- Found in 30%–40% of children with recurrent UTIs³
- Some congenital anomalies of the upper urinary tract are associated with increased risk of VUR^{5,6}

VUR and febrile UTI: A common clinical presentation

- Unexplained fever¹
- Frequent or urgent urination²
- Urine dribbling between urinating²
- Dysuria (pain on urination) ²
- Strong-smelling, cloudy, or bloody urine¹
- Abdominal, back, or side pain²

Clinical consequences of VUR

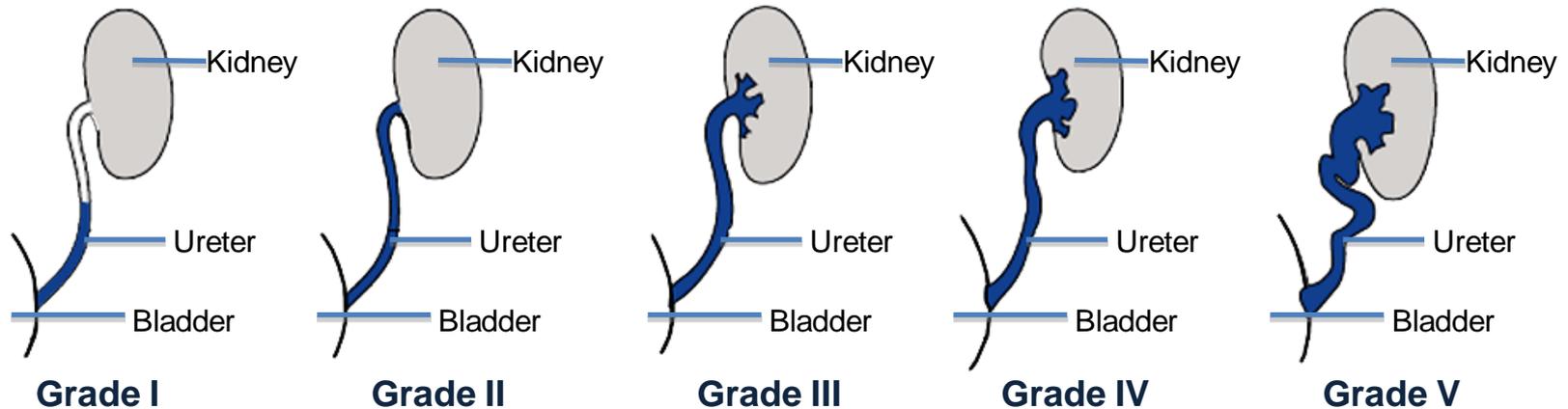


- Infected urine traveling back up to the kidneys increases the likelihood of having a febrile UTI¹
- There is a 70% overall incidence of upper UTI (acute pyelonephritis or kidney infection) in children with first febrile UTI²
- More than half (57%) of these children developed renal scars

¹Panaretto 1999; ²Lin 2003

VUR grades

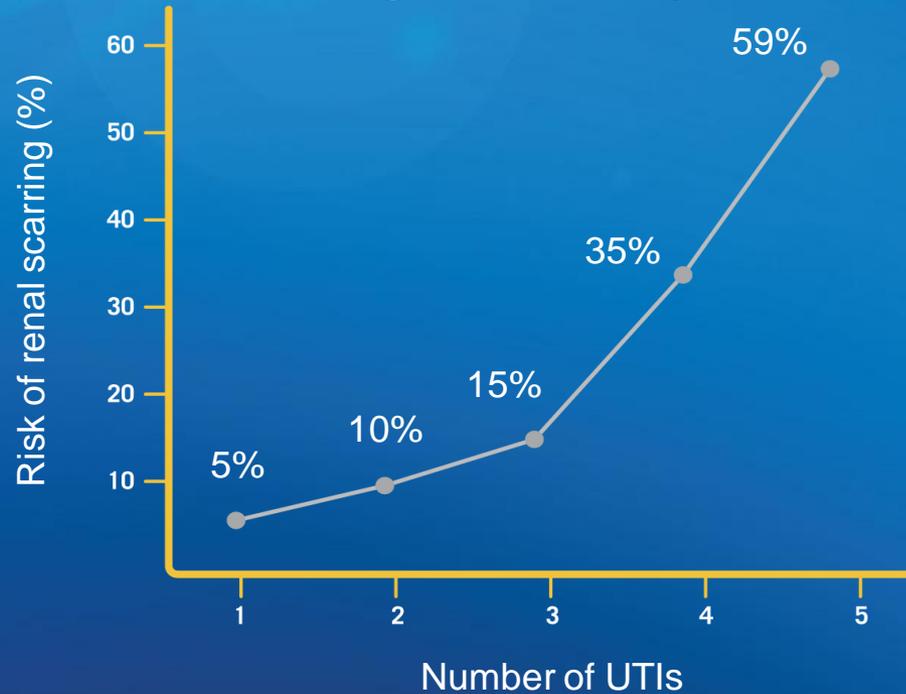
- The severity of VUR is based upon a grading system, reflecting the extent of reflux and ureter abnormality¹



- More severe VUR is associated with more severe renal scarring and increased complications^{2,3}

VUR and renal scarring

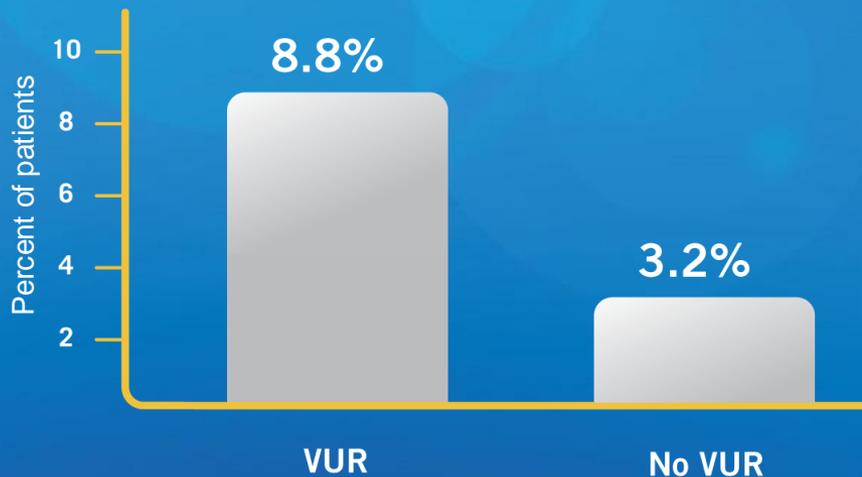
- Renal damage usually occurs within the first 3-5 years of life^{1,2}
 - In some cases renal damage can occur prenatally



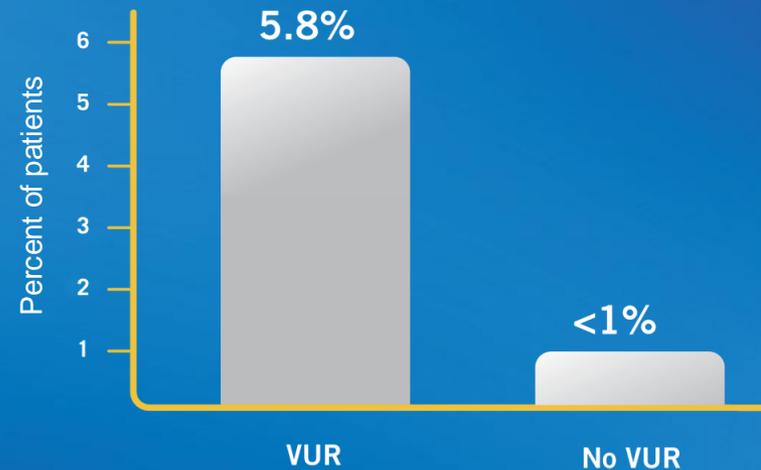
¹Sherbotie 1991; ²AAP 1999

Consequences of renal scarring and damage

Hypertension by 12 years¹⁻³



ESRD by 30 years of age¹⁻³



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 morbidity¹
- Eliminate ongoing health problems²
- Fewer voiding cysto-urethrogram (VCUG) examinations¹
- Without treatment, reflux persists for at least 4–5 years in at least half of all cases²
- Early management is recommended to reduce the incidence and severity of renal scarring³⁻⁵

Definition of success in VUR treatment

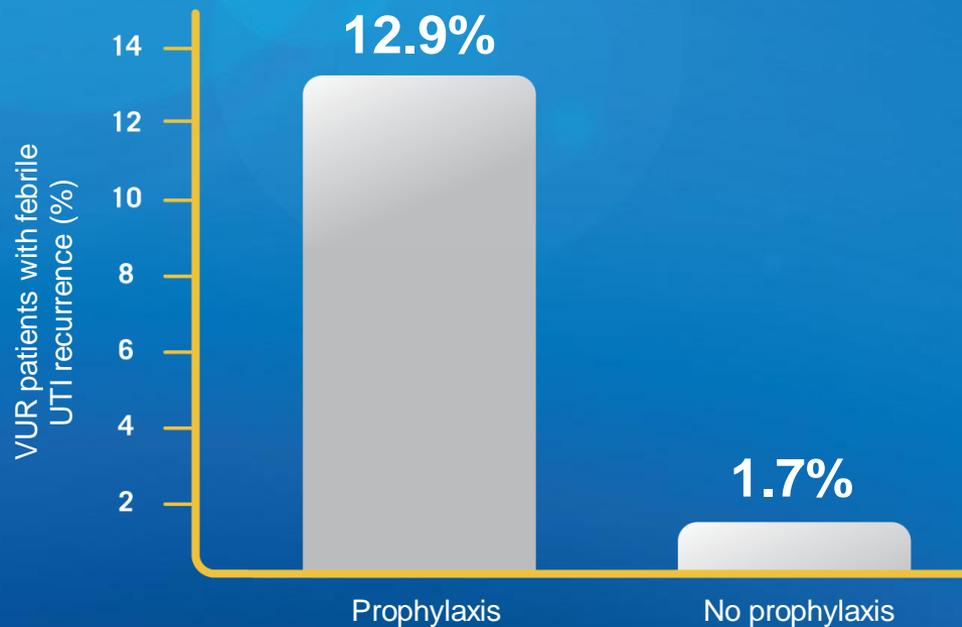
Aim of treatment

- Protect against febrile UTIs
- Prevent renal scarring

Definition of success

- The successful, durable prevention of febrile UTIs that could lead to renal scarring

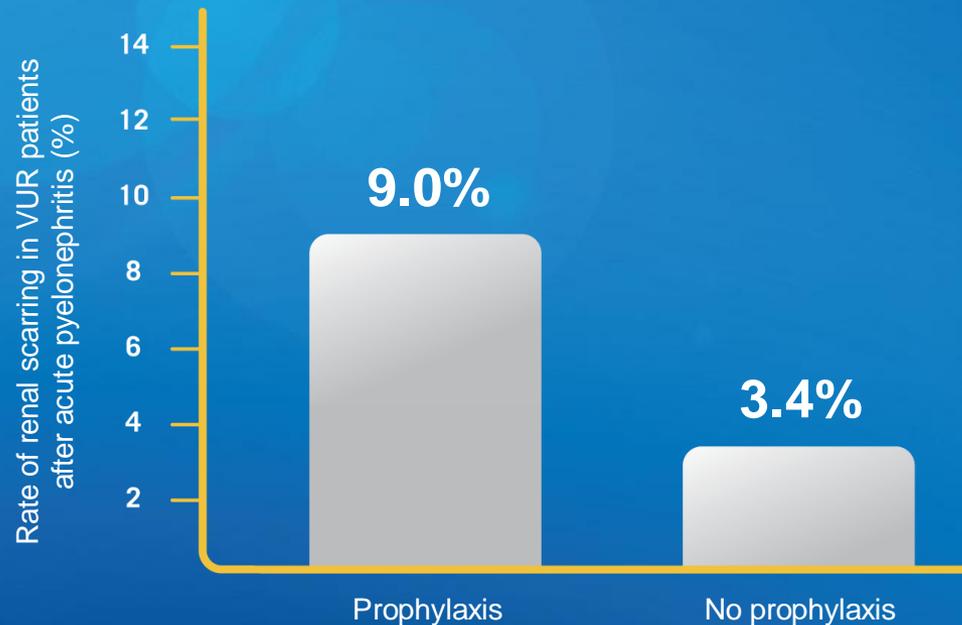
Rate of febrile UTIs higher with antibiotic prophylaxis than with no treatment at all



$P=0.0291$

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

Rate of renal scarring *higher* with antibiotic prophylaxis



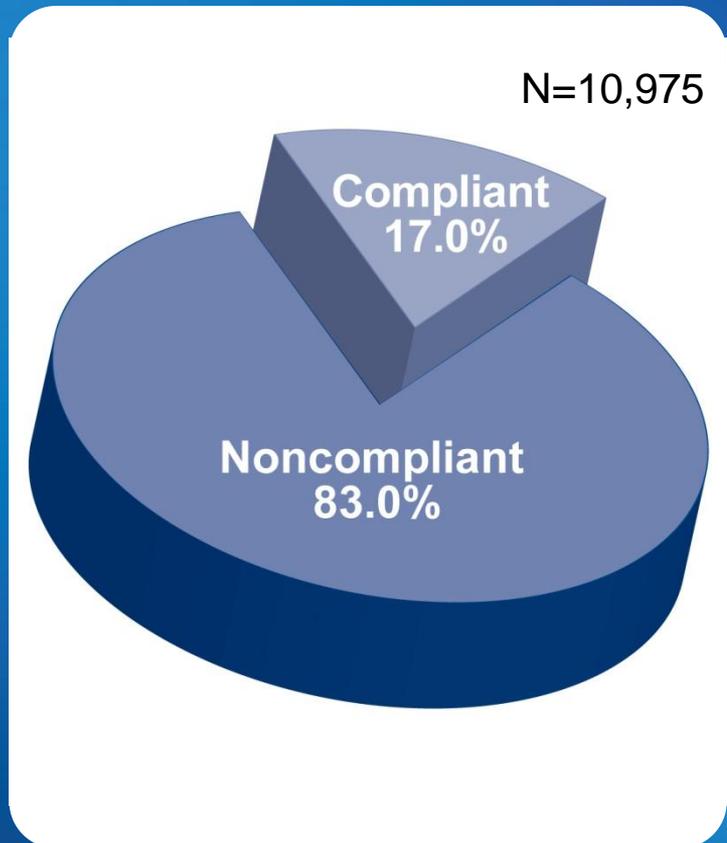
- Incidence of renal scarring increased approximately 3 fold in patients on antibiotic prophylaxis¹

¹Garin 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) values¹
- Susceptibility of resistance
 - According to the World Health Organization (WHO), patient noncompliance is a factor that encourages the spread of resistance²

Antibiotic Noncompliance¹



¹Hensle 2007b; ²WHO Antibiotic Fact Sheet

Deflux—Effective in low-to-moderate VUR

- Nearly 4x better reduction in VUR-associated UTIs than antibiotics¹
- Febrile UTI protection comparable to surgery²⁻⁶
- Durable protection against febrile UTIs⁷
- Excellent safety profile⁸

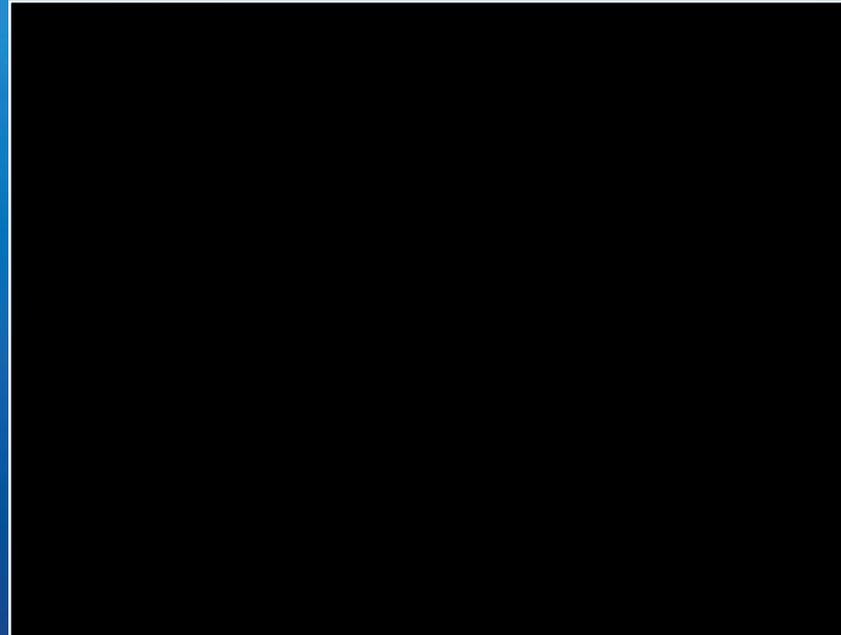
AUA Board of Directors 2007: *Deflux must be considered an option in the care of the pediatric patient with VUR.*⁹

¹Elder 2007, ²Elmore 2008, ³Stenberg 2007, ⁴Traxel 2009, ⁵Weiss 1992, ⁶Jodal 1992, ⁷Chi 2008, ⁸Deflux PI 2009, ⁹AUA Board of Directors 2007

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 ureter¹

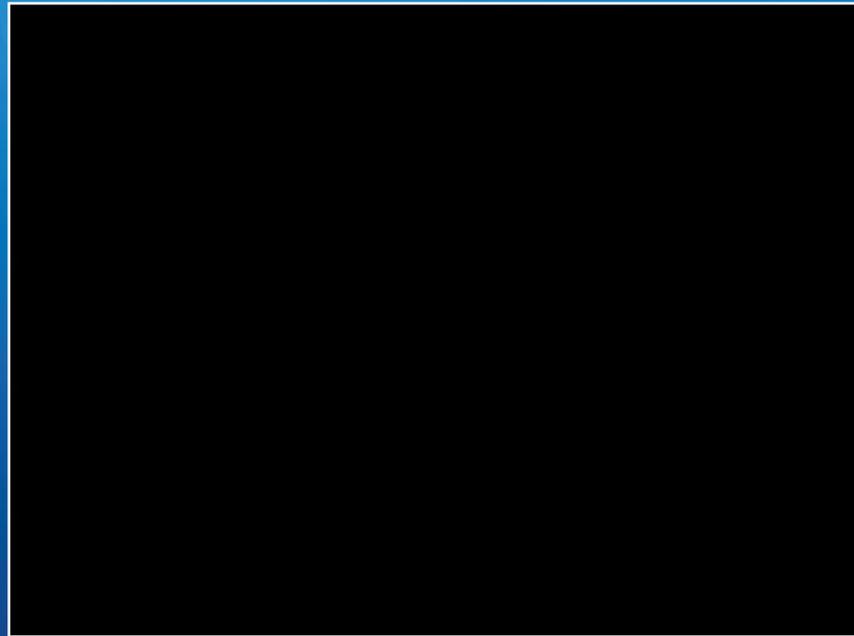
STING



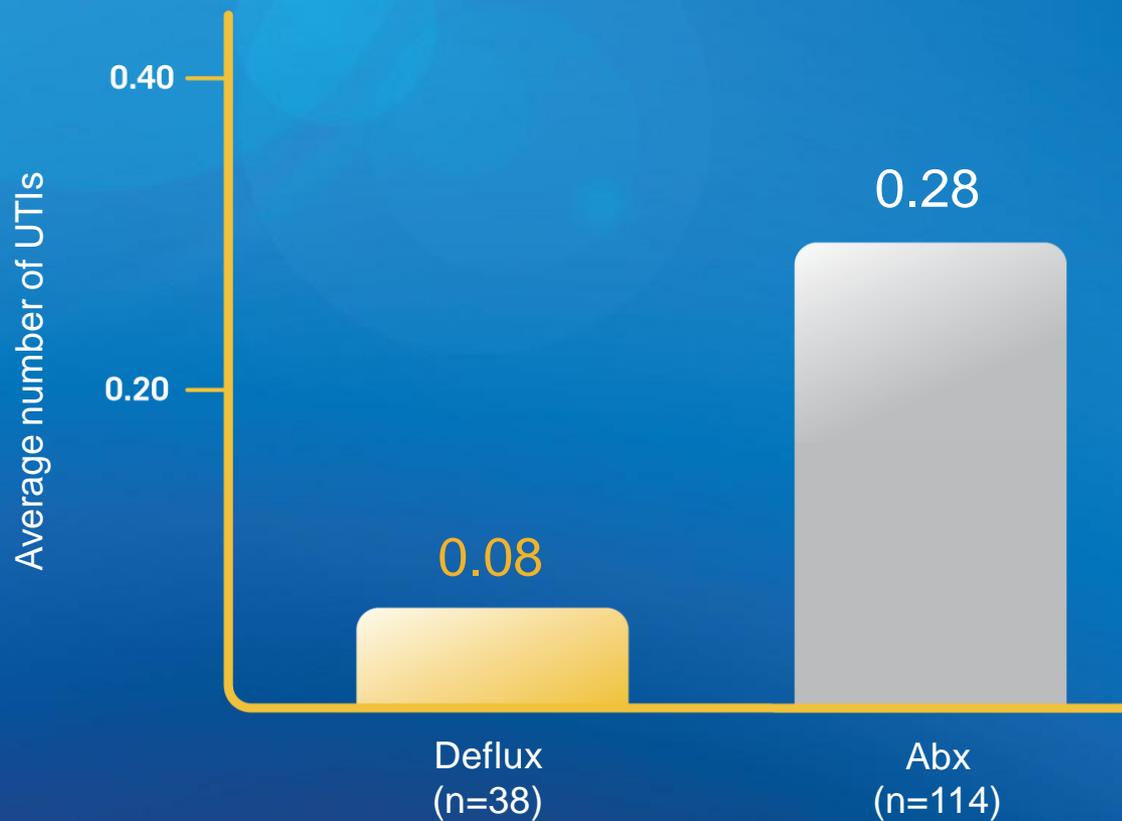
A minimally invasive endoscopic injection

- Deflux is injected in or around the ureteral opening to create a valve function and stop urine from flowing back up the ureter¹

HIT



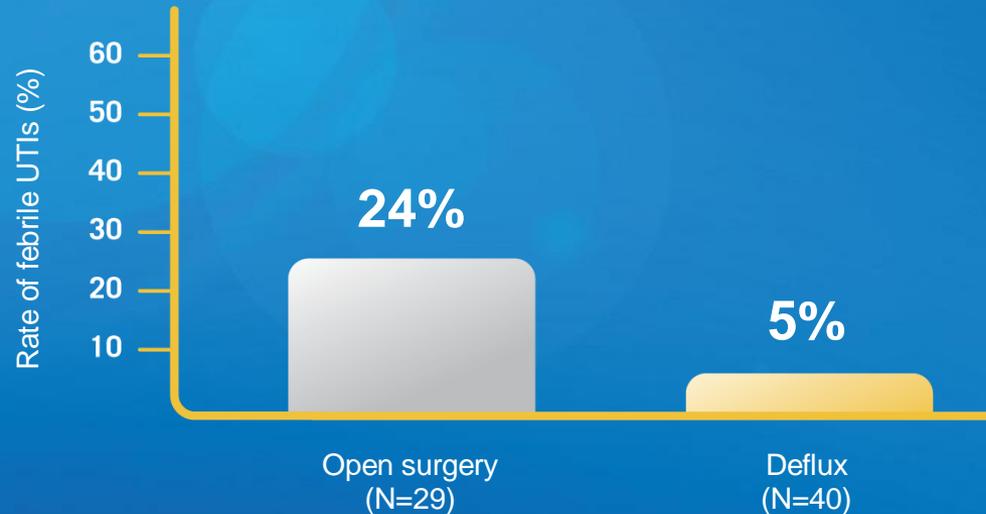
Nearly 4x fewer VUR-associated UTIs vs antibiotic prophylaxis



P=0.029

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

Overall febrile UTI protection comparable to surgery¹



P=0.02

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.¹

- The incidence of febrile UTIs with Deflux was lower than surgery in a single head-to-head, retrospective study¹

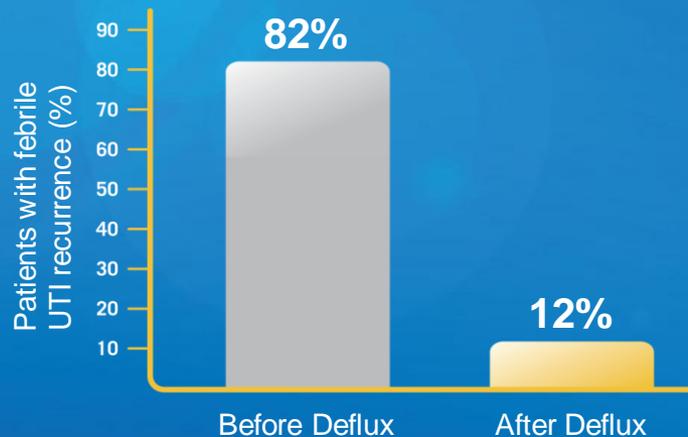
Efficacy proven in multiple studies

- 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}

¹Stenberg 2007, ²Traxel 2009, ³US Arm of International Reflux Study 1992, ⁴European Arm of the International Reflux Study 1992

Durable protection—up to 3 years¹

- Dramatic and durable reduction of febrile UTIs



- Deflux provided a >6-fold post-treatment reduction in the incidence of febrile UTI infections per year¹
- Additionally, the incidences of both febrile and afebrile UTIs were similar to those reported after surgery¹
- Long-term efficacy studies found Deflux delivered protection against febrile UTIs for up to 12 years²

¹Chi, 2008; ²Stenberg 2007

Durable protection—up to 12 years¹

- 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.

¹Stenberg 2007

Deflux[®]

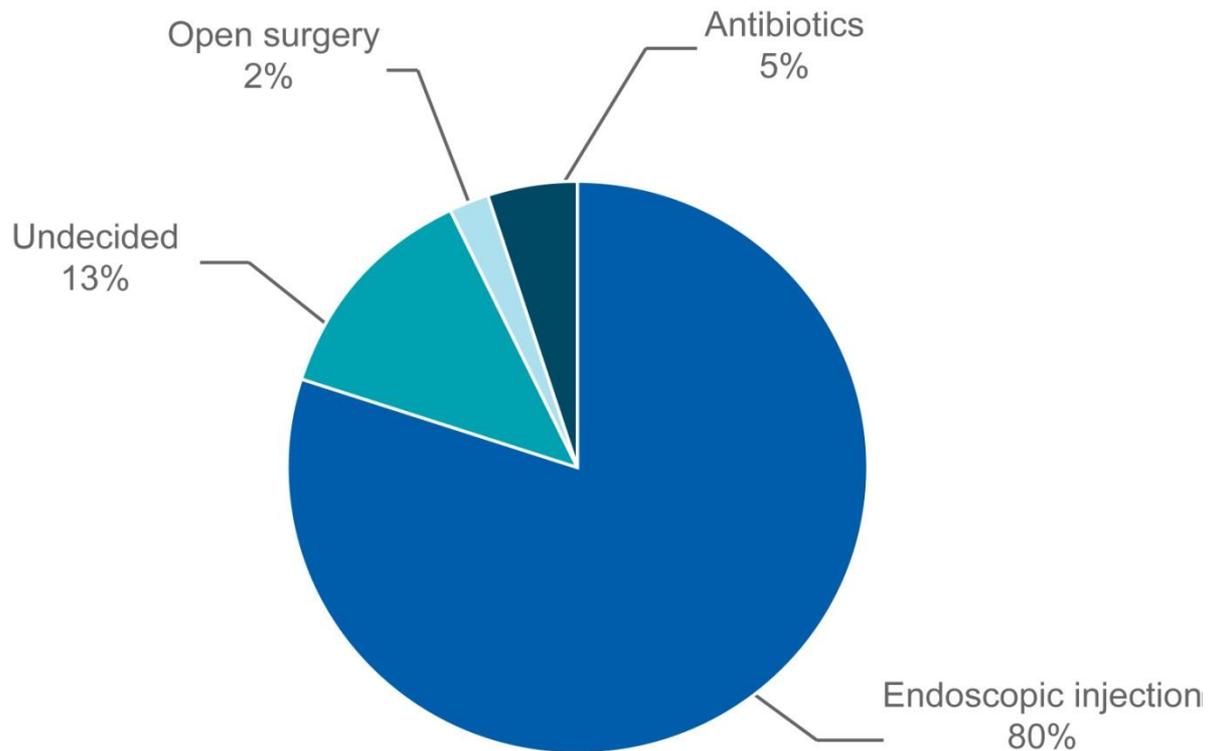
Proven safety

- Treat grade II-IV with more confidence

Low incidence of adverse events¹

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

Parent preferred¹



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

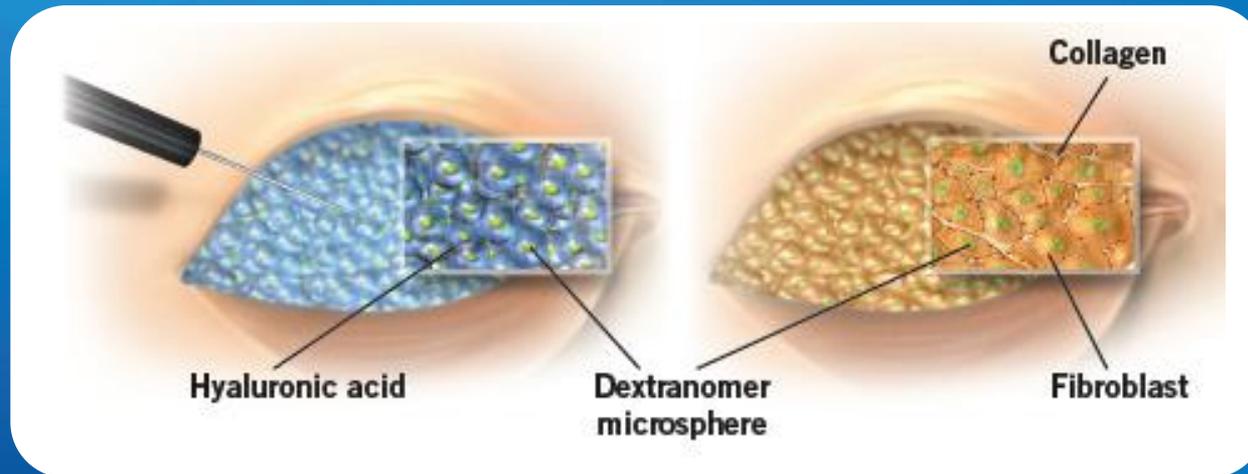
Additional Deflux Information

Deflux gel—A minimally invasive endoscopic procedure

- Outpatient procedure takes approximately 15 minutes¹
- Requires short-acting general anesthesia²
- Made from materials that have been in medical use for over a decade³
- More than 50,000 children have been treated³
- Dextranomer microspheres stay at the implant site^{1,4,5}
- Does not migrate from the injection site^{1,4,5}

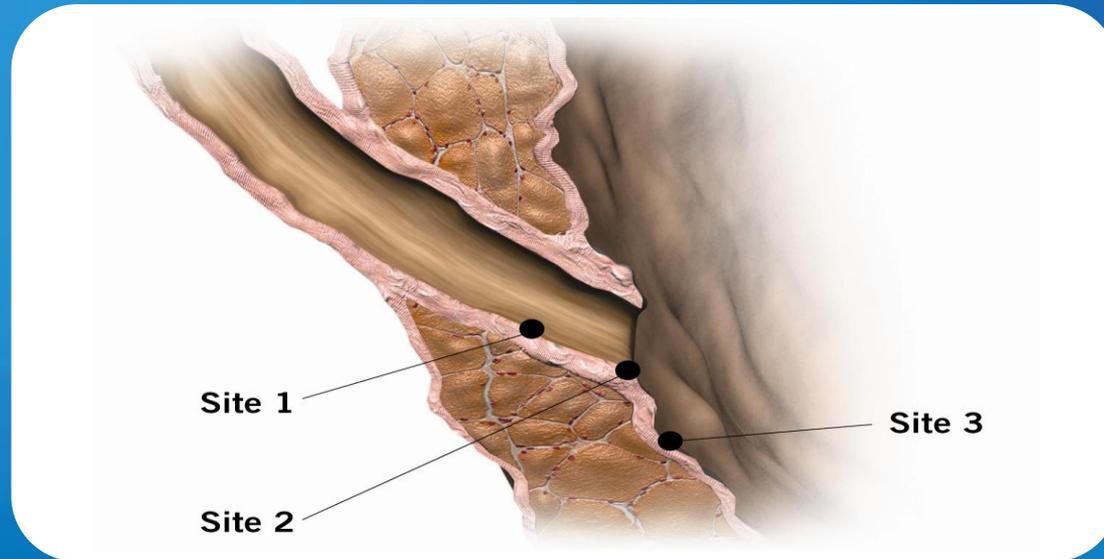
Made from biocompatible material

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



- Implant is stable, long term, remains in position, and does not disappear over time^{2,3}

Injection techniques: STING & HIT



- 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

Product information

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.

Deflux®

Product information

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.)

Adverse Event	Randomized (n=39 Deflux)	Nonrandomized (n=170)
Urinary tract infection (UTI) ⁽ⁱ⁾	6 (15.4%) ^(ii, iii)	13 (7.6%) ^(ii, iii)
Ureteral dilatation ^(iv)	1 (2.6%)	6 (3.5%)
Nausea/Vomiting/Abdominal pain ^(v)	0 (0%)	2 (1.2%)

- (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.

Product information

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.

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