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Approach to (febrile) Urinary Tract Infection

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Disclosure

- I have no conflict of interest related to the discussed topic
- I will not to endorse off-label use of medications or devices
- I will not use brand names for medications

- Medicine is full of beliefs – some true and some false, some harmful and some not

Craig JC & Williams GJ. Denominators do matter: it's a myth – urinary tract infection does not cause chronic kidney disease. Pediatrics 2011; 128: 984-985

Learning Objectives

At the conclusion of this activity, participants will be able to…

- Recognize incidence and risk factors for UTIs in various pediatric populations
- Develop an evidence-based approach to the diagnosis and treatment of UTIs in infants and children
- Understand the role of imaging of kidneys and urinary tract
- Appraise the controversies surrounding renal scarring and VUR
- Be aware of key outcomes of recent clinical trials examining antibiotic prophylaxis and surgery (recurrent infections, renal scarring, chronic kidney disease)
- Which patients to refer ?

References / Guidelines

- National Institute for Health and Clinical Excellence (NICE). Urinary tract infection in children.
  - https://www. nice.org.uk/Guidance/cg54
- American Academy of Pediatrics (AAP) guideline
  - Roberts KB et al. Urinary tract infection: clinical practice guideline for diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011;128:595-610
- Canadian Pediatric Society (CPS)
  - Robinson JL et al. Urinary tract infections in infants and children: diagnosis and management. Paediatr Child Health 2014;19:315-25
- European Association of Urology (EAU) and European Society for Pediatric Urology (ESPU) guideline
  - Stein R et al. Eur Urol 2015;67:546-58
- "Reaffirmation of AAP Pediatric Clinical Practice Guideline"
  - Pediatrics 2016; 138: e20163026
- Recent review of published guidelines
  - Okarska-Napierala M et al. Urinary tract infection in children: Diagnosis, treatment, imaging - Comparison of current guidelines. J Pediatr Urol 13: 567-573, 2017

Epidemiology of UTIs in children (1)

- Prevalence and incidence of pediatric UTI varies by age, gender, ethnicity, and circumcision status
- Incidence of UTI during 1st yr of life is 2.15 %
  - Similar in girls and boys (USA; UK)
- Prevalence of UTI
  - By age seven, 8% of girls and 2% of boys will have had at least one UTI
  - By age 16, 10% of girls and 3% of all boys will have experienced a UTI
- Recurrence risk for UTI is 10-30%
  - Most recurrences w/in 12 months of first infection

Schoen et al. Pediatrics 2000; Freedman AL J Urol 2005; Schmidt B. Urol Clin N Am 2015

Epidemiology of UTIs in children (2)

- 75-80 % of all UTIs are caused by *E. coli*
  - Remainder: other Enterobacteriaceae, *Pseudomonas* and *Proteus spp*., *Enterococcus faecalis*
  - *S. saprophyticus* [mainly cystitis in young women]
- Viral UTI is extremely rare (immunosuppressed patients)
  - Adenovirus, Polyoma virus (BK virus)

Schoen et al. Pediatrics 2000; Freedman AL. J Urol 2005;
Schmidt B, Copp HL. Urol Clin N Am 2015

What kind of specimen ? Bacterial count cut-off

- Clean catch mid-stream void, bladder catheterization or SPA for diagnosis
- Collection bag only as a method of exclusion
- Significant bacterial counts (cut-off)
  - Catheterization: $>10^4$ CFU/ml
  - Clean voided urine: $>10^5$ CFU/ml
  - SPA: any growth of bacteria

From Okarska-Napierala M et al. Urinary tract infection in children: Diagnosis, treatment, imaging - Comparison of current guidelines. J Pediatr Urol 13: 567-573, 2017

Table 2 Clinical signs and symptoms and laboratory findings in neonates and infants/young children with first UTI episode

Signs and symptoms	Neonates	Infants/young children	*P*
Fever[a]	48 (77%)	194 (83%)	0.42
Fever duration (days)	1.2±1.1	3.1±2.9	<0.0001
Fever duration under treatment (days)	0.7±0.9	1.2±1.3	0.0029
Maximum temperature (°C)	38.3±0.9	38.8±1.1	0.0011
Failure to thrive[a]	4 (7%)	34 (15%)	0.14
Poor feeding[a]	33 (48%)	65 (28%)	0.0003
Vomiting[a]	5 (8%)	25 (11%)	0.71
Diarrhea[a]	8 (13%)	4017 (23%)	0.55
Lethargy[a]	16 (26%)	14 (6%)	<0.0001
Grunting[a]	22 (36%)	11 (5%)	<0.0001
Jaundice[a]	11 (18%)	3 (1%)	<0.0001
WBC (1,000/mm^3 ± SD)	14.7±5.7	16.7±7.4	0.07
ESR (mm/h ± SD)	50±30	53±28	0.43
CRP (mg% ± SD)	4.6±3.7	5.0±4.3	0.46

[a]Number of patients with the sign or symptom mentioned of the 62 neonates and the 234 infants

Kanellopoulos et al. Pediatr Nephrol 2006; 21: 1131

Management of Pyelonephritis

- Use history and clinical presentation as guide for initial planning of management
- Empiric antibiotic treatment for PN
  - Duration at least 1 week
  - Oral: Cefixime, amoxicillin/clavulanate, ciprofloxacine, TMP/SMX (local resistance rates ?)
  - Intravenous: Gentamicin, ceftriaxone (50 mg/kg once daily); ampicillin (*Enterococcus sp*.)
- Regulate bowel movements (if constipation)
- Follow-up plan (recurrence of UTI ?)
- Parental education

Hospital admission for UTI ?

- Neonates (< 1 month)
- Infants and children
  - who do not tolerate oral meds/fluids and require IV hydration
  - severe illness and management in outpatient setting is impractical
- Consider Medical Day Hospital
  - for once-daily infusions, peripheral IV insertion etc.

Antibiotics for UTI / pyelonephritis – PO or intravenous ?

- No difference between PO versus IV (or IV, followed by PO) in western countries
- PO vs IV studied in ages >1 month
- Similar efficacy in clearing the organism
- Similar duration to defervescence (1-2 days)
- Similar reduction of inflammatory parameters (CRP, ESR)

Imaging: objectives

- Identify structural causes leading to recurrent UTI that may or may not require surgical correction
- Identify congenital or acquired anomalies leading to impaired kidney function
  - "CAKUT" = congenital anomalies of kidneys and urinary tract"

The yield of <u>clinically relevant</u> pathological results is low *in children with first-time or recurrent UTI*

Risk factors predicting CAKUT in children with a first-time UTI

- Scientific data are conflicting
  - Male gender, young age, positive family history, fever of 38 C, elevated CRP, high neutrophil ratio, pathogens other than *E. coli*, and positive blood culture …. all reported to predict VUR in children with UTI
  - Study from 2016 of 300 children with first UTI found *no correlation of lab data with presence of VUR*

From Okarska-Napierala M et al. J Pediatr Urol 13: 567-573, 2017; Yılmaz S et al. Nephron 2016;132:175-80

Abdominal ultrasound

- Anatomical information about the urinary tract and kidneys
- Renal pelvis and urinary tract dilatation and anatomical bladder abnormalities
  - Hydro(uretero)nephrosis, thick walled bladder, ureterocele, bladder diverticula
  - Presence of stones and/or obstruction
- Positional anomalies
  - Ectopic kidneys, duplication
- Renal parenchymal anomalies
  - Renal parenchymal echogenicity, cortico-medullary differentiation; cysts (number and sizes)
- NOTE: ***No reliable information on scarring, dynamic (VUR) or functional (GFR) abnormalities by conventional abdominal US***

Ultrasonography in 2 y/o girl with fever

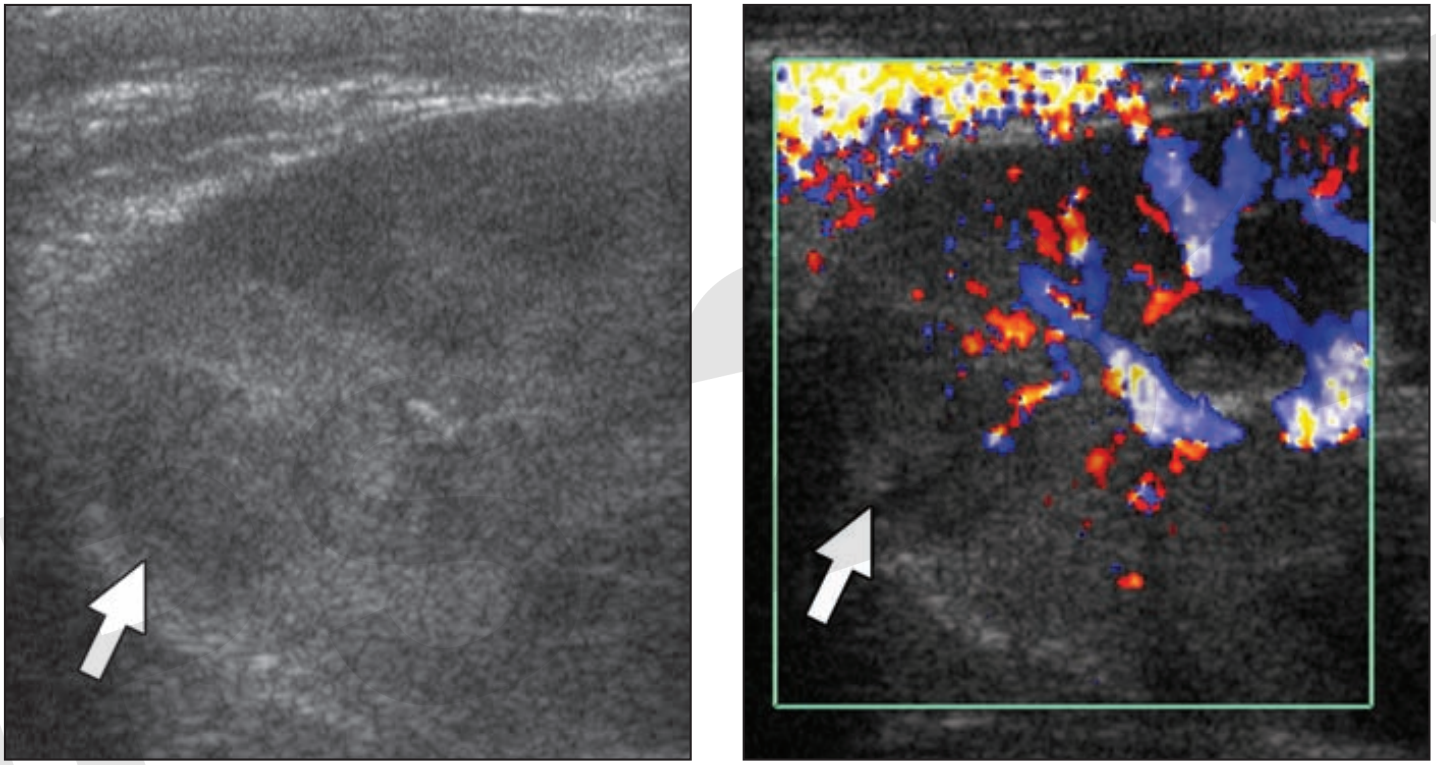


Fig. 3—2-year-old girl with fever.
A and **B,** Gray-scale (**A**) and color Doppler (**B**) ultrasound images show round, hypoechoic, poorly perfused abnormality (*arrow*) in upper pole of right kidney, consistent with acute pyelonephritis.

Lim, R. Am. J. Roentgenol. 2009;192:1197-1208

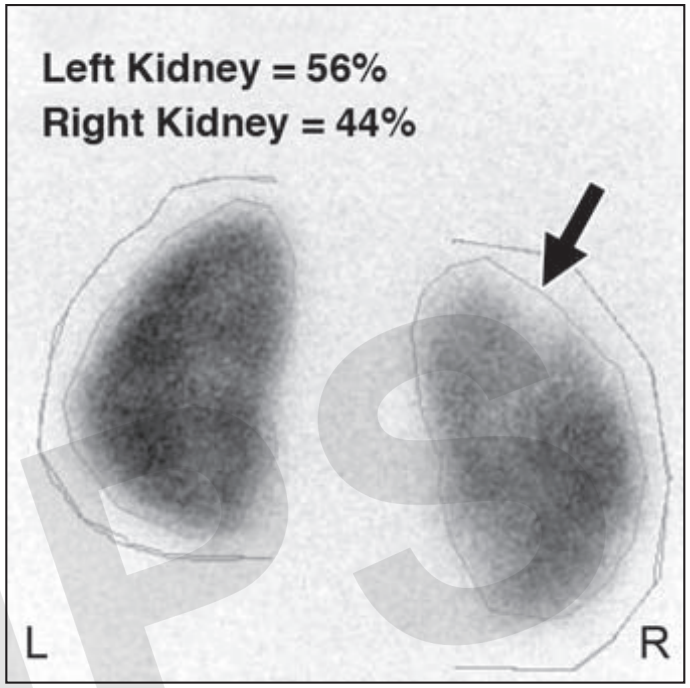
Cortical scintigraphy (DMSA renal scan)

- DMSA = ^{99m}Tc-dimercaptosuccinic acid
- Highly sensitive for acute lesions (*pyelonephritis*) and late sequelae (*parenchymal scarring*)
- Assess split renal **function**

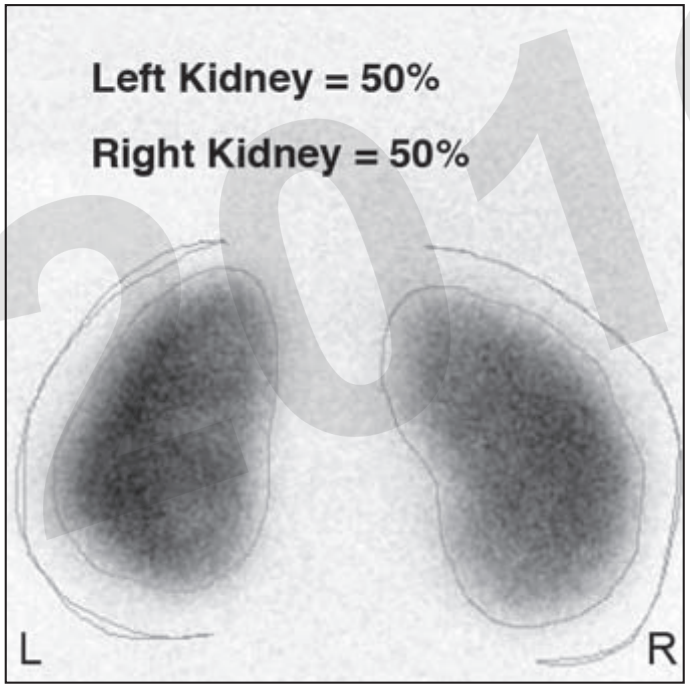
Cortical scintigraphy (DMSA renal scan)

- DMSA image represents *functional renal cortical mass*
  - Decreased function ("photopenic" lesions) in inflamed parenchyma
  - Acute lesions 3-6 months to resolve scintigraphically
  - "Gold standard" to investigate for renal cortical scarring
  - Does not distinguish spontaneously resolving abnormalities from persistent lesions
  - Detects other causes of cortical defects (e.g. renal cysts, masses)
  - Congenital dysplastic kidney can appear similar to acquired renal scarring

DMSA scan in 2 y/o girl with febrile UTI



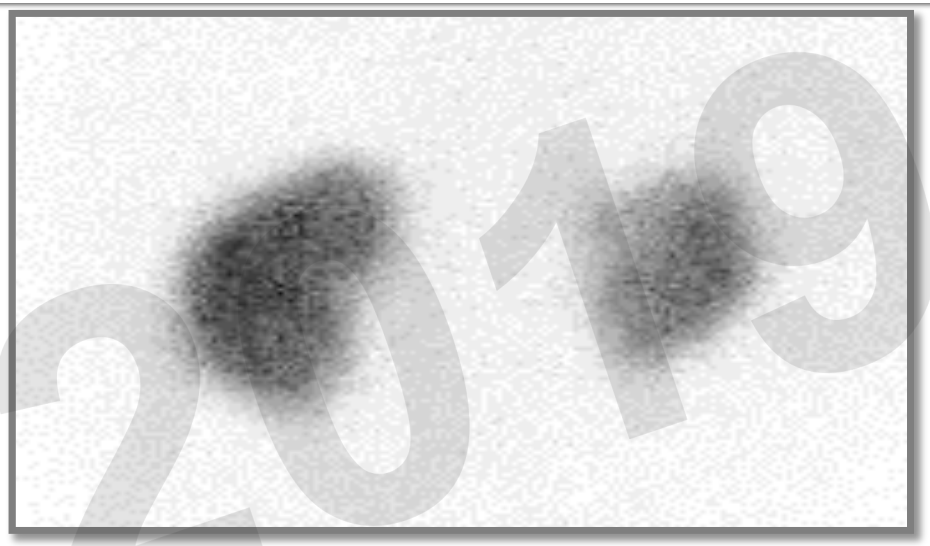
During acute infection

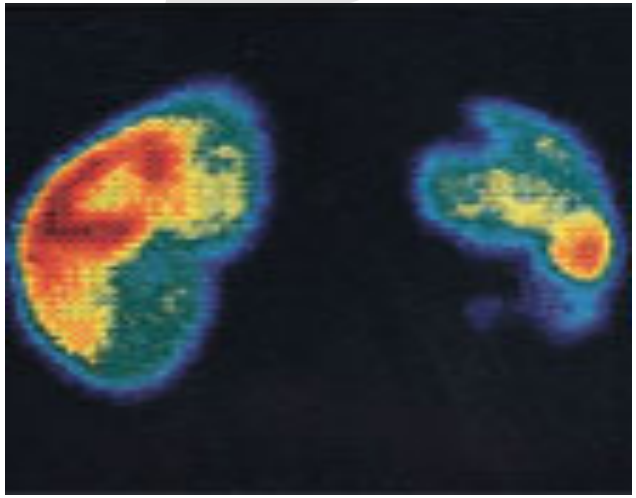


8 month follow-up

Lim, R. Am. J. Roentgenol. 2009;192:1197-1208

Renal Scars



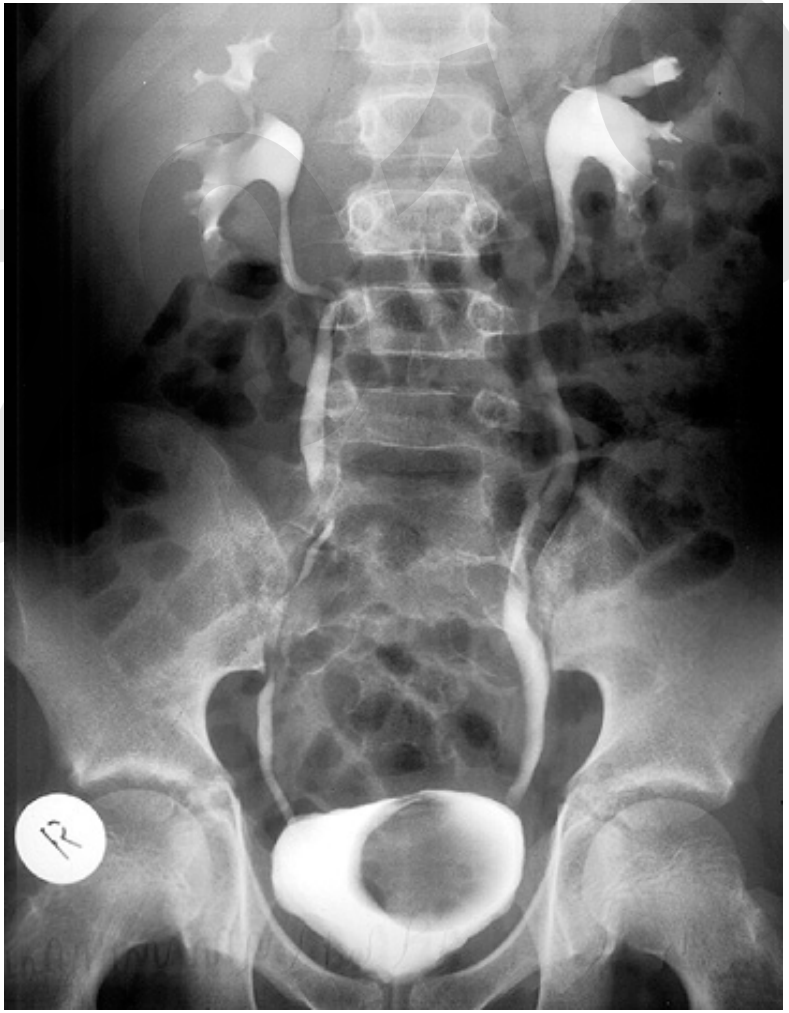


Voiding cysto-urethrography (VCUG)

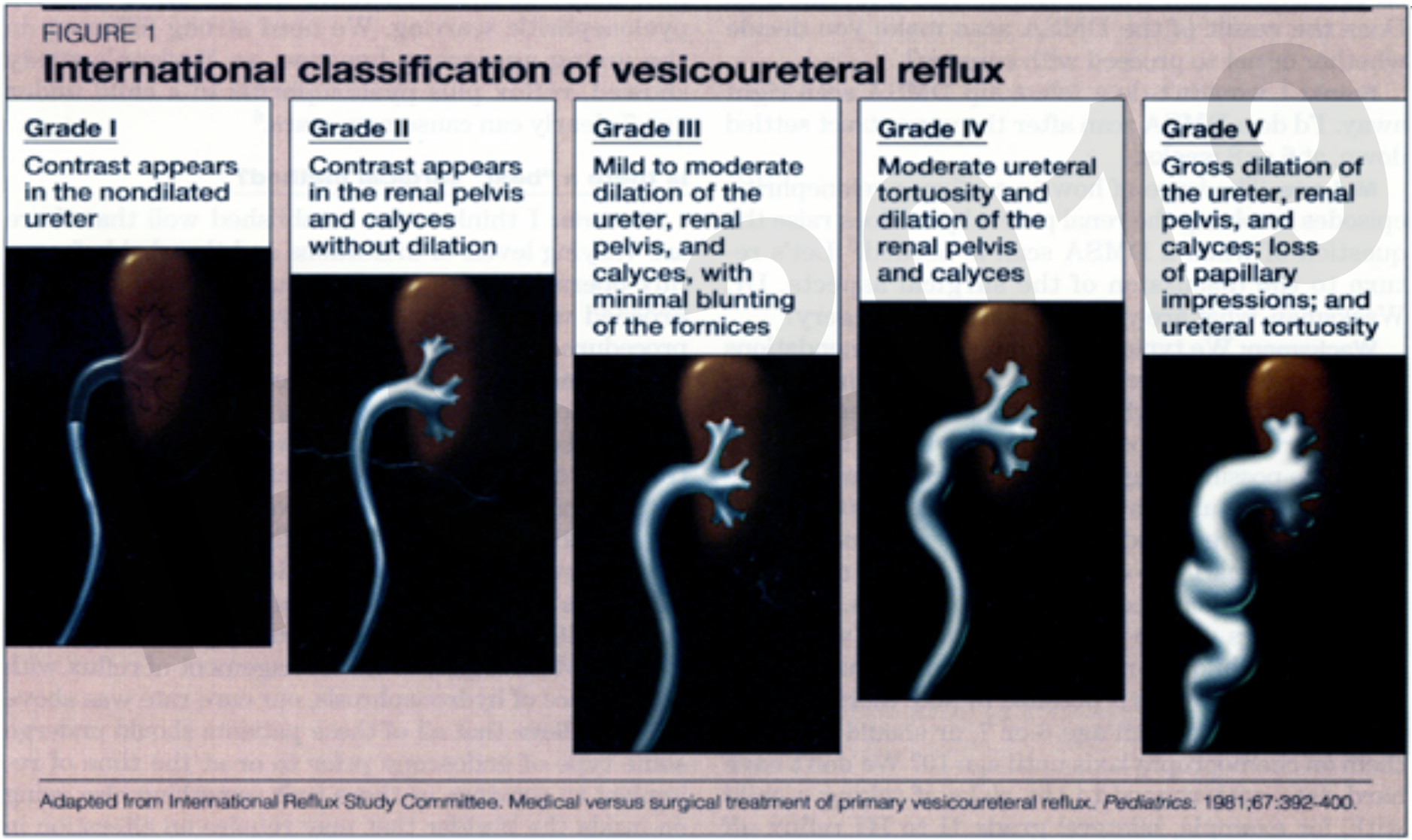
- "Classical" imaging modality for children with UTI
- Demonstrates bladder wall abnormalities (bladder diverticula, ureteroceles)
- Urethral abnormalities (posterior urethral valves [PUV])
- Vesico-ureteral reflux (VUR)

Voiding cystourethrogram (VCUG)

("Micturating cystourethrogram" , MCUG)

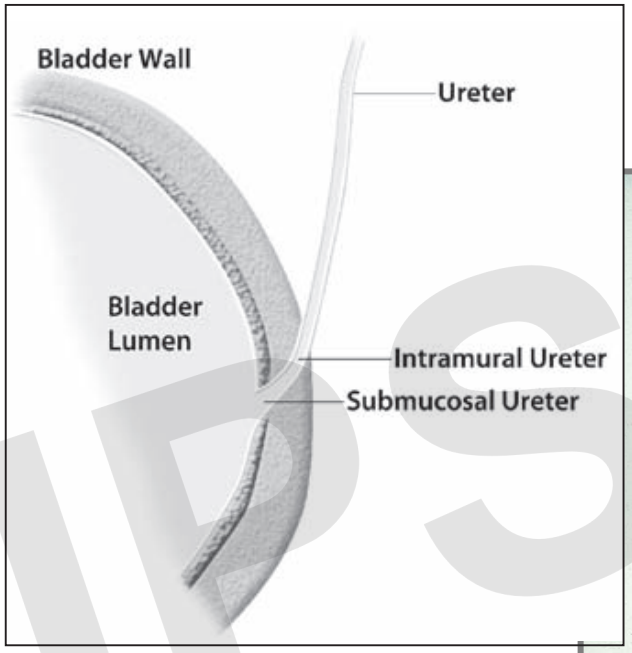


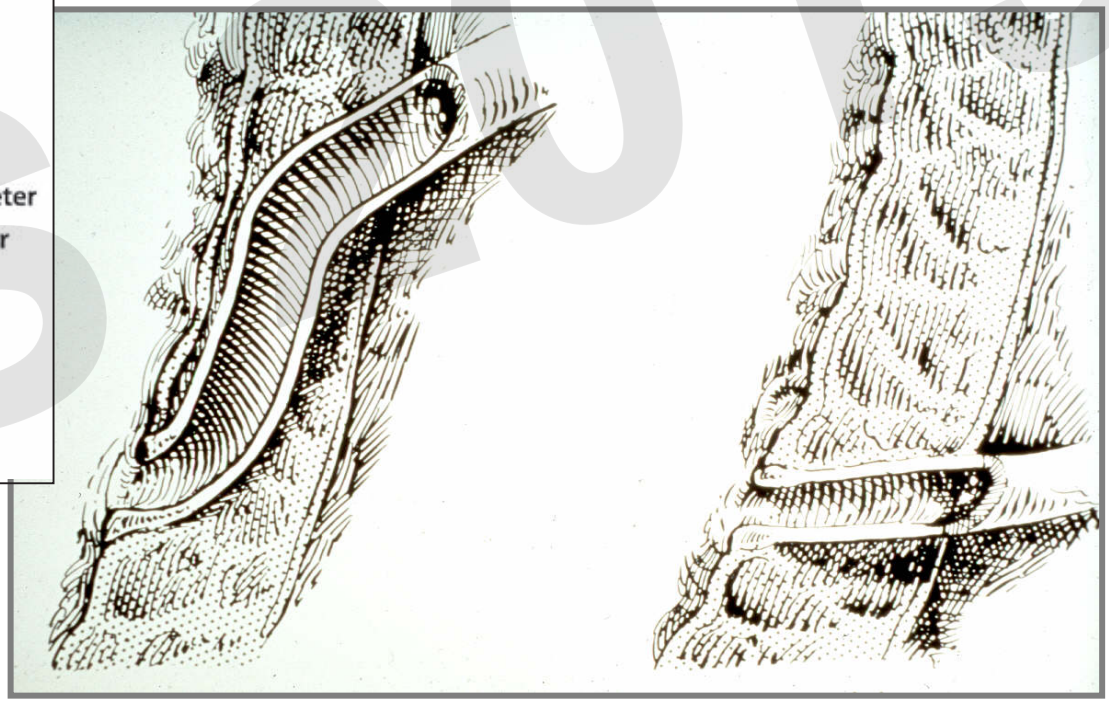
International Classification of VUR



Primary VUR

Lim, R. Am. J. Roentgenol. 2009





Campbell's Urology

What do we do when VUR is detected ?

Vesicoureteral reflux (VUR)

- VUR is the abnormal retrograde flow of urine from the bladder into the upper urinary tract
- It affects 1-2 % of all children (Craig JC et al. Pediatrics 2000)
- Only 20% of children with VUR develop UTI (Hains DS, Schwaderer AL. Pathogens 2016)
- Up to 50 % of children with recurrent UTI have VUR
- High-grade VUR (4-5) is generally seen by US (dilated ureters) and usually associated with renal abnormalities

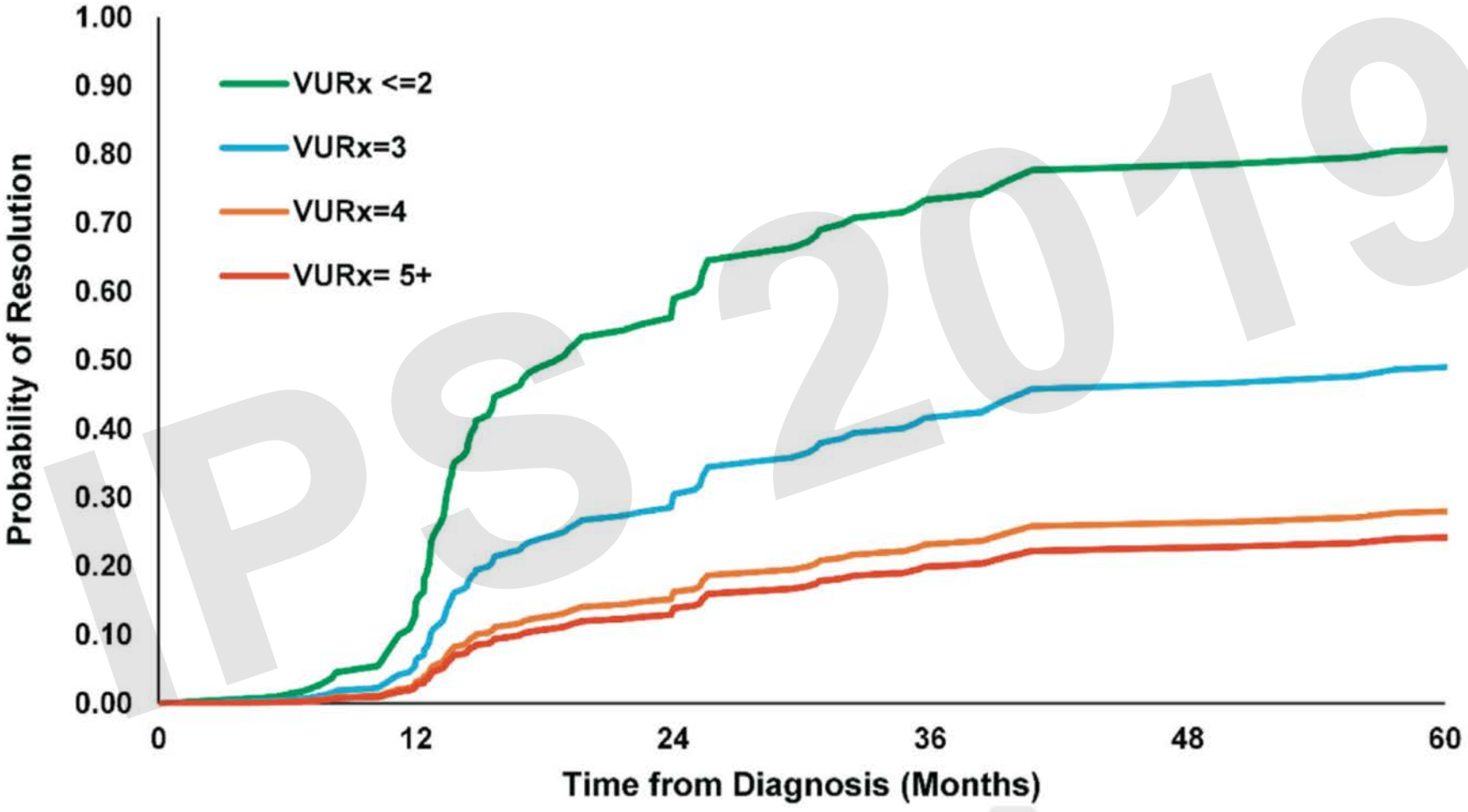
Vesicoureteral reflux (VUR)

- Diagnostic and management of VUR is controversial
  - Which children should be evaluated for reflux ?
  - Who should undergo treatment ?
  - What are the treatment goals ?
  - What are the treatment options ?

Management options of children with recurrent UTI and vesico-ureteral reflux

- Observation
  - With or without (continuous) antibiotic prophylaxis
- Surgical correction
  - Endoscopic sub ureteric injection
  - Open, minimally invasive or robotic ureteral reimplantation

Spontaneous Resolution of VUR



Garcia-Roig M et al. J Urol 2016, Fig. 1

Case scenario

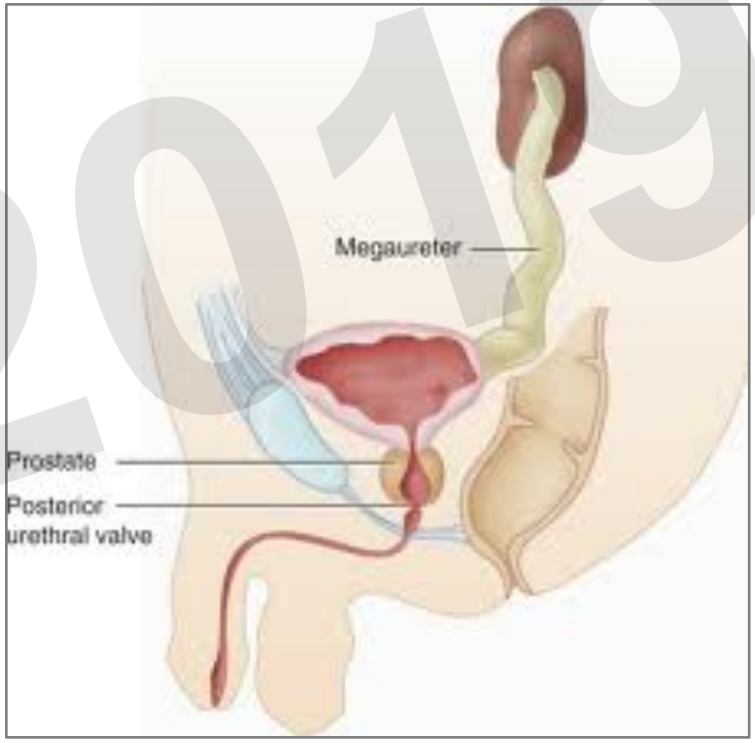
- 11 y/o boy, presents with low grade fever over 3 days; complains of dysuria and flank pain
  - Reportedly healthy, but previous episodes of dysuria that resolved spontaneously
  - Urination "normal"
  - Less energetic than peers

Case scenario

- 11 y/o boy, presents with low grade fever over 3 days; complains of dysuria and flank pain
  - Reportedly healthy, but previous episodes of dysuria that resolved spontaneously
  - Urination "normal"
  - Less energetic than peers
- Physical exam
  - Short stature (3rd %ile), BP 135/85 mmHg (>95% for age & height percentiles)
  - No apparent malformation, except some leg bowing
  - Urogenital exam: moist underwear
  - Upon questioning: frequent voiding, dribbling, primary enuresis

Posterior Urethral Valve

From: nationwidechildrens.org



mdconsult.com

Contacted irregular shaped bladder
Elongated & dilated posterior urethra.
Prominent bladder neck

Teaching points

- Importance of **detailed history and exam**
- When to think of and rule out "complicated" UTI (urine dribbling in boys; spinal dysraphism; neurological abnormalities, particularly of the lower limbs)
- **Management** aimed at preservation of residual kidney function
- **Collaborative approach** with (pediatric) urologist or surgeon in patients with structural (lower UT) abnormalities

Challenges to traditional concepts (2)

- VUR is not a prerequisite for renal damage (Jakobsson B et al. Arch Dis Child 1994)
- Newer guidelines challenge traditional strategies of antibiotic therapy and surgery
- Recognized need for randomized trials using untreated controls (Bollgren I. Acta Paediatr Suppl 1999; Winberg J Infection 1999, Suppl. 1)
- New strategy focusing on renal development and function, not VUR (Jodal U, Lindberg U. Acta Paediatr Suppl 1999)

TABLE 2 **Diagnostic Findings for 300 Children ≤2 Years of Age With a First Documented Febrile UTI**

	n (%)		
	Abnormal	**Normal**	**Total**
Ultrasonography[a]	38 (13)	262 (87)	300
Acute DMSA scanning[b]	161 (54)	139 (46)	300
Micturating cystourethrography[c]	66 (22)	234 (78)	300
DMSA scanning at 12 mo[d]	45 (15)	255 (85)	300

c) VUR grades
I – III n = 62
IV n = 3
V n = 1

Montini G et al. ***Value of imagining studies after a first febrile UTI in young children****. Data from the Italian renal infection study 1. Pediatrics. 2009;123:e239-246*

Important recent clinical trials

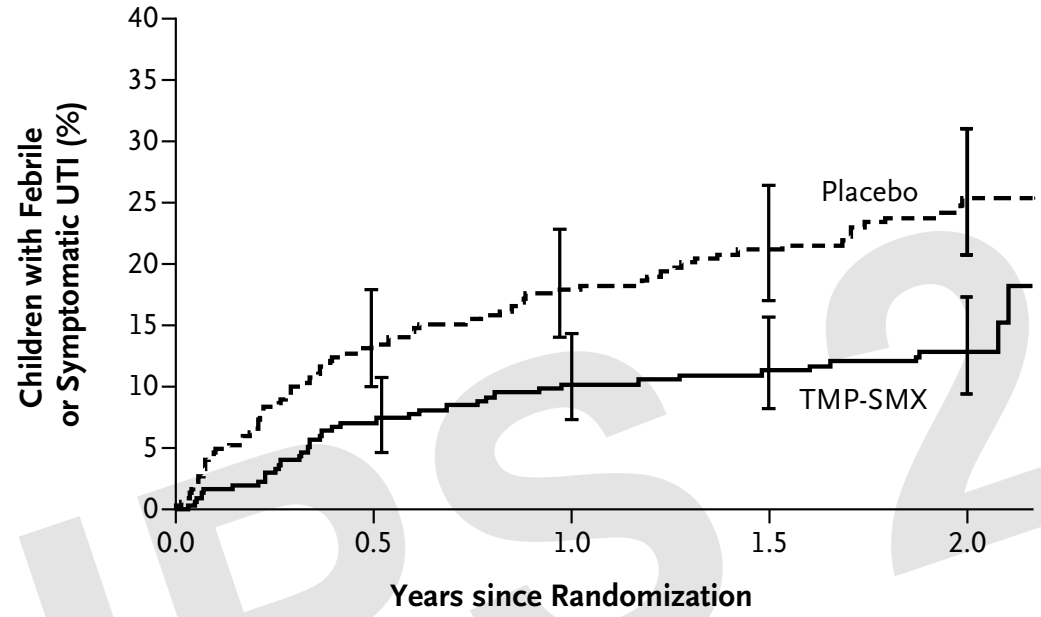
- RIVUR Trial
  - American National Institutes of Health-sponsored randomized, placebo-controlled trial
  - "**R**andomized **I**ntervention for children with **V**esico **U**reteral **R**eflux"
- Swedish Reflux Trial
  - Randomized, controlled trial in children with dilating VUR (Brandström P et al. J Urol 2010; J Pediatr Urol 2011)

RIVUR Trial

- Primary study endpoint
  - Development of recurrent UTI
- Secondary endpoints
  - Development of (new) renal scarring
  - Antimicrobial resistance
  - Treatment failure

The RIVUR Trial Investigators. N Engl J Med 2014

RIVUR Trial – Primary endpoint (time to first recurrent UTI)



No. at Risk					
TMP-SMX	302	270	252	244	128
Placebo	305	253	234	214	98

Figure 2. Time to First Recurrent Febrile or Symptomatic UTI.

Shown are Kaplan–Meier estimates of the cumulative percentage of children who had a recurrent febrile or symptomatic UTI according to study group. Fewer children assigned to TMP-SMX prophylaxis had a UTI than children assigned to placebo (P<0.001 by log-rank test). I bars indicate 95% confidence intervals.

Children with symptomatic UTI (cumulative)

The RIVUR Trial Investigators. N Engl J Med 2014

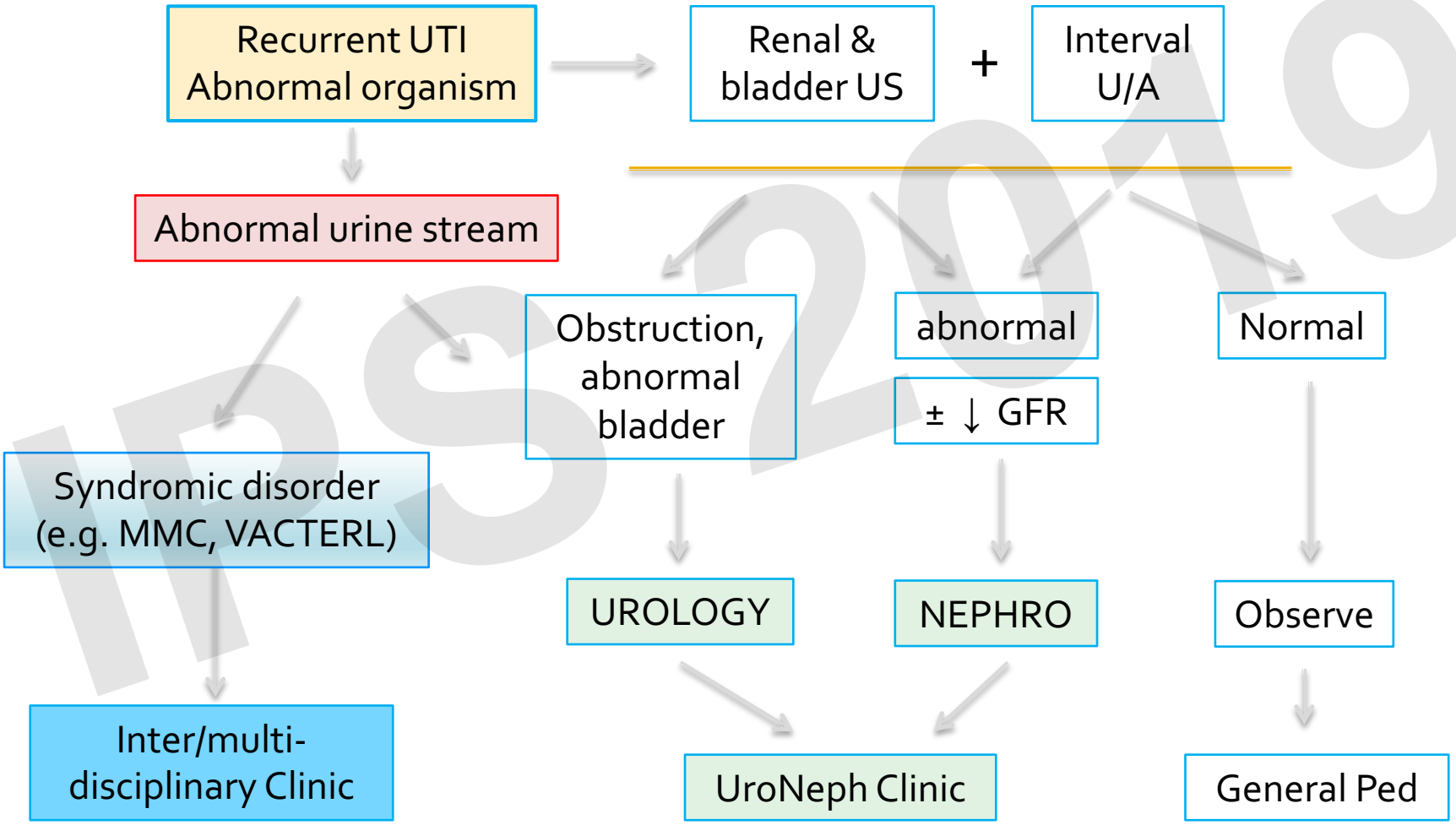
RIVUR Trial – Summary of results

- Largest published study
  - 607 patients, median age 12 months
  - Girls 92 %, boys 8 % (> 1/3 circumcised)
- TMP/SMX prophylaxis reduced risk of recurrence of UTI, but *failed to prevent renal scarring*
- Antibiotic prophylaxis increased resistance of bacterial isolates at first UTI recurrence three-fold

Swedish Reflux Trial – Conclusions

- Girls > 1 year of age with dilating VUR (grade 3 and 4) benefitted from antibiotic prophylaxis and endoscopic injection
- Prophylaxis reduced risk of recurrent UTI and of new renal parenchymal damage in girls compared with surveillance only
- Antibiotic prophylaxis, but not endoscopic injection, reduced risk of new renal parenchymal damage
- New damage occurred only in kidneys drained by ureters with VUR grade 3 or 4

Referral – whom, when and where ?



Conclusions (1)

- About 2 % of boys and girls will develop a UTI during the first year of life; by 7 years, the prevalence of UTI is 4-times greater in girls than boys
- A minority of children with febrile UTI has a dilating VUR; only 20% of children with VUR will develop UTI
- Non-dilating VUR is rarely associated with parenchymal damage of the kidney and often resolves
- Renal scars can be present without UTI

Conclusions (2)

- Antibiotic prophylaxis or endoscopic injection reduce the incidence of febrile UTIs in young children
- Antibiotic prophylaxis in children with dilating VUR and early antibiotic treatment may reduce the development of new scars
- VCUG should be limited to children with dilated urinary tract by ultrasound, including suspected PUV
- Decisions on medical and surgical interventions in children with recurrent UTI should be individualized and respect age, social factors, and parental preference

Merci !

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