Current Management of Vesicoureteral Reflux

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This is ISN

Bridging Gaps

Global Outreach

Humanitarian

Worldwide

Awareness Raising

Education

Collaborating

Scientific

Collegial
The International Society of Nephrology (ISN) is a global not-for-profit society dedicated to improving kidney care and reducing the incidence and impact of kidney disease worldwide.

Through its global network and programs, ISN brings together the developing and developed worlds in a collaborative effort in fighting and treating kidney disease on a global scale.

- Established in 1960
- 9,000 professional members from 129 countries
- Collaborating with over 70 national and regional societies around the world

Visit us at www.theisn.org
ISN – The Scientific Society

Meetings

ISN World Congress of Nephrology is the leading biennial educational event in international nephrology
Next Congress: Sustainability & Diversity - March 13-17, 2015, Cape Town
www.wcn2015.org

ISN Nexus Symposia bridge the gap between basic research and clinical practice
Next Symposia:
• Hypertension and the Kidney - September 25-28, 2014, Brisbane, Australia
www.isnnexus.org

ISN Forefronts Symposia focus on emerging and groundbreaking research
Next Symposia:
• Genetic Basis of Renal Disease - September 11-14, 2014, Boston (MA), USA
www.isnforefronts.org

Advancing Nephrology around the World
ISN – The Scientific Society

ISN Education

ISN Education is a comprehensive collection of educational resources with a database of articles, case studies, guidelines, presentations, and images. www.theisn.org/education

Publications

Kidney International (KI), ISN’s official journal, is one of the most cited in nephrology and widely regarded as the world’s premier journal on the development and consequences of kidney disease. www.nature.com/ki

Nature Reviews Nephrology, an official publication of ISN, is a peer-reviewed journal for nephrologists and affiliated healthcare professionals. www.nature.com/nrneph
ISN – The Outreach Society

ISN Capacity Building Programs

The Sister Renal Centers Program (SRC) links renal centers in emerging countries with supporting centers of excellence in the developed world. With this educational support and guidance, self-sufficient renal centers are created in emerging countries.

Application Deadline: September 15

www.theisn.org/src

The Fellowship Program helps educate physicians coming from emerging economies, giving them hands-on training opportunities unavailable in their home nations.

Application Deadlines: December 15 and June 15

www.theisn.org/fellowship

The Continuing Medical Education Program (CME) brings essential teaching and training to some 14,000 doctors in over 40 settings every year. CME meetings take place in the developing world, where expert speakers from the developing and the developed world share their knowledge and experience in clinical care and research.

Applications: Throughout the year

www.theisn.org/cme
The Educational Ambassadors Program sends experts to developing renal centers for one to four weeks to provide hands-on training or help develop new services, community-based research or screening programs.

Application Deadlines for Institutions: May 1 and October 1

www.theisn.org/eap

The Clinical Research and Prevention Program aims in part to educate people in developing countries about the importance of having healthy kidneys. Many of the projects funded through the program set up screening and education to raise awareness and improve the understanding of kidney disease.

Application Deadlines: April 1 and October 1

www.theisn.org/rp

These and other ISN programs work together to vastly improve standards of renal care in less developed countries. ISN members contribute to and lend support to the educational and humanitarian work needed to further advance kidney care worldwide.
World Kidney Day (WKD), a joint initiative of the ISN and the International Federation of Kidney Foundations (IFKF) informs and educates health policy-makers, medical staff, and the general public worldwide about chronic kidney disease to drive the earliest possible diagnosis and optimal treatment.

www.worldkidneyday.org

The recently launched Saving Young Lives Project offers realistic, collaborative, sustainable and better care opportunities for low-resource health settings to look after AKI patients. A partnership between International Society of Nephrology (ISN), International Pediatric Nephrology Association (IPNA), International Society for Peritoneal Dialysis (ISPD) and Sustainable Kidney Care Foundation (SKCF).

ISN – The Outreach Society

ISN Awareness Building Initiative

ISN Better Care Program
ISN Programs CME Supported Speakers

ALANEPE (Asociación Latinoamericana de Nefrología Pediatrica) and ACONEPES (Asociación Colombiana de Nefrología Pediatrica)

• Dr. Ron Shapiro (Colombia)
• Dr. Carlos Estrada (Colombia)

*The Travel expenses of the ISN Speakers for this meeting are supported by an unrestricted educational grant of F. Hoffmann-La Roche*.
Connect with Us

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International Society of Nephrology

Facebook
www.facebook.com/isnkidney
Topics To Cover

• New AAP guidelines regarding infants with febrile UTI
• Vesicoureteral reflux
• Antibiotic prophylaxis for VUR
• Surgical management of VUR
2011 AAP Guidelines
Evaluation of the Infant with Febrile UTI

• First revision of AAP guidelines since 1999
• Takes into account newer data regarding diagnosis and treatment of UTI, imaging evaluation, and use of antibiotics
• Panel comprised of pediatricians, infectious disease specialists, radiologists, and 1 pediatric urologist
2011 AAP Guidelines
Evaluation of the Infant with Febrile UTI

• Seven Recommendations
  – **Diagnosis of UTI**
    1) If clinical suspicion of UTI, obtain urine prior to antibiotics via suprapubic tap or catheter
    2) In reasonably well infants, assess risk of UTI based on risk factors (gender, race, age, temp, fever duration, and other source) - low risk infant can be considered for observation
    3) UTI diagnosis requires both a urinalysis AND a positive culture (>50,000 cfu)
2011 AAP Guidelines
Evaluation of the Infant with Febrile UTI

• Seven Recommendations
  – UTI treatment
    4) Oral or parenteral treatment with appropriate antibiotics for 7-14 days; take local sensitivity patterns into account if possible; adjust treatment according to the sensitivity profile of the isolated organism
2011 AAP Guidelines
Evaluation of the Infant with Febrile UTI

• Seven Recommendations
  – Post-UTI evaluation
    5) Infants with febrile UTI should have a renal and bladder ultrasound
    6) VCUG should be deferred until the SECOND febrile UTI, unless the ultrasound is abnormal
  – Post-UTI management
    7) Parents should be instructed to seek prompt evaluation for future febrile illnesses
2011 AAP Guidelines
Evaluation of the Infant with Febrile UTI

• Rationale for the change in recommendation of VCUG timing after febrile UTI
  – Most infants will not have recurrent UTI
  – Most infants do not have severe anatomic abnormalities amenable to surgical correction
  – Identification of VUR in infants is of unproven clinical benefit
  – Most infants with VUR have low-grade VUR, which will resolve spontaneously in most cases
  – Even if VUR is identified, antibiotic prophylaxis has not been shown to be effective in preventing VUR recurrence
Topics To Cover

• New AAP guidelines regarding infants with febrile UTI
• **Vesicoureteral reflux**
• Antibiotic prophylaxis for VUR
• Surgical management of VUR
VUR

• Retrograde urine flow from bladder into ureter

• Incidence of 1-2% in general population (???)
  – 15-70% among children with UTI
  – 15-25% among children with antenatal hydronephrosis
  – 25-40% among siblings of VUR patients
  – 66% among offspring of VUR patients

• Associated with recurrent UTIs
VUR

- Grades I - V
Voiding cystourethrogram (VCUG)
Radionuclide cystogram (RNC)
VUR
Genetic associations and VUR

- VATER-VACTERL association
- Townes-Brock syndrome
- Cat eye syndrome
- Casamassima – Morton - Nance syndrome
- Renal coloboma syndrome
- Branchio-oto-renal syndrome
- Frasier syndrome
Primary versus **Secondary** VUR

- Obstructive uropathy
  - Posterior urethral valves
- Neurogenic bladder dysfunction
- Non-neurogenic bladder dysfunction
- Bladder exstrophy and other major anomalies
The Traditional Paradigm:

– VUR gives bacteria in the bladder access to the upper tracts (cystitis $\rightarrow$ pyelonephritis)
– Pyelonephritis in the young kidney results in inflammation and scarring, with permanent loss of renal function
– Repeated episodes result in a small, scarred kidney
– Prophylactic antibiotics can reduce risk of infection and sequellae
Reflux Nephropathy

• Cause of progressive renal failure, to end-stage renal disease (ESRD)
• Decrease in proportion of ESRD cases attributable to VUR since 1960’s (???)
  – Other studies have shown no change
• Changes due to effectiveness of treatment? changes in diagnostic methods? Definitions?
DMSA Scintigraphy

• Superior to IVP in documenting renal scars in several studies
• Good correlation with histopathology in animal data
• Considered “gold standard” for identifying renal parenchymal changes
DMSA Scintigraphy
VUR, UTI and Renal Scarring

However:

- Renal scars may occur without VUR
  - Scars occur after pyelonephritis with or without VUR
- “Renal scars” in 30-35% of children with prenatal VUR (no UTI); ? Parenchymal dysplasia?
- The associations between VUR, infection, scarring, and congenital renal dysplasia are still not well defined
VUR Natural History

FIGURE 1A. Cumulative Resolution Rates for Boys with Uni- or Bilateral VUR and Girls with Unilateral VUR

FIGURE 1B. Cumulative Resolution Rates Girls with Bilateral VUR
### FIGURE 2A. Resolution Nomograms for Boys with Uni- or Bilateral VUR and Girls with Unilateral VUR

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### FIGURE 2B. Resolution Nomograms Girls with Bilateral VUR

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</table>
The VUR Resolution Rate Calculator is a tool that can be used to predict a child’s chance of resolving reflux at a given year after diagnosis.

Calculate your resolution rate...

1. Child category
   - Select one

2. Clinical presentation
   - Select one

3. Age at presentation
   - Select one

4. Ureter anatomy
   - Select one

5. Time to resolution (years)
   - Select one

6. Grade of VUR
   - Select one

Submit  Cancel
VUR & Voiding Dysfunction

- Treatment of dysfunctional voiding may help VUR resolution

6.5 year old girl with several febrile UTIs. Reported to be a “holder” with occasional incontinence. RNC: Gr 3 left VUR

Started on timed, double-void regimen. RNC repeated 7 months after first.
Topics To Cover

• New AAP guidelines regarding infants with febrile UTI
• Vesicoureteral reflux
• **Antibiotic prophylaxis for VUR**
• Surgical management of VUR
Therapy for VUR

• Medical management
  – Low-dose antibiotic prophylaxis for prevention of recurrent UTI
  – Stems largely from uncontrolled series in 1970’s
  – Based on several assumptions
    • Most VUR, especially Grade I-III, resolves
    • Renal damage is rare in the absence of infection
    • Long-term antimicrobial prophylaxis is safe
    • Long-term antimicrobial prophylaxis is effective
Therapy for VUR

• Medical management
  – **Amoxicillin**
    • Agent of choice for newborns
  – **Trimethoprim/sulfamethoxazole**
    • Widely used, well-tolerated, convenient
  – **Nitrofurantoin**
    • Low rate of resistance
    • Liquid form expensive, tastes terrible
  – **Cephalosporin**
    • Higher rate of resistance?
Therapy for VUR – Controversy

• Recent publications have challenged conventional wisdom regarding efficacy of antibiotic prophylaxis
• Some practitioners are reconsidering medical management of VUR

_BUT_

Lets not be too hasty!!
Recent studies evaluating antimicrobial prophylaxis for VUR/UTI

<table>
<thead>
<tr>
<th>Study</th>
<th>Blinded?</th>
<th>Ages</th>
<th>VUR Grade</th>
<th>UTI Dx</th>
<th>F/U time</th>
<th>ABX</th>
<th>No ABX</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garin (Pediatrics, 2006)</td>
<td>No</td>
<td>1 mo–18 yr</td>
<td>I-III</td>
<td>Cath or voided</td>
<td>12 mo</td>
<td>13/55 (24%)</td>
<td>12/58 (21%)</td>
<td>1.1 (0.6-2.3)</td>
</tr>
<tr>
<td>Roussey (J Urol, 2008)</td>
<td>No</td>
<td>1-36 mo</td>
<td>I-III</td>
<td>Bag</td>
<td>18 mo</td>
<td>18/103 (17%)</td>
<td>32/122 (26%)</td>
<td>0.7 (0.4-1.1)</td>
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<tr>
<td>Pennesi (Pediatrics, 2008)</td>
<td>No</td>
<td>0-30 mo</td>
<td>II-IV</td>
<td>Bag</td>
<td>24 mo</td>
<td>18/50 (36%)</td>
<td>15/50 (30%)</td>
<td>1.2 (0.7-2.1)</td>
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<tr>
<td>Montini (Pediatrics, 2008)</td>
<td>No</td>
<td>2-84 mo</td>
<td>I-III</td>
<td>Bag</td>
<td>12 mo</td>
<td>10/82 (12%)</td>
<td>9/46 (20%)</td>
<td>0.62 (0.3-1.4)</td>
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<tr>
<td>Craig (NEJM, 2009)</td>
<td>Yes</td>
<td>0-18 yr</td>
<td>0-V</td>
<td>Cath or voided</td>
<td>12 mo</td>
<td>36/288 (13%)</td>
<td>55/288 (19%)</td>
<td>0.65 (0.4-.96)</td>
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<tr>
<td>Swedish Trial (Brandstrom J Urol 2010)</td>
<td>No</td>
<td>12-24 mos</td>
<td>III-IV</td>
<td>Bag</td>
<td>24 mos</td>
<td>8/43 (19%) (girls only)</td>
<td>24/42 (57%) (girls only)</td>
<td>0.33 (0.17-0.64)</td>
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</tbody>
</table>
Randomized Intervention for children with Vesico-Ureteral Reflux (RIVUR)

- Randomized trial of trimethoprim-sulfamethoxazole vs. placebo
- Boys and girls, age 6 wks-5 years
- First or second febrile/symptomatic UTI
- Grade I-IV VUR on VCUG

- 2 year follow-up
  - *Primary outcome*: Recurrent UTI
  - *Secondary outcome*: Renal scarring, antimicrobial resistance
The RIVUR Study

Antimicrobial Prophylaxis for Children with Vesicoureteral Reflux

The RIVUR Trial Investigators

- 607 children
- Prophylaxis – 13% recurrent UTI
- Placebo – 24% recurrent UTI
- No difference in renal scarring (12 v. 10%)
- E. Coli resistance – 63% in prophy v. 19% in placebo
Return to the 2011 AAP Guidelines

- Seven Recommendations
  - Post-UTI evaluation
    6) VCUG should be deferred until the SECOND febrile UTI, unless the ultrasound is abnormal

The CPG assumes that prophylaxis is NOT effective – but the final word on prophylaxis is not yet written

My feeling is that there is probably a subset in whom prophylaxis is beneficial
VUR and antibiotics – Take Home Message

• The jury is still out!
• We still recommend prophylaxis for most patients with VUR

Especially:
• Febrile UTI
• High grade VUR
• Renal scarring
• Dysfunctional elimination
Topics To Cover

• New AAP guidelines regarding infants with febrile UTI
• Vesicoureteral reflux
• Antibiotic prophylaxis for VUR
• **Surgical management of VUR**
Therapy - Surgery

- Anti-reflux Surgery - generally reserved for patients who:
  - Have breakthrough UTI’s
  - Have VUR that does not resolve after years of surveillance
  - Are unable/unwilling to comply with prophylaxis
  - Have high-grade VUR that is unlikely to resolve spontaneously
Therapy - Surgery

• Surgical management – Open surgery
  • Reconstruct the ureterovesical junction with anti-reflux mechanism
  • Intravesical versus extravesical approach
• 1-2 day hospital stay
• 95%+ success rate (resolution of VUR)
Surgical Therapy - Open

Create a submucosal tunnel
Therapy - Surgery

• Surgical management – Endoscopic treatment
  • Injection of bulking agent at uretero-vesical junction
    – Dextranomer/hyaluronic acid copolymer
    – Marketed as Deflux®
    – Approved by FDA in 2001
    – Macroplastique (Not used in U.S.)
  • Outpatient procedure
  • No incision
Therapy - Surgery

• Surgical management – Endoscopic treatment
  • Less effective in higher-grade VUR
  • Overall, 75-90% success rate
  • May need more than one procedure to achieve success injection
  • Risk of recurrent VUR despite initial success
    – May reduce long-term success rate to ~50%
Therapy - Surgery

• Question of the day
  • Should the availability of a “less-morbid” therapy (Deflux) alter the threshold for surgical intervention?

• This becomes a more challenging question if we assume that antibiotic prophylaxis is not effective
So what should we do?
Current Treatment Remains Traditional

• Imaging evaluation, including VCUG, for most children with febrile UTI
  – AAP guidelines officially sanction waiting until a second febrile UTI to do a VCUG
  – This is controversial
• Antibiotic prophylaxis for children with VUR
• Surgery reserved for children with breakthrough UTI or persistent VUR

But

• All of these points continue to be debateable!!!
Gracias!

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