MEDICAL INSIGHTS

ankura hospital
for women & children

Message From The Editor

Dear friends,

On behalf of Ankura hospitals, we wish you all a very happy new year.

In the last edition, we discussed about evidence-based medicine and its advantages. We understood that evidence-based medicine is about finding scientific evidence to make clinical decisions. Now imagine you are faced with a patient who was recently diagnosed Covid positive. The family wants you to prescribe some medication to reduce the risk of severe disease. When you discuss with your colleagues, you get conflicting advice. How do you find the right answer? You will find the right answer by looking at the current available evidence. In this edition, we will discuss about the steps involved in evidence base practice. These include:

1. Asking a question: the first step is to convert the information we need into an answerable question.
2. Finding evidence: the second step is to find the best evidence for the information we need by a systematic search.
3. Critically appraise the evidence: the third step is to systematically examine the evidence for its trustworthiness, value, and relevance in the current context.
4. Implementing the evidence: the fourth step is integrating the evidence with your own clinical experience and the patients' preferences.
5. Evaluation: the final step is evaluating how effectively you have executed the steps 1-4 and seek ways to improve.

We will discuss these steps in detail in the following editions. This month we are bringing forward an important topic-urinary tract infection in children. Section A deals with common questions faced in the management of UTI in children. Section B deals with VUR and its management.

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Quiz

Please identify the investigation performed and abnormal findings in below images:
(answers given at the end of section A)

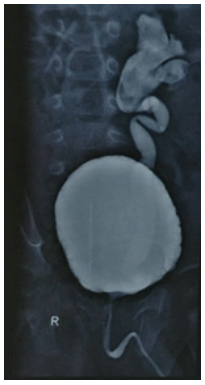

Image 1

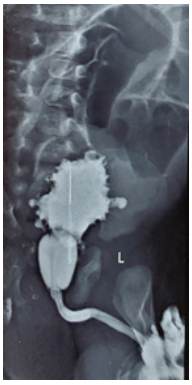

Image 2

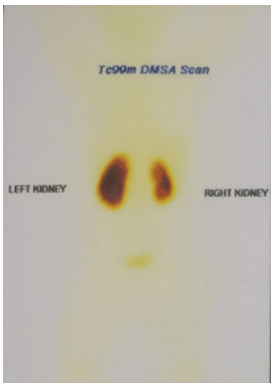

Image 3

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What are the various clinical presentations of UTI in children?

The clinical manifestations depend upon the age and severity of infection. In neonates, UTI is usually a part of septicemia and presents with fever, vomiting, lethargy, jaundice, inadequate weight gain and seizures. Infants and young children present with recurrent fever, vomiting, abdominal pain, diarrhea, & poor weight gain. Older children show fever, dysuria, urgency, frequency and abdominal or flank pain. Adolescents may have symptoms restricted to the lower tract, and fever may not be present. Patients with features of systemic toxicity are considered as having complicated UTI, while those without these features are referred to as simple UTI[1].

How can we confirm the diagnosis of UTI in children?

The gold standard for the diagnosis of UTI is urine culture. A properly collected specimen of urine must be obtained for culture prior to therapy with antibiotics. The bacterial counts required in different samples to diagnose UTI are mentioned in table 1

Method of Collection	Colony Count	Probability of infection
Suprapubic aspiration	Any number of pathogens	99%
Urethral catheterization	$>5x10^4$ CFU/mL	95%
Midstream clean catch	$>10^5$ CFU/mL	90-95%

CFU:colony forming units

Table 1: Colony counts required for diagnosis of UTI [1]

Urinalysis/CUE enables a provisional diagnosis of UTI. Although CUE can be used to select children for immediate treatment, it should never be a substitute for obtaining a urine culture.[1,2,3] Significant pyuria is defined as >5 leukocytes/hpf in a centrifuged sample. The sensitivity and specificity of various parameters in CUE are mentioned in the table 2.

Test	Sensitivity (Range),%	Specificity (Range),%
Leukocyt esterase test	83(67-94)	78 (64-92)
Nitrite test	53(15-82)	98 (90-100)
Leukocyte esterase or nitrite test positive	93 (90-100)	72 (58-91)
Microscopy,WBCs	73 (32-100)	81(45-98)
Microscopy,bacteria	81 (16-99)	83 (11-100)
Leukocyte esterase test, nitrite test ,or microscopy positive	99.8 (99-100)	70 (60-92)

Table 2: Sensitivity and specificity of various parameters in CUE [2]

What is the best method to collect urine sample in children?

Clean catch mid-stream urine sample is the recommended method for urine collection in toilet trained children and baby boys. In neonates and infants urine sample is obtained by bladder catheterization [1]. Urine collected by bag method should only be analyzed for urinalysis and not for culture. A negative urine culture in a bag sample of urine can rule out UTI. However, a positive culture usually indicates contamination by perineal flora and requires fresh sample by bladder catheterization

What are the common bacteria causing UTI in children?

Escherichia coli are responsible for over 90% of pediatric UTIs. Other common gram-negative organisms including Klebsiella, Proteus, Enterobacter, and occasionally Pseudomonas are also responsible in some cases. Gram-positive pathogens include group B Streptococcus and Enterococcus can cause UTI in neonates and infants, and Staphylococcus saprophyticus in adolescent girls [4]. Fungal infections are much less common and are usually seen in patients who are immunocompromised, or have bladder catheters, particularly those also on long-term antibiotic therapy.

What antibiotics should be given in a child with suspected UTI?

Antibiotics should be started only after obtaining urine sample for culture & sensitivity. The indications for hospital admission & IV antibiotics are infants less than 3 months of age, children of any age who are toxic, dehydrated, unable to tolerate oral fluids/-medications & complicated UTI [1,2]. Rest of the children can be treated with oral antibiotics at home. The choice of antibiotic should cover common uropathogens including E.coli; hence Cefixime or Amoxycillin-clavulanic acid are preferred. The treatment should be modified only if the child is not better on the initial antibiotic therapy. The various antibiotics and their dosages are mentioned in table 3.

Medication	Dose, mg/kg/day
Parenteral	
Ceftriaxone	75-100, in 1-2 divided doses IV
Cefotaxime	100-150, in 2-3 divided doses IV
Amikacin	10-15, single dose IV or IM
Gentamicin	5-6, single dose IV or IM
Coamoxiclav	30-35 of amoxicillin, in 2 divided doses IV
Oral	
Cefixime	8-10, in 2 divided doses
Coamoxiclav	30-35 of amoxicillin, in 2 divided doses
Ciprofloxacin	10-20, in 2 divided doses
Ofloxacin	15-20, in 2 divided doses
Cephalexin	50-70, in 2-3 divided doses

Table 3: antibiotics commonly used for the treatment of UTI in children [1]

Where indicated, intravenous therapy is given for the first 2-3 days followed by oral antibiotics once the clinical condition improves. The duration of therapy is 10-14 days for complicated UTI and 7-10 days for uncomplicated UTI . Adolescents with cystitis may be treated with shorter duration of antibiotics lasting up to 3 days.

How do we assess recovery from UTI?

Response to therapy is ascertained by resolution of fever (usually, it takes 2-4 days for fever to resolve on appropriate antibiotics), improved well-being, & initial reduction /resolution of pyuria (less than 10 cells/hpf). Often, the child responds to oral antibiotic, but the culture report shows that the bacteria is resistant to the currently used antibiotic. We do not need to change the therapy as long as the above resolution parameters are present since there is often a difference between in-vitro & in-vivo susceptibility. Antibiotic would need to change only if the child is not better or immuno-compromised. A repeat urine culture is NOT recommended after 2-3 days or end of therapy to confirm resolution of UTI. This has been demonstrated in several studies. Also, persistence of bacteriuria or growth of new organism in repeat culture in the child who has improved could be due to faulty technique of urine collection or delay in plating the sample. Often, the antibiotic sensitivity pattern is also different from the initial culture report and that adds to parental anxiety.

When should we consider further investigations in children diagnosed with UTI?

The evaluation of UTI is generally dependent on the age of the child. The aim of investigations is to identify patients with functional or anatomic abnormalities that might place them at risk for recurrent UTI and subsequent renal scarring and possibly chronic renal failure. The algorithm for investigation is given in figure 1 below:

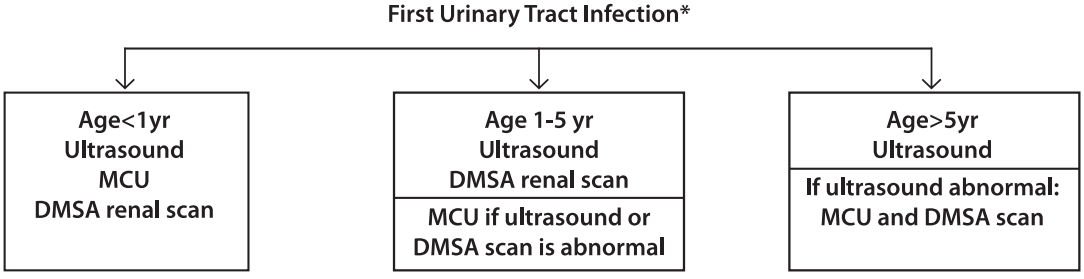

Figure 1: algorithm for investigation following first UTI [1]

Ultrasonography should be done soon after the diagnosis of UTI. MCUG is recommended 2-3 weeks later, while the DMSA scan is carried out 2-3 months after treatment.[1]

Can there be any long-term sequelae of UTI in children ?

UTI in children has potential for renal parenchymal damage and scarring. Renal scarring is the main culprit for the long-term clinical sequelae of UTI such as hypertension, preeclampsia during pregnancy, proteinuria, and chronic renal insufficiency [5] .

What are the risk factors for recurrent UTI in children?

A child who experiences two or more discrete episodes of UTI is said to suffer from recurrent UTI[1]. Underlying problems such as obstructive uropathy, VUR, PUV, neurogenic bladder, and bowel-bladder dysfunction are common risk factors for UTI [6]. In older children, detailed history for voiding dysfunction and constipation should be taken – an important and common contributor to recurrent UTI and persistence of VUR.

Which group of children should be started on prophylactic antibiotics?

Antibiotic prophylaxis is recommended for patients with

- UTI below 1 year of age, while awaiting imaging studies
- Children with VUR
- Frequent febrile UTI (3 or more episodes in a year) even if the urinary tract is normal [1] .

Antibiotic prophylaxis is not advised in patients with urinary tract obstruction (e.g., posterior urethral valves), urolithiasis and neurogenic bladder, and inpatients on clean intermittent catheterization.

What should we look for when examining in a child with UTI?

History of unexplained fever interrupted urinary stream, poor weight gain in young infants. In older children, details of voiding habits, holding behavior, constipation, and water intake (reduced intake to avoid using restrooms). Any history of previous surgery (urinary tract, anorectal malformation or meningomyelocele)[1] should be elicited. A detailed history of antenatal scans (renal anomalies), amniotic fluid index, family history of CKD or hypertension in young adults. Physical examination should focus on growth parameters, BP measurement, abdominal examination (bladder or renal mass, fecal loaded colon, genitalia) spine and lower limbs (for neurological signs).

What are the Consequences of Untreated UTI /partially treated UTI?

In Untreated UTI , the infection can spread up to the kidneys and bloodstream (sepsis) and can become life-threatening. The infection can cause kidney damage and scarring. Adequate treatment of UTI can prevent the above. Outcomes of short courses (1–3 d) are inferior to those of 7 to 14 d courses in febrile UTI [2] .

What is asymptomatic bacteriuria, and do we need to treat it?

Asymptomatic bacteriuria is the presence of significant bacteriuria in the absence of symptoms of UTI. Its frequency is 1-2% in girls and 0.2% in boys . Asymptomatic bacteriuria is a benign condition, which does not cause renal injury and requires no treatment [1]. Also, treatment of asymptomatic bacteriuria leads to elimination of innocuous bacteria with more virulent organism. Hence, it is not recommended to routinely obtain urine culture in children with VUR or neurogenic bladder unless the child has symptoms of UTI.

How can we prevent antibiotic resistance?

Antibiotic resistance is a growing problem as highlighted by the significantly increased uropathogen resistance to TMP/SMX & quinolones [7]. Lack of urine testing, poor empiric prescribing practices and nonselective use of prophylaxis exacerbate this problem. However, small changes in practice patterns may curb the growing resistance rates:

- Always send urine cultures prior to starting antibiotics and tailor broad-spectrum therapy as much as possible.
- Appropriate use of antibiotic prophylaxis followed by counseling regarding the importance of compliance.
- Use of local antibiograms, particularly pediatric-specific antibiograms, with inpatient and outpatient data.

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Answer key

- Image 1: MCUG showing unilateral grade 5 VUR (likely primary).
- Image 2: MCUG showing PUV with trabeculated bladder and diverticuli.
- Image 3: DMSA scan shows diffuse scarring and contracted right kidney; small focal scarring in the upper pole of the left kidney.

SECTION B: VESICO-URETERIC REFLUX IN CHILDREN

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Clinical Scenario

Case 1: A 1-year-old girl presented with febrile UTI and was diagnosed as bilateral primary Grade 4 VUR. She continued to have recurrent febrile UTI despite antibiotic prophylaxis (break-thru infections), with DMSA showing evidence of reflux nephropathy. She underwent endoscopic treatment (cystoscopic Dextranomer/Hyaluronic Acid injection) which cured her VUR (Fig.1). Her VUR was cured and her UTI stopped

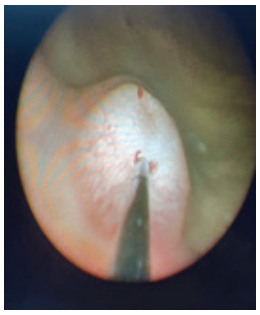

Fig. 1: Dx/HA injection at ureteric orifice showing nipple appearance.

Case 2: A 4-yearold boy had been diagnosed with bilateral VUR grade 4 when he was 2-years old. He was kept on antibotic prophylaxis for 2 years, when a repeat MCUG showed persistent bilateral VUR. He underwent bilateral Vesicoscopic Ureteric reimplantation (Fig 2) which cured his VUR. Post-operatively, he is off antibiotic prophylaxis and doing well.

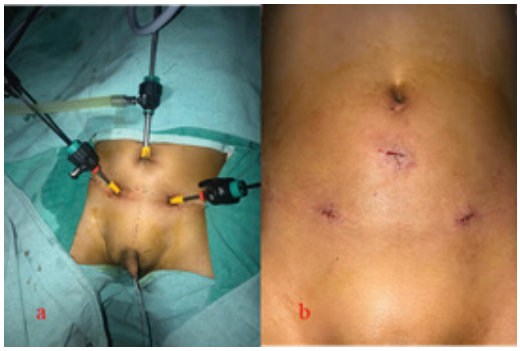

Fig. 2: a) Port placement in vesicoscopic reimplantation, b) Good cosmetic appearance after reimplantation.

Introduction

Primary VUR is one of the commonest congenital urological anomalies in children that requires surgical management. Although many cases of VUR (especially grades 1-3) can be successfully managed by conservative management (observation & antibiotic prophylaxis), persistent high-grade (grade 4-5) VUR and VUR causing recurrent UTI and progressive renal damage are common indications for surgical management. Traditional open surgery for VUR has a high success but with high post-operative morbidity. To reduce the morbidity of open surgery, several minimally invasive surgical techniques have been developed. These techniques are technically demanding but give excellent results with minimal morbidity to the child.

Endoscopic Injection treatment (ET) for VUR

This works well for grades 2-4 VUR and is the most common procedure performed for moderate grade VUR in the western countries. It involves cystoscopic injection of a bulking agent (Dextranomer/Hyaluronic Acid or Dx/HA) at the refluxing ureteric orifice to narrow the opening (refluxing ureteric orifices are wide and gaping) & stop the VUR. It is a simple, outpatient procedure with 75-80% success in expert hands. It is a safe procedure with practically no side effects; we now have the experience of doing this procedure in over 200 ureters with good success.

Vesicoscopic Ureteric Reimplantation

This is a laparoscopic technique specially developed for treatment of VUR. In this technique, the standard technique of open ureteric reiplantation is exactly reproduced by using just 3 laparoscopic ports, without the need to open the abdomen or the urinary bladder. Thus, this operation has a very high success rate (over 95% success), while the morbidity is significantly reduced, compared to open surgery. Even associated anomalies like bladder diverticulum or duplex ureters can be successfully managed with this technique. Because of the minimally invasive nature of the surgery, most children are discharged in 48 hours after such a major reconstructive operation.

Is There a role for open surgery for VUR?

With the available minimally invasive techniques described above, over 95% of cases of VUR can be successfully managed without open surgery. In our practice, open surgery is reserved for the rare cases of VUR with very complicated anatomy, re-operations (previous failed open surgery) or secondary VUR management.

Etio-pathology

Normal VUJ allows antegrade intermittent flow of bolus of urine and prevents retrograde flow of urine. Functionally intravesical ureter (intramural ureter and submucosal ureter) forms a "flap-valve" mechanism leading to compression during bladder filling. Based on etiology, VUR can be categorized into primary or secondary. Primary VUR is due to incompetent vesico-ureteric junction (VUJ), whereas secondary VUR is an acquired condition due to elevated bladder pressures.

In Primary VUR, abnormal ureteric bud origin leads to lateral displacement and abnormal ureteric orifice.[5] Primary VUR can be either isolated or associated with duplex anomalies. Primary VUR is an inheritable disorder. VUR rate in siblings is 40-50%[6] & in parent to child transmission is nearly 60%.[7] Autosomal dominant inheritance is found by Feather et al, in most of families.[8]

Other modes of inheritance includes autosomal recessive and X-linked inheritance.

Secondary VUR is due to higher intravesical pressures secondary to bladder anomalies like neurogenic bladder and bladder outlet obstruction (posterior urethral valves, urethral strictures etc.). Most common cause of secondary VUR in boys is PUV and in girls is obstructed ureterocoele.

Clinical presentation

Most cases of VUR can be presented either as antenatal hydronephrosis or recurrent UTI. Antenatal cases can be either asymptomatic or develop UTI. VUR is seen in 30-50% of children presenting with febrile UTI. In a few cases, VUR can be associated with other structural anomalies like duplex system with ectopic, hypospadias, pelvi-ureteric junction obstruction. Secondary VUR can have symptoms of bladder outlet obstruction (PUV) or neurogenic bladder. Dysfunctional voiding and constipation may increase incidence of febrile UTI in underlying VUR.

Diagnosis and work up

USG KUB: is the most commonly performed investigation which shows hydronephrosis (HDN)or Hydroureteronephrosis (HDUN). USG is not a sensitive imaging modality in diagnosing VUR. Ureteric jet during bladder filling phase can be used for diagnosis, but practical use is very low.[9]

Micturition Cysto-urethrogram (MCUG): Gold standard investigation for diagnosis of VUR. Both grading of VUR and structural anomalies can be seen on MCUG. It has disadvantage of UTI and higher radiation exposure. In order to reduce the incidence of UTI, MCUG is performed under antibiotic cover.

Direct radionuclide cystography (DRCG): Alternate for MCUG in diagnosis and evaluation of VUR. It had advantage of lesser UTI and lesser radiation exposure. But structural anomalies cannot be evaluated by DRCG. It is most preferred for follow up after surgical intervention.

^{99}Tc Dimercaptosuccinic acid (DMSA): After diagnosis of VUR, renal scarring can be evaluated by DMSA scan. Acute pyelonephritis also will have similar cortical deficits on DMSA. Hence DMSA is conducted at least 6-12 weeks post UTI for renal scarring.

Medical management of primary VUR

Long term antibiotic prophylaxis is used as first line of management (table 1).

VUR grade	Management
Grades I and II	Antibiotic prophylaxis until 1 yr old. Restart antibiotic prophylaxis if breakthrough febrilr UTI.
Grades III and V	Antibiotic prophylaxis up to 5 yr age. Consider surgery if breakthrough febrile UTI.
	Beyond 5 yr: Prophylaxis continued if there is bowel bladder dysfunction.

Table 1: antibiotic prophylaxis regimens for VUR

There are inconsistent results on efficacy of prophylaxis in VUR in randomized trials (table 2). Management of bladder and bowel dysfunction also carries a major role in prevention of UTI. Circumcision in infants can be helpful in preventing recurrent UTI in boys.

Study	Objective	Outcome
RIVUR trial [10]	Efficacy of prophylaxis	Prophylaxis decrease UTI by 50%
PRIVENT trial [11]	Efficacy of prophylaxis	Benefit of 6% with prophylaxis

Table 2: studies looking at efficacy of long-term antibiotic prophylaxis

When we compare antibiotic prophylaxis versus surgical management, Cochrane review revealed no significant difference in UTI or scarring between the two interventions 12. The results of some studies comparing surgical and medical management are summarized below (table 3).

Trial	Comparison	Result
Birmingham Reflux study group [13]	Surgical Vs Medical management	Higher resolution of reflux in surgical patients
International Reflux study in children [14]	Surgical Vs Medical management	No significant difference
Swedish Reflux trial [15]	Endoscopy Vs Prophylaxis Vs Surveillance	Resolution of VUR higher with endoscopic management

Table 3: studies comparing surgical versus medical management of VUR

Surgical Management of primary VUR

Indications for surgical management are recurrent break through UTI or appearance of new scar on DMSA while on antibiotic prophylaxis. All the surgical procedures were based on the concept of intravesical ureter lengthening. Various methods of surgical management are ureteric reimplantation and injection therapy

Ureteric reimplantation: : This can be done by intravesicular and extravesicular techniques. Among the intravesical techniques, Cohen's cross trigonal ureteric reimplantation is (most commonly performed). Ureteric reimplantation can be performed by either open or minimal invasive approach. Success rate following ureteric reimplantation for primary VUR is nearly 97-99%[16]. A systemic review on primary management of VUR by both antibiotics and surgery showed 57% reduction in febrile UTI[17] . Recent years vesicoscopic reimplantation and laparoscopic reimplantation curtailed long hospital stay, avoided cumbersome catheters and more cosmesis with similar success rates.

Injection therapy: This procedure involves sub ureteric injection of inert polymer in trigone area resulting in narrowing of ureteric orifice and apparent lengthening of submucosal ureter. Most commonly Dextranomer/ Hyaluronic acid co-polymer is injected cystoscopically. Various techniques of injection like STING, HIT and double HIT were used according to grade of VUR and hydrodistension grading on cystoscopy. Endoscopic injection had advantage over reimplantation in terms of lesser hospital stay, minimal surgical morbidity. Even though success rate is slightly lesser than reimplantation, good success rates are seen except in high grade VUR. A recent meta-analysis showed success rates of 72-78.5% in grade II-III VUR.[18]

Follow up and outcome

Following surgery, these patients are followed up regularly by monitoring growth, BP, and investigations as needed19. Most of the VUR resolves by time. Resolution is higher in low grade VUR (Grade I- 72%) compared to high grade VUR (32% in Grade IV) [19]. Long term sequalae with VUR can be proteinuria, hypertension, and end stage renal disease (ESRD). Incidence of ESRD in reflux nephropathy is very low due to early interventions and varies from 1.5%-9%.[20]

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Our Centers

Kukatpally	:	JNTU- Hi Tech City Road, KPHB Colony
Banjara Hills	:	ICICI Bank Lane, Road No. 12, Banjara Hills
A.S. Rao Nagar	:	Beside ICICI Bank, A.S. Rao Nagar
Boduppal	:	Opposite - Big Bazar, Boduppal
Madinaguda	:	Opp. Maangalya Shopping Mall, Madinaguda
Balanagar	:	Opp. IDPL Colony, Adarsh Nagar, Balanagar
Mehdipatnam	:	Opp. Pillar No. 34, Rethibowli, Mehdipatnam
LB Nagar	:	Opposite Pillar No. 1643, Kothapet, LB Nagar
Khammam	:	Balaji Nagar, Khammam, Telangana
Tirupati	:	Korramenugunta, Renigunta Road, Tirupati

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