URINARY TRACT INFECTION IN CHILDREN

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Urinary tract infection (UTI) is a common problem in childhood and the primary health care practitioner is usually the frontline in diagnosis and management. The development of better imaging techniques, revised understanding of host defencenbacterial virulence interactions in UTI, together with the results of several longitudinal studies on the implications of renal scarring in children, have prompted us to revise our management protocols for children with UTI.

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Significance of UTI in childhood

Urinary tract infection (UTI) is a common problem in childhood, with a reported incidence of 1.7/1000 boys and 3.1/1000 girls at risk per year. In infancy, this ratio is reversed.

1. UTI in infants may be associated with bacteremia and sepsis. Acute pyelonephritis may result in permanent renal parenchymal scars in susceptible children, especially infants.

2. UTI is often a pointer to an associated congenital urinary tract malformation or vesicoureteric reflux. Further uroradiological investigations, particularly in infancy, may be necessary to exclude underlying problems such as obstructive uropathies, which require surgical intervention, as well as to diagnose VUR.

3. **Long Term Implications of renal scarring:**
   a. Significant cause of end-stage renal failure in young adults (3-12% of patients entering dialysis-transplant programmes)
   b. Associated with hypertension (38% of patients) with a history of reflux nephropathy,
   c. Increased incidence of toxaemia of pregnancy and fetal loss.

**Diagnosis of UTI and its Problems**

A high index of suspicion is necessary to diagnose UTI in children. Furthermore, obtaining appropriate urine culture specimens in children is not an easy task.

1. **Non-specificity of clinical signs and symptoms in young children**
   Children, especially infants, with UTI pose a diagnostic problem as many of their symptoms are non-specific.
   a. **Neonates** may present with fever, lethargy, irritability, failure to feed, vomiting or jaundice.
   b. **Older infants and toddlers** often present with high fever, with or without convulsions. Non-specific manifestations include failure to thrive, vomiting, diarrhoea and abdominal pain. Urinary frequency, dribbling and malodorous urine may be noted on careful observation. All infants with febrile episodes without a definite focus such as the respiratory tract, should be screened for UTI.

2. **Screening tests for bacteriuria**
   Screening strips e.g. Combur-9, Multistix-7 and Uristix-4 are helpful in the outpatient diagnosis of UTI. Pyuria is non-specific as there are many causes of “sterile” pyuria. Gram-stained organisms on a smear are significant if done on a fresh specimen.
Table 1: Screening tests for bacteriuria in children

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity M</th>
<th>Specificity M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocyte esterase (wbc)</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>Nitrites (bacteria)</td>
<td>87</td>
<td>80</td>
</tr>
<tr>
<td>Microscopy for pyuria</td>
<td>82</td>
<td>81</td>
</tr>
<tr>
<td>Microscopy for bacteria</td>
<td>80</td>
<td>83</td>
</tr>
</tbody>
</table>

Algorithm 1: Diagnosis of UTI

- Infants and toddlers
  - not toilet-trained
    - Non-specific symptoms especially fever
    - High index of suspicion
  - Septic infants
    - Urine dipstick for nitrites and/or leucocyte esterases
    - Urine microscopy for pyuria
    - Urine microscopy for bacteria
    - positive
    - Urine culture: 
      - Midstream ($\geq 10^5$ pure growth)
      - Catheter ($\geq 10^9$ pure growth)
      - Suprapubic aspiration ($\geq 10^2$ pure growth)

- Toilet-trained children
  - Febrile illness
  - Symptoms suggestive especially fever
  - pyelonephritis or cystitis

3. Collecting urine for culture
The diagnosis of UTI is based primarily on the results of urine culture.

a. **Clean-catch midstream** samples are extremely difficult to obtain in neonates, infants and children who are not yet toilet-trained. Kass defined significant bacteriuria as the presence of $> 105$ colonies/ml of a single species in fresh uncentrifuged voided midstream urine. Repeated cultures increase the chances of correct diagnosis. Therefore, a definitive diagnosis of UTI is made when significant bacteriuria is detected in at least 2 properly collected urine specimens. In practice, if the clinical picture is suggestive of UTI, a single positive culture of pure growth is sufficient.
b. The use of “sterile” bags attached to the genital area is widely practised but there is a high risk of false positive results. The bacterial contamination rate for urine collected by this technique can be minimised if the periurethral area is properly cleaned, the bag applied properly, then removed no later than 30 minutes after application and sent immediately to an on-site microbiology laboratory. Hence in our current hospital practice, a negative urine culture from a bag collection can be interpreted as the absence of UTI.

In the group of patients where a rapid, accurate diagnosis with institution of early treatment is important, suprapubic bladder puncture or urethral catheterisation is required for collection of the urine sample.

Classification of UTI

1. Complicated versus uncomplicated UTI
   Children with complicated UTI require hospitalisation, parenteral antibiotic therapy and evaluation for the presence of an underlying abnormality. Complicated infections are:
   a. Patients with pyelonephritis
   b. Children with known mechanical or functional obstruction of the UT.
   c. All febrile infants especially neonates with suspected UTI are likely to be complicated and should be treated as such.

2. Lower Tract Infection
   a. Asymptomatic bacteriuria is not uncommon in school-age girls and should not be classified as UTI. Treatment is unnecessary; antibiotic therapy changes the bacterial isolates and symptomatic UTI may develop. However in boys, we recommend further investigations if preputial contamination has been excluded.
   b. In older children with a first episode of afebrile cystitis, an ultrasound examination is usually sufficient. Those who have recurrent symptoms would need investigations.

Uroradiologic investigations

1. Identify the patient in need of uroradiological investigations
   a. The prevalence of underlying structural anomalies is higher in infants and boys.
   b. Younger children are at higher risk of renal scarring due to infection.

2. Algorithm 2 for the uroradiological workup of children with UTI
   a. In boys of any age with confirmed UTI and girls under 5 years of age, ultrasonography of the kidneys and bladder, 99mTc-DMSA scan and MCU are recommended as initial investigations of febrile UTI.
   b. Since the prevalence of VUR and the likelihood of renal scarring decreases with age, in girls older than 5 years of age presenting usually sufficient. The 99mTc-DMSA scan is useful to detect renal scarring in this age group if there is a history
of recurrent UTI, clinical features suggesting obstruction of the urinary tract, hypertension or renal impairment.

Algorithm 2: Initial investigations of UTI

CONFIRMED UTI

Ultrasound

Boys

Pelvicalyceal Dilatation ≥ 1 cm

DMSA + MCU

DTPA renogram or MAG3 renogram

Girls

≤ 5 yrs

DMSA and MCU

1st Febrile UTI

Recurrent UTI

≥ 5 yrs

DMSA

Positive MCU

3. Uroradiological investigations used in the evaluation of UTI in children

a. Ultrasonography of the renal tract

This is a non-invasive procedure which gives information on the renal size and shape, bladder size and configuration, bladder wall thickness, presence of absence of pelvicalyceal and ureteral dilatation.

b. Micturating cystourethrogram (MCU)

The MCU gives information on bladder and urethral lesions, on competence of the vesicoureteric valves and the grade of VUR if present.

c. 99mTc DTPA or MAG3 radioisotope scan

If the ultrasound scan of the kidney shows significant pelvicalyceal dilatation, the next investigation would be a 99mTc DTPA or MAG3 renogram to distinguish between a true mechanical obstruction and nonobstructive pelvicalyceal dilatation. It also gives the differential function of both kidneys.

d. 99mTc DMSA scan

This radioisotope scan picks up focal areas of decreased uptake on the DMSA scan, useful for diagnosing acute pyelonephritis in the acute stage whereas scans performed 3-6 months later may demonstrate the presence of established scars. Differential function of the 2 kidneys can be estimated from this scan.
e. Other studies

Intravenous urogram (IVU) is required only if anatomical delineation of the UT is required, such as definition of an obstructed duplex system. It is less useful under 6 months of age because of poor concentrating ability of kidneys and difficulty in bowel preparation. **Invasive studies** such as cystoscopy or retrograde pyelography are performed only if indicated.

**Antimicrobial therapy**

The aim of treatment should be to eradicate infection and prevent further recurrences.

1. **Choice of an appropriate antibiotic**
   This is based on the general principles of antimicrobial therapy, namely:
   a. The organism should be susceptible to the antimicrobial drug, hence the importance of appropriate urine cultures before starting.
   b. The drug should have minimal adverse effects on the major organ systems.
   c. A high concentration of the drug should be present in the urine after administration.
   d. The drug should have a convenient route of administration.

Table 2 lists oral antibiotics commonly used for the treatment of urinary tract infections in children.

2. **Uncomplicated Infections**
   For uncomplicated infections, **oral antibiotics** for 5 to 7 days can be used to initiate treatment. Amoxycillin and co-trimoxazole are useful oral antimicrobial agents. Response to the chosen antibiotic should be seen after 3 days of treatment. If repeat urine cultures done then are still positive, one must consider the possibility of resistant organisms, inadequate drug dosage or drug interactions, or an obstructed urinary tract. Oral cephalosporins are good second-line drugs.

3. **Complicated Infections**
   Therapeutic doses of the appropriate antimicrobial drugs should be used for 7 to 10 days in complicated urinary tract infections. Initial treatment should include a combination of parenteral ampicillin and an aminoglycoside such as gentamicin as E. coli is the most common urinary tract pathogen. This should control the symptoms within 48-72 hours of instituting therapy. Once results of the antibiotic sensitivity tests are available, one single, appropriate drug should be continued. Use of aminoglycosides may be hazardous in children with underlying renal structural abnormalities and renal impairment, due to their nephrotoxic and ototoxic adverse effects. If the organism is ampicillin-resistant, a second/third-generation cephalosporin or ampicillin/amoxycillin-beta lactamase inhibitor combinations such as Unasyn (r) or Augmentin (r) may be useful.
Once the infection is under control, as confirmed by a repeat urine culture after 72 hours of treatment, the child can be continued on the appropriate oral antibiotics such as amoxycillin, co-trimoxazole or a cephalosporin. Urinary antiseptics such as nitrofurantoin and nalidixic acid should not be used for initial treatment of complicated urinary tract infections.

4. **Prophylactic Antibiotic therapy**

   This is recommended for:

   a. children with **obstructive uropathies** before surgery and up to 6 months post-surgery if the urinary tract remains grossly dilated.

   b. those with **VUR on conservative medical therapy**. This will be discussed in the section on VUR.

   c. Some children with recurrent UTI in the absence of anatomical defects. **Local factors** should first be excluded e.g. poor perineal hygiene, constipation with infrequent voiding pattern, preputial contamination, incorrect cleaning after defaecation, tight clothing with perineal moisture accumulation. Patient and parental education are useful in minimising the infective episodes. In boys with problems due to preputial colonization, circumcision is recommended. If these factors are corrected but the infections persist with troublesome symptoms of cystitis, such as frequency, dysuria or enuresis, these children may benefit from 6 to 12 months of antibiotic prophylaxis.

Either co-trimoxazole, trimethoprim alone or nitrofurantoin as a single nightly dose are useful prophylactic drugs.

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**Table 2.: Common oral antibiotics used in treating UTI in children and infants**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Therapeutic dose po (mg/kg/day)</th>
<th>Prophylactic dose po (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>50 q6h</td>
<td>12.5 nightly</td>
</tr>
<tr>
<td>Ampicillin/sulbactam (UnasynO)</td>
<td>30-50(ampicillin component) q12h</td>
<td></td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>40 q8h</td>
<td>10 nightly</td>
</tr>
<tr>
<td>Amoxycillin/Potassium clavulanate (Augmentin')</td>
<td>q8h</td>
<td></td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>80 q12-24h</td>
<td>7.5 nightly</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>40 q8-12 h</td>
<td>10 nightly</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>25-30 q6h</td>
<td>7.5 nightly</td>
</tr>
<tr>
<td>Cefixime</td>
<td>8 q12-24h</td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>6-8 q12h</td>
<td>2 nightly</td>
</tr>
<tr>
<td>Sulphamethoxazole</td>
<td>80-40 q12h</td>
<td>10 nightly</td>
</tr>
<tr>
<td>Nalidixic acid*#</td>
<td>50 q6h</td>
<td>25 q12h</td>
</tr>
<tr>
<td>Nitrofurantoin*#</td>
<td>5-7 q6-8h</td>
<td>1-2 nightly</td>
</tr>
</tbody>
</table>

Contraindicated in *patients with GOD deficiency, # infants under 3months.
Special Mention of Vescicoureteric Reflux

As VUR is the commonest underlying abnormality in children with UTI, we will elaborate on some issues related to VUR.

1. **Natural history of VUR**
   It has been shown that cessation of VUR occurs more frequently in lower grade VUR; and in unilateral VUR compared with bilateral.

2. **Is surgery superior to medical therapy in the treatment of children with severe grade VUR?**
   It is now well proven that surgery is not superior to long-term antibiotic prophylaxis in preventing renal scarring, thinning or growth inhibition. Proponents for surgery in unresolved VUR, especially in girls, argue about the possibility of future pregnancy-related complications. A large study done reported that persistent VUR was not associated with increased foetal loss or maternal risk. Impaired renal function prior to conception, and bilateral renal scarring were associated with increased foetal and maternal risk such as toxaemia in pregnancy.

   Surgery may best be reserved for those who cannot be kept from recurrences of UTI by medical treatment i.e. prophylactic antibiotics. Surgery usually involves reimplantation of the ureter; endoscopic transurethral subureteric injection (STING) can be done in selected patients.

3. In the medical management of children with VUR, how long should antibiotic prophylaxis be given?
   The prevailing consensus among paediatric nephrologists is to continue with long-term antibiotic prophylaxis in children (< 5 years of age) with unresolved higher grade VUR (grades III-V), based on the earlier observations that the risks of new scars and recurrent infections appear to decrease after the age of 5 years. However, recent studies have shown that the risk of scarring is highest in the first year of life; and neither covert bacteriuria nor persistence of VUR influenced progressive reduction in renal growth of children. Therefore, there is a trend now to discontinue antibiotics at an earlier age and reserving long-term antibiotic prophylaxis for patients with a susceptibility to recurrent febrile UTI.

4. Which children do we need to follow-up for the long-term, that is, who are at risk of developing progressive renal damage?
   The combination of both scarring and VUR at presentation, or 1 of these but accompanied by subsequent documented UTI was associated with a 17-fold increase in the relative risk of progressive renal damage. Hence this group of children should be followed up long-term with monitoring of the following parameters: blood pressure, proteinuria and renal function.
Algorithm 3: Management of Primary VUR in Children

1st VUR

Monitor urine cultures
- convert bacteriuria
- febrile episodes

Grades I-II

Monitor urine culture
No prophylaxis
Recurrent febrile breakthrough UTI
DMSA scar

Grades III-IV

Antibiotic prophylaxis till 3 to 5 yrs old depending on reflux severity
Surgery
- STING
- Re-implantation
DMSA scar

VUR + scar or VUR + UTI or UTI + scar

Long term follow-up
- BP, proteinuria
- Renal function + renal growth