URINARY TRACT INFECTIONS IN CHILDREN : EPIDEMIOLOGY, ETIOLOGY AND DIAGNOSIS

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Urinary tract infections (UTI) in children are important not only because of the frequency of their occurrence, but also because of their potential to cause lasting damage. UTI related kidney damage is most often the result of unrecognized or inadequately managed infection during infancy or early childhood. UTI in children have diverse clinical manifestations, and classical symptoms suggestive of UTI, such as dysuria, frequency and urgency are observed only in the older child. Neonates, infants and young children present more commonly with non-specific symptoms, like a brief febrile episode, failure to thrive and poor feeding, irritability and other signs not pointing to the genito-urinary tract, and unless specifically looked for, the diagnosis of UTI is easily missed. The incidence of UTI is highest in the earliest years of life, and the propensity to renal damage is also the greatest: hence a very high index of suspicion should be maintained, and frequent urine cultures should be asked for, during this age period.

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Epidemiology

Data on the incidence and prevalence of symptomatic UTI in Indian children is lacking, but Western literature suggests that 1 out of 100 boys and 3 times as many girls suffer from UTI during their pediatric years(1). In male children, UTI is essentially a disease of early infancy. The risk of a male child falling ill with a UTI during infancy is more than the cumulative risk over the subsequent 15 years. The risk is highest in the first month, declines gradually over the next 5 months, and then rapidly over the second 6 months of life. The risk per month in the second 6 months is 1/50 of that during the first month(1).

In female children too, the first year of life is the most susceptible period for the development, but with increasing age, girls too 'grow out' of this susceptibility, but at a slower rate than that of boys. A small proportion of girls continue to have many reinfections–thus, school aged girls form the bulk of UTI cases seen by most Pediatricians. Girls predominate over boys at all ages except during the first month of life, when twice as many males as females have UTI.

After the first documented episode of UTI, many children will suffer from recurrent episodes: about 50% with symptomatic UTI and 80% with asymptomatic bacteriuria (ABU) will have at least 1 recurrence(2). The chance of recurrence increases with every preceding infection: the risk of a second infection is 25% higher, and that of a third infection (after 2

previous infections) is 50% higher than that of a first UTI(1).

The prevalence of asymptomatic bacteriuria in pre-school and school aged girls is about 1%(2). A few studies available indicate a relatively lower incidence of ABU in Indian children(3).

Etiology

Without an underlying abnormality, *E. coli* is the commonest infecting organism at all ages during a first infection. The other organisms include *Klebsiella, Proteus, Staphylococcus saprophyticus* and others as shown in *Table I*. Nearly 70 to 80% of recurrent UTI are also caused by *E. coli. E. coli* strains isolated from urine are usually the same serotypes present in the fecal flora during an episode. *Klebsiella* species is most commonly seen in newborns and is rare at other ages. *Proteus* species common invader in older boys, and is also seen in hospital acquired infections and in the presence of 'infection stones' (magnesium-ammonium-phosphate). Coagulase negative staphylococcus, *Staph. saprophyticus*, has of late been recognized to be an important pathogen among adolescent girls and in this group, may be responsible for 1/3 of all infections. *Pseudomonas* species is usually seen in hospital acquired infections.

Diagnosis

UTI can be diagnosed only by bacteriological confirmation. There is no place for presumptive diagnosis and treatment of UTI as these cases are unlikely to be investigated further. However, urine culture in children is replete with pitfalls, and these should be clearly understood for the accurate diagnosis of UTI. Urine examination should be meticulous and interpretation meaningful.

Microscopic Examination of Urine

Freshly voided urine should be examined as it allows optimal evaluation of the urinary sediment. A semi-quantitative cell count is the most popular method, but this procedure needs to be standardized. Ten ml of urine is centrifuged at 2000 RPM for 5 minutes and the sediment is resuspended in 1 ml of urine. The microscopic examination is done at 400 magnification and the result expressed as number of cells per high power field (HPF). Normal males should have no more than 3 pus cells/HPF and normal females no more than 5 pus cells/HPF. Presence of pyuria suggests infection, particularly in a symptomatic child, but may be present in the absence of infection in dehydration, calculi, chemical

TABLE I–*Bacterial Etiology in Apparent First UTI*

Bacteria	Neonates	Girls		Boys	
		1 mo-10 yrs	10-16 yrs	1 mo-1 yr	1-16 yrs
E. coli	75	83	60	85	33
Klebsiella	11	1	0	2	2
Proteus	0	3	0	5	33
Staphylococcus saprophiticus	1	1	30	0	12
Others and unknown	13	12	10	8	20

[Adapted from (1)]
Figures indicate percentages.

irritation and renal tuberculosis. Conversely, pyuria may not always accompany infections, particularly recurrent infections. Presence of WBC casts suggests renal involvement. Microscopic examination is especially useful in 3 situations: (*i*) in making a tentative diagnosis in acutely ill patients before results of culture are available. (*ii*) in supporting the diagnosis in patients with low level of bacteriuria, with symptoms of doubtful significance or with asymptomatic bacteriuria, and (*iii*) in all boys less than 4 years in whom preputial bacteria may contaminate, the urine sample heavily. The presence of bacteria in a fresh unspun urine specimen indicates the presence of a significant number of organisms. Normal urine should have no organisms per oil immersion field in an uncentrifuged specimen and not more than 20 organisms per oil immersion field in a centrifuged specimen.

Urine Culture

Significant bacterial growth on urine culture is the only valid way to document UTI. A count of 10^5 organisms/ml of 'clean-catch' midstream urine is taken as a significant count. It should be understood that this count is only a statistically defined limit, and with such a count there is an 80% chance of the presence of UTI in adult females(4). In children however, such a count will give a larger number of false-positives if urine is collected by the 'clean-catch mid-stream' method. Lower counts may be significant in children receiving antibiotics. Any number of organisms grown from a suprapubic puncture specimen is significant. The problem of misinterpretation of 'significant bacteriuria' arises very frequently in clinical practice because of improper collection and transport of urine.

Proper collection of urine cannot be overemphasized because this is the cornerstone of accurate diagnosis. Urine can be collected by (*i*) urine bag collecting system, (*ii*) 'clean-catch' midstream specimen, (*iii*) suprapubic bladder aspiration, and (*iv*) catheterization. Bag collection is a convenient method especially in newborns and small infants, but gives unacceptably high false positive results. Negative cultures from bag specimens, however, helps to rule out infection. A 'clean catch' midstream specimen is the most widely used method of urine collection because of its convenience, but in small children the results should be interpreted with caution. In small children the periuretheral area and the prepuce are heavily contaminated with enteric organisms. It is the duty of every clinician, to explain to the mothers, in detail the exact procedure of urine collection, especially in small children. The urine collecting bottle is not to be opened or washed before collection. The urine is to be collected directly into the bottle, and not as sometimes done, collected in one container and transferred to the bottle. The uretheral meatus in girls should be cleansed with water, and the preputial area in boys irrigated. No antiseptics should be used. The bottle should be opened during the actual process of micturition, and the urine 'caught' as 'downstream' as possible. Early morning specimens are the best and the easiest to collect, as the time of micturition can be anticipated by most mothers. A convenient method of urine collection from female infants is for the mother to sit on a low stool, sit the baby on the mother's knee (back facing mother) and legs wide apart. The mother separates the baby's labia with her hands, and the urine is collected as far from the genitals as possible. Inspite of all these precautions, the

reliability of a 'clean catch' specimen is only 42% in children under 18 months of age; it increases to 71% in 3 to 12 year olds(5). Supra-pubic bladder aspiration is the most reliable method, and is the 'gold standard' against which other methods are compared. It is especially useful in neonates and young infants (in whom the full bladder is an abdominal organ) who cannot cooperate to give a specimen and in whom other methods of urine collection may give unacceptably high false positive results. The success rate in obtaining a specimen by this method is over 90%, and complications are few; hematuria occurs in about 0.2 to 3%(6). This method of urine collection needs to be practised more frequently, for greater specificity in the diagnosis of UTI in children. Bladder catheterization, though very reliable, may cause trauma and introduce infection in the bladder, and is thus not recommended for routine purposes.

Urine storage and transport are unfortunately much neglected aspects of urine culture. Bacteria multiply rapidly in urine, and after 24 hours storage at room temperature, the organisms may multiply upto seven fold, making interpretation meaningless. However, urine stored at 4°C for 24 hours does not allow bacterial multiplication, and colony counts correlate well with fresh specimens. Since an infant or a young child may not always oblige with a specimen when needed most, collected urine should always be stored in a refrigerator till transport to the laboratory.

Level Diagnosis

Localization of the infection site is mainly a research objective, and inspite of the numerous methods available, none is infallible. The various methods available are enumerated in *Table II*. Clinical and simple tests are probably sufficient for most clinical situations. The bladder washout test as described by Fairly *et al.*(7) and the uretheral catheterization technique of Stamey(8) are extremely cumbersome, and indicated only when unilateral nephrectomy is under consideration. Raised levels of C-reactive protein and sedimentation rate have positive correlations with upper tract infections, but their sensitivities are questionable. A transient decrease in renal concentrating capacity or an increase in serum antibody titre against the 0-antigen of the infecting bacteria (as determined by hemagglutination or direct agglutination) indicates renal involvement. Although these tests are valuable in defining a group of patients, their use in individual cases is limited. Auto-antibodies to Tamm-Horsfall (TH) proteins is a more reliable method for the detection of upper UTI, but a reliable assay of TH-antibodies is not available in most clinical situations. The presence of antibody coated bacteria (ACB) in the urine has been shown to have good correlation with pyelonephritis in adults, but even this test in children is less reliable, especially in recurrent infections(9). In balance it appears that localization studies will have much impact on the clinical management of UTI in children.

Conclusions

UTI is common in children, and the results can be potentially dangerous. Gross symptoms are often lacking, especially in neonates and small infants; thus a very high degree of suspicion should be maintained, and frequent urine cultures should be done–repeated cultures may be required if results are equivocal. For neonates and young infants, urine cultures are manda-

TABLE II—*Methods to Evaluate 'Level of Infection' in UTI*

Method	Remarks
Clinical	
Fever >39°C	
Flank pain	
Leucocytosis	
Oligo-anuria	
Azotemia	
Raised ESR	Good correlation with first infections
Raised C-Reactive protein	
WBC 'casts' in urine	Presence indicates upper UTI. Absence does not rule out
Direct Methods	
Ureteral catheterization (Stamey)	Required only if unilateral nephrectomy contemplated
Bladder catheterization (Fairly)	Extremely cumbersome; hardly ever indicated in children
Kidney biopsy	No indication in pediatric UTI
Indirect Methods	
Decreased renal concentrating capacity	Not useful in recurrent infections
Raised antibody titre against 0-antigen of infecting organism	
Auto-antibodies to TH proteins	Reliable. Assay not widely available
Antibody coated bacteria in urine	Not reliable in neonates and infants
Presence of enzymes in urine, lactic dehydrogenase (LDH) esp IV and V isoenzymes, β-glucoronidase, N-acetyl β-glucosaminidase and lysosome	Assay not widely available

tory even for brief febrile episodes. Proper collection, transportation and interpretation of results are of paramount importance for accurate diagnosis.

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PHARMACOTHERAPY OF NEONATAL APNEA

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An apneic spell is defined as cessation of respiration for 20 seconds or longer, with or without decrease in heart rate; it also includes spells of lesser duration if associated with bradycardia or cyanosis. Apnea may be secondary to disorders of various organ systems in preterms or fullterm infants or primary "Apnea of prematurity". The latter is not associated with any other pathologic condition and characteristically develops within 3-5 days of life, in 25% preterms weighing ≤1800 g or born before 34 weeks gestation(1).

Besides treating the primary cause, where one exists, treatment of apneic spells comprises the following: tactile stimulation, proprioceptor stimulation by placing infant on an oscillating waterbed, maintenance of ambient temperature in lower neutral thermal zone, nasal continuous positive airway pressure of 2-4 cm water, use of respirogenic drugs and finally, mechanical ventilation where all other interventions fail. This review focuses on the pharmacotherapy of neonatal apnea.

Drugs that have been widely used in the treatment of neonatal apnea are the methylxanthines (theophylline and caffeine) and doxapram.

1. Theophylline

First used successfully by Kuzembo and Paala(2) in 1973, is currently the drug of choice in the treatment and prevention of neonatal apnea. It crosses the blood brain barrier and exerts its action centrally by stimulation of brain stem respiratory centre, and also increases the sensitivity of this centre to carbon dioxide. It antagonizes narcotic induced respiratory depression, improves diaphragmatic contractility rendering it less susceptible to fatigue, and hence regularizes the breathing pattern. Theophylline increases cardiac output and vital capacity thereby preventing recurrence of apnea, by eliminating hypoxia which is a primary factor in its occurrence.

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