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Urinary Tract Infection in Childhood

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Definitions

URINARY TRACT INFECTION (UTI) is defined as the presence of an excessive number of bacteria in freshly voided urine.

(A) Pyelonephritis is a term applied to children with UTI in whom clinical, radiological, immunological or pathological evidence indicates involvement of renal parenchyma. The term is often qualified as acute, recurrent or chronic. The disease behaves uniquely in the newborn. *All UTI in children should be regarded as pyelonephritis until proven otherwise.*

(B) Cysto-Urethritis is a term applied to a group of symptoms relating to the lower urinary tract. These include urgency, frequency, dysuria, and precipitancy and may be bacterial (UTI) or abacterial in origin. The term cysto-urethritis (or cystitis) should *not* be used for UTI in a child unless clinical, radiological and immunological proof that the kidneys are normal exists. This is rarely the case.

(C) Obstructive Uropathy is a term applied to any condition in which the free flow of urine from the renal pelvis to voiding is obstructed. The blockage may be pelvi-ureteric, ureteric, vesico-ureteric, bladder neck or urethral. UTI may or may not be present, but if calculus infection arises, infection almost invariably persists.

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(D) Neurogenic Bladder may occur as part of a severe lesion such as meningomyelocele, neoplasia affecting the spinal cord, or trauma. Two basic forms occur, spactic or flaccid in type.

(E) Latent ("Asymptomatic") Bacteriuria. As revealed by screening programmes on girls and boys, some children have unrecognized persisting bacteriuria. Usually symptoms are reported on questioning and often underlying changes in renal structure and function can be demonstrated.

PREVALENCE

UTI in children and adolescents is extremely common. It is by far the most important kidney disease and probably the commonest bacterial illness affecting the childhood population of Britain at any point in time. It is estimated to affect some 1 % of newborn babies (affecting males and females equally), and some 1.5 % of school entrants (0.3 % males; 2.6 %females - mair, 1973), and is present in 4.5 % of women screened at our antenatal clinics. If some 400,000 girls aged five start school annually in the United Kingdom, then 10,000 will have latent persisting bacteriuria indicating UTI of a varying degree of severity. At school (aged 5-16) are some 120,000 girls who had undetected bacteriuria on entering and if only 10 % (a very conservative estimate) have significant underlying disease then 12,000 such girls are at school today with significant disease of which we are in ignorance. The figure for boys is not clear but is less than 10 % of that for girls.

The absolute incidence of obstructive uropathy is not known but minor degrees probably exist in 1 % of boys and substantially fewer girls. The incidence of myelomeningocele varies from one area to another but probably a figure of 0.1 % would be a low estimate. All have bladder involvement to some degree. Several illnesses such as nephrotic syndrome, chronic renal failure and immunosuppressant therapy make children specially vulnerable to UTI. Taking all types of UTI into account it seems certain that *at least* 2 % of all children of this country will have some form, varying from silent and asymptomatic persisting bacteriuria to fulminating and potentially lethal neonatal pyelonephritis. The figure has been placed as high as 5 % of girls by the age of sixteen years.

MORTALITY

Mortality in childhood today is largely confined to the newborn, the undiagnosed and those with severe underlying disease such as calculus

or developmental disorder. Very many children move through adolescence with grossly scarred or hydronephrotic kidneys, chronic veticoureteric reflux and poor renal function. They presumably continue to relapse and to deteriorate with pregnancies and aging. When do they die? The nephrologists are very unsure but some must die, since few are dialysed or transplanted. These dramatic procedures tend to be made available to younger adults who die of glomerulonephritis. The morbidity, chronic illness, discomfort, chronic ill health and enuresis occasioned by recurrent UTI in women are known to all practitioners.

ETIOLOGY OF UTI

The cause of UTI is by definition a bacterial infection of the kidney, pelvis, ureter, bladder or urethra. In fact it nearly always involves the kidneys. The bacteria responsible vary widely depending on the type of patient concerned, but the predominant organism is E. Coli (= 85 %) with Proteus Spp as second most frequent (= 9 %). In time, circulating antibodies to the specific strain of E. Coli involved can be demonstrated in the serum of affected children. Recurrences of UTI may be associated with the same strain but more commonly with a differing one. The importance of latent L-forms persisting is still debatable.

PATHOGENESIS

The pathogenesis of UTI is a spread to renal tissue either by blood borne spread or backward spread up the ureters. It seems generally agreed that neonatal pyelonephritis is blood spread and may be due to coliform enterococcal or staphyloccoal bacteremia. The mode of spread in older children, obstructive uropathy and neurogenic bladder is less clear. Winberg (1973) takes the view that in older children spread is from fecal organisms to urethra, to bladder and up the ureters to the kidney. The presence of a large bladder with sluggish emptying and a stagnant bladder residue of urine as in neurogenic bladder, obstructive uropathy and vesico-ureteric reflux are clearly contributory. Lymphatic spread from anatomicaly proximate organisms remains unproven. Calculus formation may be due in part to the presence of infection but usually proves an insuperable barrier to eliminating UTI with infection holding out against antimicrobial therapy in the deep interstices of the stone. Certain illnesses such as the nephrotic syndrome and treatment with cytotoxic drugs predispose to UTI. Similarly pregnancy does so in older chlidren. UTI may precipitate acute renal failure on top of incipient chronic renal failure.

PATHOPHYSIOLOGY

In the early stages the feature is a failure to concentrate urine with a relatively normal glomerular filtration rate. This is present even in latent "asymptomatic" bacteriuria. In chronic renal failure there is a complex picture of uremia, metabolic acidosis, hyperkalemia, hyperphosphatemia and anemia.

PATHOLOGY

The blood borne infection of the newborn results in multiple small abscesses scattered throughout the renal parenchyma. If untreated these may suppurate and produce pyonephrosis but in any case scarring may follow healing leaving an irregular distorted kidney. Perirenitis is a rare complication but a severe one. Both cortex and medulla are affected.

The renal pelvic mucosa is usually affected with wide streaks appearing. On histological examination there is polymorphonuclear infiltration of interstitial tissue, early abscess formation and edema. The tubules may be distended and contain casts, protein and bacteria. In a later stage glomeruli may be sclerosed. Eventually in the chronic stage, the kidney is contracted, scarred irregularly and fibrosed. Glomeruli may be hyalinised or show proliferation and crescents. Tubules are atrophied and dilated and dilute isosthenic urine and high output failure occurs. Hypertension may be present with subsequent cardiovascular changes.

CLINICAL PICTURES OF UTI

The clinical picture varies greatly and the newborn infant requires special consideration. The newborn with UTI may be asymptomatic or may present non-specifically with failure to thrive or to gain weight or weight loss. Culture of urine should be a routine, certainly on all babies with these findings. Routine screening of newborn infants by reliable methods such as suprapubic aspiration have indicated latent asymptomatic bacteriuria in less than one per cent affecting males and females equally. At the other end of the scale is the fulminant picture of E. Coli, septicemia with acute pyelonephritis, severe and often obstructive jaundice, hemolysis and meningitis, an acute life-threatening situation.

Between these extremes lies a group of neonates who are fevered and listless, who may vomit and have loose stools and in whom impairment of renal concentrating capacity produces azotemia. Routine examination of all newborn should include examination of the umbilical

vessels. A single umbilical artery may indicate underlying renal disease. The bladder should be palpated routinely and a large bladder raises the possibility of obstructive uropathy just as the presence of spina bifida or meningomyelocele raises that or neurogenic bladder.

In the toddler, two acute clinical pictures tend to predominate. In the first group the child is unusually cross, fevered and toxic. Convulsions may occur and a clinical picture reminiscent of acute meningitis is seen. The tongue is furred and the child has some dysuria and frequently shivering may be noted. The mother may complain that the urine has a strong smell. In the second group the predominant symptoms are dysuria, frequency, urgency and precipitancy of micturition. Hematuria is often noted. (UTI is probably the commonest cause of hematuria in children in the United Kingdom). The *return* of enuresis is highly significant of UTI and thirst may be noted. Diurnal enuresis may recur.

Second and subsequent attacks of UTI in the child tend to be much less productive of symtoms and indeed the latent cases (2.5% of five year old girls)indicate how unobtrusive UTI may be. The onset of chronic renal failure is usually silent and unobtrusive. Polyuria, polydipsia and enuresis are easily overlooked. Failure to thrive and to grow is non-specific. The metabolic acidosis and anemia are noticable only when extreme. Systemic hypertension is unobtrusive. For these reasons the chronic failure is usually far advanced with renal osteodystrophy and gross anemia before medical advice is sought on this account.

INVESTIGATIONS

Investigations can be divided into three groups:

(a) Clinical examination
(b) Collection and examination of urine.
(c) Serological, radiological and biochemical tests.

CLINICAL EXAMINATION

Whether at home or in the hospital the ailing newborn should be examined for a palpable large bladder, for abnormalities of the penis and for tender or unduly palpable kidneys. In the older child, the abdomen should be palpated for tenderness in the suprapubic region and in the lumbar areas. The blood pressure should be recorded and the external genitalia inspected. Non-specific tests such as those for leucocytosis or E.S.R. are of little value. A well taken history may be virtually diagnostic.

COLLECTION AND EXAMINATION OF URINE

Urine may be collected by a variety of methods:

(a) Clean catch of mid-stream (MSU)
(b) Bladder puncture and suprapubic aspiration (BPU)
(c) Catheterization (CSU)
(d) Plastic bag collection (Bag-Urine)

The first three methods (MSU, BPU and CSU) all yield highly reliable and comparable results. The fourth (bag-urine) is always suspect as contaminated.

Clean-Catch Mid Stream Urine (MSU)

From birth onwards the projected arc of male urine is relatively easy to catch provided the nurse is patient and skilled. A sterile disposable galley pot or universal container may be used. The optimal time is immediately after a feed (or 5-10 mg. frusemide intravenously). The female baby is a much more difficult proposition and may prove to be impossible. Urine from the female toddler may be obtained by sitting her on a pot with a sterile container set anteriorly. Initial and terminal urine drips vertically whereas midstream flow projects forwards. A commercial model of this pot is available.

In older toddlers and early school children (male or female) best results are obtained by having the child stand upright in the bath with a little water running, or on the ground facing his mother. The child voids and mid-stream urine is caught. This is a particularly suitable technique for screening programmes, especially with "Dipstream" culture (V. 1) Older children will be able to void normally standing over a W.C. and the M.S.U. is caught as for adults.

Catheter Specimen of Urine (CSU)

With a sterile disposable catheter, gentle cleansing of the labia with soap and water and reasonable skill on the part of the operator, catheterization of young girls is simple and safe. Infection of a previously healthy bladder is rare and much confusion has resulted from data concerning pregnant women, prostatic men and previously infected urinary tracts. A soft polyvinyl catheter is useful. Nevertheless, CSU is second best to bladder puncture which is now certainly the method of choice in hospitals.

Bladder Puncture and Aspiration (BPU)

Desirably the bladder should be full, palpably and percussably. This is performed shortly after a feed or immediately after 5-10 mg.

frusemide intravenously. The skin between symphisis pubis and umbilicus is cleaned with soap and water and dried. An intravenous needle attached to a 5 ml. syringe is introduced through the midline ilnea alba, just above the symphisis pubis and slid slightly caudally into the bladder and urine aspirated. This technique is excellent for infants up to one year of age but becomes progressively less easy as the child becomes more active and difficult to restrain. By the age of two years it should seldom be necessary. This technique is very safe and suitable for use in Health Centers, well equipped surgeries and any hospital. Standards are so much improved that 103 colonies/ml are abnormal and any growth mandates another culture.

Plastic Bag Collection (Bag-Urine)

A wide range of plastic bags, sterile, unsterile, single or double chambered are available. These are attached around the penis orvulva, adhere to and often irritate the skin and collect urine when voided. Prior to attaching the bag the perineum and perivulvar region is cleaned with soap and water and dried. The labia are washed with sterile water and dried. Contamination begins as soon as the bag is approximated to the skin, increases rapidly with time and is grossly increased when urine begins to swill around. It is therefore imperative to select a time when voiding is likely (during or after a feed) and to detach the bag as soon as the urine is voided and culture immediately. Various warning devices have been produced (privately) to buzz, whistle or wink when urine appears. Not only is rapid removal essential for reasonable accuracy but for the patient's safety. It is said that a small girl jumping up and down in a bath introduces bath water to her bladder; a liquid culture of E. Coli and other bacteria sealed to and swilling round the vulva is not optimal.

EXAMINATION OF URINE

The urine may have an unpleasant smell, be of low specific gravity (or osmolallity) and is likely to be highly acid if the infection is coliform. Turbidity is totally unreliable. Testing for proteinuria by Albustix or other methodology is of *no* reliable value in diagnosing UTI and bacteriuria and should never be employed for this purpose. Many children with significant UTI have no significant proteinuria and many children with significant proteinuria have no significant UTI.

The following tests are used:-

(a) Microscopy for pyuria, casturia, hematuria and bacteriuria
(b) Culture for bacteriuria.
(c) Tests of renal function.

Microscopy for pyuria, casturia, and erythrocyturia

Such tests must be quantitative per unit volume to be meaningful. Provided a standard lens (i.e. magnification) is used and a standard thickness of film of urine by using a rigid coverslip, an approximation can be made by one individual counting per high (or low) power field. This is crude, personal and barely quantitative. Many bacteria may be seen.

Desirably, the freshly voided urine is placed in a quantitative counting chamber such as the Fuchs-Rosenthal. The number of white cells, and red cells per cu. mm. is then counted and should *not* exceed 10/cu. mm. save in the newborn (Houston count, 1963). Many other methods have been described, usually and undesirably involving centrifugization and re-suspension which diminish accuracy.

Culture for Bacteriuria

This is the only reliable method of diagnosing UTI. Conventionally the counts are described as colonies per ml. on culture on a solid medium. The terminology used here for culture for all but bladder puncture urine is:

Positive : ...105 colonies/ml.
Doubtful : ...104 - 105 colonies/ml
Negative : ...104 colonies/ml

With bladder puncture urine, all cultures of 10^3 or more per ml. are accepted as positive.

The following methods of culture are available today in order of accuracy:

(A) Quantitative Dipslide Culture: By Uricult of Oxoid plane type dipslide followed by colony counting. Dipping or Dipstream technique. (Arneil, 1970, 1971, and 1972)

(B) Petri-Dish Laboratory Culture: Second best because of many errors introduced by delays and difficulties in getting specimens to laboratories during working hours without gross multiplication of contaminents or death of pathogens. The validity fo storing at refrigerator temperature in some doubt. Pour plate technique required for accuracy.

(C) Semi-Quantitative Culture: This can be by using one of a variety of curvaceous dipspoons or blotting paper. Provides a culture but not accuracy comparable to plane dipslide or to pour-plate, Petri dish culture.

Modern quantitative plane dipslide culture has made all other forms of quantitative primary culture for bacteriuria obsolete by permitting instant quantitation on plane solid media by "dipping" immediately after voiding or as in screening by "dipstream" technique (inserting the slide in the urine flow). This eliminates the frequent and gross errors of delay, warmth and cooling prior to plating in a bacteriological laboratory which may be distant, closed and overworked. Dipslides once dipped are safe for quantitation and can be delayed for days in post or transit and still be as accurate quantitatively as fresh urine voided and pour-plated instantly in a sophisticated bacteriological laboratory. It is imperative that plane dipslides be made readily and freely available to practitioners, health centers, clinics and schools, and hospitals. They save the time of bacteriological technicians *and* improve accuracy. Antimicrobial therapy may be started once the urine has been dipped; that is five minutes after voiding and after some days the sensitivity of the infecting agent will be known. This is applied to acute UTI. The minimal glycosuria testing for bacteriuria is unreliable giving 25 % false negative results which is unacceptable.

TESTS OF RENAL FUNCTION

The simple tests in use are those of concentrating ability, osmolality and clearance tests such as creatinine clearance. They are of little use diagnostically and are mainly confined to hospitals interested in investigation save when serial values on chronic renal failure are being observed.

OTHER INVESTIGATIONS

Where UTI and bacteriuria are known to exist other tests may be employed such as serology, radiology and ultrasonography.

Serology

This is usually a research or academic investigation often employed to determine whether or not repeated UTI is due to the same strain of E. Coli or not. It is also used to discriminate between pyelonephritis in which antibodies to the organism should appear, and lower UTI in which the kidney is not infected and antibodies do not appear.

Radiology

In any form of UTI a considerable probability exists that an underlying developmental abnormality, obstructive uropathy or urolithiasis may be demonstrable by radiographic techniques. Even in the mildest of UTI (latent persisteng bacteriuria) some abnormality may be seen in 1.5 per cent of school entrant girls and significant abnormality in 1.0 per cent. The question arises as to whether *all* children with proven UTI should not be screened by radiography. Objections can be raised on grounds of workload, expense and unnecessary exposure to ionising radiation. In general it seems that the probability of finding significant defects is so high that routine examination should be varied out wherever practicable. Certainly indications would be:

(a) UTI in the first year of life.
(b) Recurrent UTI
(c) UTI due to organism other than E. Coli
(d) Palpably enlarged bladder
(e) Other atypical features

Radiological examination consists of four phases, the first three being routine. Micturating cysto-urethrography is included if a significant bladder residue is found on the post micturition film, or a non-functioning kidney.

(1) **Straight film of kidneys, ureteres and bladder** (KUB)

This detects abnormalities in position, size and shape of kidneys stones in kidneys, ureters and bladder and calcification elsewhere.

(2) **Intravenous Urography** (IVU)

This demonstrates speed and intensity of excretion of contrast material, abnormalities of calyces, pelvis, pelvi-ureteric junction, ureters, vesico-ureteric junction and bladder.

(3) **Post-micturition film** (PM)

This may indicate reflux up one or more ureters directly or indirectly as a significant bladder residue.

(4) **Micturating Cysto-urethrography** (MCU)

This fills the bladder and may demonstrate a filling defect, diverticula, vesico-ureteric reflux, gross hydroureter, hydronephrosis of functioning or non-functioning kidney.

DIFFERENTIAL DIAGNOSIS

In the newborn, diagnosis is from other causes of failure to thrive, septicemia, meningitis and jaundice. The critical test is for significant bacteriruria and where septicemia is suspected, blood culture and culture of C.S.F.

In the toddler the diagnosis is from other causes of fever, convulsions, polyuria, enuresis and dysuria. The critical measurement is again for bacteriuria which is positively diagnostic. It is difficult to envisage a situation in 1973 in which antimicrobial therapy should be started before dipslide culture is obtained since this is so easily done. Glucosuria will indicate diabetes mellitus and sterile urine with hypotonic urine suggests diabetes insipidus. Psychological disturbances such as compulsive water drinking (causing frequency of micturition) stop when the child goes to sleep and produces concentrated urine. The acute case which is fevered, convulses and may simulate meningitis should present no problem since urine is voided frequently and contains abundant pus cells and bacteria. Chronic renal failure presents a diagnostic problem between chronic pyelonephritis and chronic glomurelonephritis which may be insupperable unless scarred and irregular kidneys can be shown radiologically. Acute UTI on chronic renal failure produces acute renal failure which may be most difficult to recognize and to define.

MANAGEMENT

The diagnosis of UTI is followed almost invariably by antimicrobial therapy. As soon as the diagnosis is suspected a reliable specimen of urine should be obtained as described above and a dipslide dipped. If this modern facility is not available, the urine should be chilled at once in a universal container to 4°C., *kept* at that temperature until it arrives at the bacteriological laboratory and after it arrives there until it is cultured. Sending urine by post for culture is useless unless as a dipslide culture. When the patient is acutely ill, antimicrobial treatment can be started as soon as the culture is obtained (and the diagnosis preferably confirmed microscopically) and should not wait until the bacteriology report is to hand. The "best-guess" principle makes the selection of an effective antimicrobial highly probable. This takes into account the age of the patient and the distribution of organisms for UTI in that age group in the district concerned.

In less acute situations a high fluid intake with alkali therapy (sodium bicarbonate 500 mg. six-hourly) will ameliorate symptoms very rapidly.

CHOICE OF ANTIMICROBIAL

Acute UTI in the Newborn

The infant is likely to be ill, anorexic and possibly vomiting. The infection is likely to be due to E. Coli or other gram-negative organisms with staphylococcus aureus or streptococcus faecalis as less likely causes. Treatment should be by subcutaneous or intramuscular injection whilst results of urine and blood culture are awaited and could be:

(a) Ampiclox (ampicillin and cloxacillin), 100 mg. of each per Kg. body weight per day in devided intramuscular dosage, six-hourly.
or

(b) Cephaloridine, 40 mg. per Kg. body weight per day in divided intramuscular dosage, twice daily.

ACUTE URINARY TRACT INFECTION IN TODDLERS

If the child is vomiting, unconscious or uncooperative then intramuscular treatment may be required. Generally however, oral treatment is possible and could be:

(a) Sulphadimidine - 150 mg./Kg./day

(b) Oral nitrofurantoin (Furadantin) - 6 mg./Kg./day
50 mg. six-hourly for a 5 year old child

(c) Oral co-trimoxazole (Septin, Bactrim) - 4 mg. trimthoprim, 20 mg. sulphamethoxazale /Kg./day

(d) Ampicillin (Penbritin) - 50 mg./Kg./day orally or intramuscularly
250 mg. six-hourly for a five year old child.

In each case clinical improvement and loss of pyuria and bacteriuria should be reviewed when laboratory results come to hand and the therapeutic dose continued for two weeks or changed as indicated. Where the illness is less acute the result of antimicrobial sensitivity testing from the laboratory can be awaited. The appropriate agent may then be prescribed for a period of two weeks.

Therapeutic treatment may be followed for a further period of six months by prophylactic therapy, as is our practice. This is aimed at reducing the risk of further infection and thereby allowing the kid-

neys to heal and to grow. Prophylactic therapy should be with sulphadimidine, nitrofurantoin or naladixic acid. Nitrofurantoin (Furadantin) costs approximately five times as much as sulphadimidine, and naladixic acid (Negram) approximately eight times as much. There is no proven difference in effect in practice. Co-trimoxazole (Septrin, Bactrim) is approximately six times as costly as sulphadimidine and contains a folic acid antagonist (trimethoprim) which does not seem ideal or long-term therapy. At the end of six months free of infection (which is checked for every month by dipslide culture, possibly obtained by the mother at home) the therapy is stopped. One month later the urine is cultured again to make sure that stopping antimicrobial treatment has not occasioned a relapse. If infection breaks through the antimicrobial prophylaxis the urine is cultured again. The new organism is again treated with two weeks of therapeutic treatment followed by six months prophylactic treatment. If there is obstructive uropathy. vesico-ureteric reflux or renal calculus present then prophylactic therapy is continued for a minumum of two years. It has been said that this merely postpones the inevitable relapse. In children if this means normal renal growth which would not otherwise have occurred, surely this is a tribute not a condemnation!

DOUBLE AND TRIPLE VOIDING

When vesico-ureteric reflux has been demonstrated on micturating cysturethrography the technique of double or triple voiding should be taught. The girl should empty her bladder, wait five minutes and repeat the process (double voiding), wait a further five minutes and micturate again (triple voiding). In my experience girls find double voiding a nuisance but tolerable and triple voiding, too much of a nuisance. This is why double voiding is advocated. Double voiding means that urine which has refluxed up the ureters on first voiding, returns to the bladder and is voided at the second attempt.

With high pressure reflux (only present when the bladder is contracting) prophylactic antimicrobial therapy for two three years and double voiding for the like period often leads to the reflux disappearing.

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