Today's Treatment

Diseases of the urinary system

Urinary tract infection in children

R H R WHITE

British Medical Journal, 1977, **1**, 1650-1652

Urinary tract infection (UTI) is a common complaint of childhood. Population studies show prevalence rates of 1-2% in neonates, mostly boys, and up to 2% in schoolgirls, some 50 times more than those of boys of similar age. Such figures as are available for preschool children suggest that it tends to become commoner in girls during infancy. The management of UTI in childhood presents problems unique to the age group, because of the high incidence of underlying abnormalities of the urinary tract, especially vesicoureteric reflux, coupled with the greater vulnerability of the growing kidney to scarring.

Because UTI responds so rapidly to treatment with an appropriate antibiotic, it is easy to understand the reluctance of the busy practitioner to defer treatment to achieve bacteriological confirmation of the diagnosis, when he can issue a prescription with the virtually certain knowledge that the child's symptoms, and the parent's anxiety, will soon be relieved. Why, then, is this uncritical approach contrary to the interests of children? Experience in a paediatric renal clinic has taught me that there are three main reasons: firstly, most prepubertal girls with frequency and dysuria do not, in fact, have UTI and are prescribed needless antibiotics; secondly, many children with genuine UTI do not have "urinary" symptoms, and in them the possible existence of potentially serious underlying renal disease may escape detection and treatment; and thirdly, radiological investigation of the urinary tract is mandatory in children with proved UTI, but the pelvic irradiation is hard to justify in doubtful cases. It is against this background that I believe some comments on diagnosis are needed.

Diagnosis

Frequency and dysuria are not usually apparent in infants wearing nappies, who more often present with anorexia, poor weight gain, misery, and occasional vomiting. Even in older children the symptoms may not point to the urinary tract, and the syndrome of acute pyelonephritis—loin pain, fever, rigors, and vomiting—is unusual. An awareness of the possibility of UTI is therefore essential in any sick child without leading symptoms.

Frequency, and especially dysuria, may be caused by genital inflammation. While balanitis is readily diagnosed, minor degrees of vulvitis often escape detection through failure to inspect the genitalia carefully. The mucosal lining of the lower third of the female urethra is similar to that of the vulva, which until it becomes stratified under the influence of oestrogens at puberty is commonly inflamed. Indeed, a 10-days' course of 0·16% dienoestrol cream, applied twice daily, often cures. After puberty, a normal mucous vaginal discharge may increase the risk of contamination, which is suggested by finding squamous epithelial cells as well as leucocytes on microscopical examination of the urine.[1]

Confirmation of UTI is based on finding appreciable numbers of pathogenic bacteria in the urine, and necessitates distinction from contaminant micro-organisms. The female genital tract is colonised by enterobacteria, which gain entry into the bladder via the urethra. During voiding the urine is readily contaminated with organisms that are ordinarily regarded as pathogens. Such contamination may be minimised by obtaining a midstream urine sample. Distinction between true bacteriuria and contamination relies on the fact that bladder urine, at body temperature, is a good nutrient medium permitting multiplication of pathogens over a period of two to four hours. This principle, however, may be undermined if the delay between voiding and plating the specimen exceeds one to two hours, since contaminants may multipy to "significant" numbers.

The interpretation of a bacterial colony count must therefore take into account both the method of specimen collection and the arrangements for transport to the laboratory. Most older children will collect their own midstream urine sample, given simple instructions; younger ones will need their mothers' help. Girls may sit astride the lavatory or be held over a pot; alternatively, the rather costly but very effective midstream urine sample collector devised by Huttunen *et al*[2] may be used. This works on the principle that the midstream is propelled in a forward direction under full voiding pressure, whereas initially and terminally the flow is a low-pressure, downward dribble. Experience has shown that genital cleaning, which is embarrassing to the older child and adolescent, is unnecessary. In infants a collecting bag must be applied; and the only satisfactory design is the Hollister U-Bag, which minimises contact of the voided urine with the perineum. It is often necessary, however, to confirm the diagnosis by suprapubic aspiration, especially in girls.

Delay in culturing the specimen may be eliminated either by arranging for the child to void urine at hospital or by using dipslides. These have proved completely reliable in hospital and community practice, and can be directly inoculated in the case of most children aged 5 years or more by the "dipstream" technique—that is, by holding the culture medium in the urinary stream.[3] By contrast, chemically impregnated strips that detect a reduction in urinary glucose concentration often give misleading results.[3] It is widely believed that pro-

The Children's Hospital, Birmingham B16 8ET
R H R WHITE, MD, FRCP, consultant paediatrician and nephrologist

teinuria is an indication of UTI, but I have rarely observed more than trace or 1+ Albustix reactions in proved cases. A simple and rewarding, yet neglected, diagnostic technique is microscopical examination of well-mixed, uncentrifuged urine for bacteria and leucocytes. This procedure provides an instant result of acceptable reliability[1] and substantially reduces the number of specimens that must be cultured.

Antibacterial treatment

The commonest infecting organisms during childhood are *Escherichia coli*, *Klebsiella* spp and faecal streptococci. In general practice these are mostly sensitive to sulphonamides, but patients reaching hospital are more likely to have acquired resistant strains. In the absence of acute and distressing symptoms it is preferable to await the result of culture and sensitivity tests before starting treatment. A selection of suitable antibacterial agents is given in the table. Sulphadimidine is cheap and comparatively non-toxic. Co-trimoxazole is more expensive but need be given only twice daily. Nitrofurantoin often causes nausea, although this may be lessened by giving the drug after food or by using the crystalline preparation, Macrodantin. Personal experience of the use of nalidixic acid has been coloured by severe hypersensitivity reactions in four children, in the form of acute, benign intracranial hypertension, presenting with severe frontal headaches and vomiting. Amoxycillin and cephalexin are also suitable for treating active infection. Tetracycline should not be used because it may discolour the teeth in very young children and also tends to promote bacterial strains with multiple resistance.

Of the drugs listed, all except nitrofurantoin and nalidixic acid are suitable for use in impaired renal function. Nitrofurantoin and nalidixic acid are not recommended because sufficient urinary concentrations cannot be achieved without potentially toxic serum levels. With severely impaired renal function, the doses of all drugs must be reduced or given less often.

Treatment with full therapeutic doses (see table) should continue for two weeks; longer treatments do no more than postpone the next episode in those children who are prone to reinfection.[5] Nevertheless, since a third of all children with UTI may have underlying abnormalities of the urinary tract, it is wise to continue with prophylactic dosage until investigations are complete.

PROPHYLAXIS

The choice of an antibacterial agent for long-term prophylaxis needs to be considered in the light of recent knowledge about the development of bacterial resistance. It is now firmly established that most infections are caused by enterobacteria derived from the patient's own bowel. Prolonged use of antibiotics will alter the intestinal flora and the development of resistant strains in the bowel will lead to recurrent UTI. Resistance may develop as a result of mutation or the acquisition of an R factor.[6] The latter is a DNA molecule carrying genes that determine antibiotic resistance; once acquired, it is replicated at each cell division, conferring permanent resistance to all its host's progeny. It is also capable of transmission between species in mixed bacterial populations such as are found in the intestine. R factors have not been found to confer resistance to nitrofurantoin or nalidixic acid but are capable of doing so to sulphonamides, trimethoprim, penicillins, and cephalosporins.

To date, however, R factor-mediated trimethoprim resistance has rarely been found in children, and the combination of a low incidence of resistance with minimal toxicity and greater palatability places co-trimoxazole slightly ahead of nitrofurantoin as a prophylactic. Nevertheless, vigilance is needed to recognise the emergence of trimethoprim-resistant strains and to limit their spread. Recent experience has confirmed the effectiveness of a single daily dose of either co-trimoxazole or nitrofurantoin, equivalent to as little as one-quarter to one-eighth of the daily therapeutic intake (see table); it is best given at night time to ensure an effective concentration in the bladder urine for the longest possible period.

Subsequent management

Further management of the child with UTI hinges on the presence or absence of underlying urinary tract defects, which may be seen radiologically in about one-third of girls and most boys. A predisposition towards recurrent UTI is associated particularly with dilatation and stasis within the urinary tract, of which there are three main diagnostic categories: (*a*) vesicoureteric reflux; (*b*) mechanical obstruction—for instance, posterior urethral valves (boys only), obstructive megaureter, and pelviureteric obstruction; and (*c*) functional obstruction due to neurological defects, such as spina bifida.

It is therefore imperative to obtain an intravenous urogram (IVU) in all children with bacteriologically confirmed UTI. The teaching that serious underlying abnormalities will declare themselves in time, with recurrent infections, is not acceptable since such reinfections may be asymptomatic. An IVU that shows abnormalities such as dilatation of the collecting system or irregular cortical loss indicates a need for cystourethrography. If the IVU is normal in a child aged 5 years or more this need not be carried out immediately; treatment may be discontinued but cystourethrography should be performed in the event of reinfection. In children under 5 I believe that, despite its unpleasantness, cystourethrography should generally be performed even if the IVU is normal, since we have found that this does not exclude the possibility of reflux severe enough to cause subsequent damage.[7]

Obstructive lesions do not resolve spontaneously and need surgery if they are associated with upper tract dilatation, with a high risk of eventual renal damage, or intractable UTI. Urology in infancy and early childhood is expanding and highly specialised, and it would be inappropriate to discuss surgical procedures in this article. Until surgery has been undertaken, however, continuous chemoprophylaxis is advisable because of the high risk of recurrent UTI.

Suggested dosage scheme for antibacterial treatment of urinary tract infection (after Wood[4])

Antibacterial agent	Doses a day	Active infection				Prophylaxis (once nightly)*
		2 wk-1 yr	1 yr	7 yr	Adult	
Sulphadimidine	4	25 mg/kg	250 mg	500 mg	1 g	Not recommended
Co-trimoxazole	2	4 mg/kg	40 mg	80 mg	160 mg	Half-dose
Amoxycillin	4	6·25 mg/kg	62·5 mg	125 mg	250 mg	Not recommended
Nitrofurantoin	4	2·50 mg/kg	25 mg	50 mg	100 mg	Half-dose
Nalidixic acid	4	25 mg/kg	250 mg	500 mg	1 g	Half-dose
Cephalexin	4	12·5 mg/kg	125 mg	250 mg	500 mg	Not recommended

*Proportion of individual dose for age.

VESICOURETERIC REFLUX

Reflux is diagnosed radiologically by cystourethrography, sometimes during bladder filling but more often during micturition, which must be included in the examination. It is sometimes transient and may be missed without screening. If reflux is absent or confined to the lower part of the ureter renal scarring is extremely unlikely to occur; but reflux reaching the renal pelvis, especially when it causes ballooning of the calyces, is often associated with scarring.[7-10]

If scarring is bilateral and extensive the child's health, and ultimately life, may be threatened by the advent of chronic renal failure. When unilateral, there is a small risk of renin-mediated hypertension developing. In children with established scarring the main aim of treatment is to prevent extension of the scars and encourage normal growth of the kidneys, and long-term chemoprophylaxis generally achieves this.

SURGERY IN REFLUX

Unquestionably reflux may be corrected surgically, by reimplanting the ureter in a manner that increases the ratio of its intramural length to its calibre. Such procedures may, on occasion, cause obstruction and possibly need revision; they are technically more difficult in small infants. The success of the procedure, however, must be measured not only by its ability to correct vesicoureteric reflux, but also in terms of its influence on renal growth and scarring. Moreover, it must take into account the finding that reflux disappears spontaneously in over half of affected children,[8] presumably as a result of maturation of muscle fibres around the ureterovesical junction. In man, the exact role of the mechanical back-pressure associated with vesicoureteric reflux is uncertain, since renal scarring is rarely seen in the absence of active or previous UTI. The presence of continuing reflux encourages recurrent UTI, because the return of refluxed urine to the bladder after voiding provides a residue for bacterial multiplication. This may be controlled, however, by chemoprophylaxis and helped by double micturition in those children old enough to be taught to practise it, and is not, per se, an indication for surgery.

Most, though not all, renal scars are already diagnosable radiologically on initial investigation, and there is substantial evidence that scarring begins early in life.[7-10] There is, therefore, increasing doubt about the benefits of indiscriminate ureteric reimplantation, particularly after the age of 5 years, and because of this uncertainty we are currently conducting a controlled comparison of surgical and conservative management at the Birmingham Children's Hospital.

Long-term care

Because 75% of girls with UTI have recurrent infections, whether or not they have underlying defects such as reflux, medical care should not stop at treating the initial infection. If the urinary tract is radiologically normal antibacterial treatment may be stopped, but a further urine culture should be obtained after one or two months, since relapses are quite often asymptomatic. Thereafter checks should be made three or four times a year, and if infection has not recurred within two years the child may safely be discharged. The child who experiences repeated symptomatic infections may need chemoprophylaxis for 6-12 months, and IVU should be repeated after two years to ensure that the kidneys are growing normally and remain free from scarring.

We do not yet understand the reasons for repeated bacterial invasion of the female bladder. Although bacteriuria is more prevalent among lower social classes, the role of hygiene is not clear. Wiping away from the vulva after defecation is the practice most commonly, though not always, taught by mothers, and should be encouraged. Urodynamic studies have shown raised midurethral voiding pressures in girls with recurrent UTI, while a "spinning-top" urethra is a common cystourethrographic finding; urine may possibly reflux from the urethra into the bladder, carrying with it enterobacteria that colonise the periurethral mucus glands. Although meatal stenosis is rare, instrumental dilatation of the urethra sometimes cures girls who develop renewed infection every time chemoprophylaxis is stopped. Constipation is an associated factor in some cases, perhaps encouraging bacterial invasion of the bladder by external trauma to the urethra, just as sexual intercourse may in women. Dietary regulation by including bran-containing cereals or wholemeal bread should be the goal, although temporary stimulation of the bowel with a preparation such as Senokot may be needed at first.

This tendency towards recurrent UTI generally improves after puberty, perhaps owing to oestrogen-induced genital mucosal changes. The advent of promiscuous sexual intercourse, however, often leads to exacerbation in teenagers, who should be advised not to disregard suggestive symptoms. Possibly oral contraceptives may increase the risk of UTI by causing dilatation of the upper urinary tract, but this needs further study. Before discharge from supervision girls should also be warned of the risks of UTI recurring during pregnancy and advised to obtain regular checks.

The child with established renal scarring needs regular supervision until adulthood, when renal growth ceases. The IVU should be repeated at intervals of two to three years throughout childhood to monitor renal growth and scars, while cystourethrography should be repeated at similar intervals until reflux has disappeared. Chemoprophylaxis should be maintained so long as reflux is present, and longer if renal growth is retarded. The blood pressure should be measured once or twice a year and, when scarring is bilateral, renal function should occasionally be assessed.

I have purposely emphasised the problems affecting a few patients, and most children with UTI may be given a reassuring long-term prognosis, with adequate medical supervision. To achieve the standard of care suggested may imply a big work load, but this may be diminished by adopting simple screening procedures[1] and by carefully selecting at-risk patients through accurate diagnosis.

References

1 Robins, D G, *et al*, *Lancet*, 1975, **1**, 476.
2 Huttunen, N-P, Mella, E, and Mäkelä, P, *Lancet*, 1970, **1**, 22.
3 Edwards, B, *et al*, *British Medical Journal*, 1975, **2**, 463.
4 Wood, B S B, *A Paediatric Vade-mecum*, 9th ed. London, Lloyd-Luke, in press.
5 Stansfeld, J M, *British Medical Journal*, 1975, **3**, 65.
6 Harkness, J L, Anderson, F M, and Datta, N, *Kidney International*, 1975, **8**, S-130.
7 Shah, K J, Robins, D G, and White, R H R. In preparation.
8 Smellie, J, *et al*, *Kidney International*, 1975, **8**, S-65.
9 MacGregor, M E, and Freeman, P, *Quarterly Journal of Medicine*, 1975, **44**, 481.
10 Smellie, J M, and Normand, I C S, *Archives of Disease in Childhood*, 1975, **50**, 581.

ONE HUNDRED YEARS AGO A boy, twelve years old, had been struck on the upper part of the back some months before. The symptoms gradually developed were: pain and tenderness over the epigastrium, great protrusion of the abdomen, no apparent action of the diaphragm, sleeplessness, and a most peculiar noise during respiration. At first, inspiration only was noisy; but gradually expiration also became resonant. The sound resembled the clucking of a hen; but, as the disease advanced, every breath was exactly like the scream of a peacock. Under gelseminum, strychnia, and faradisation of the phrenic nerves, the diaphragm regained its power in about three months; but fully ten months elapsed before the noisy respirations ceased. (*British Medical Journal*, 1877.)