Urinary infections in adults – 1985

W.R. Cattell

The Royal Hospital of St. Bartholomew, London EC1A 7BE, UK.

Introduction

‘Of all the diseases of the urinary tract that the practitioner has to diagnose and treat, chronic infections are the most common and the *Bacillus coli* is the infecting agent in the majority of cases’ wrote Sir John Thomson-Walker in his article published in the January 1926 copy of the first volume of the *Postgraduate Medical Journal*. With qualification of the word ‘chronic’ the same can be written today. Thus, after respiratory infections, ‘cystitis’ is the commonest cause of ill health in women in the United Kingdom and has been calculated to account for 6 million visits to physicians per annum in the USA! This, despite the fact that in 1985 we have made major strides in our understanding of the problem, its pathogenesis, natural history and management. Why then does it remain such a problem? Partly because we still lack the fundamental therapeutic measures to prevent infection in the first place and partly because of poor clinical application of measures currently available.

‘Breakthroughs for advance’

Although Thomson-Walker’s article of 1926 is quite remarkable in the accuracy with which he describes clinical syndromes, he lacked at that time two important diagnostic tools which have revolutionized our understanding and treatment of urinary tract infection – quantitative urine culture and intravenous urography.

Quantitative urine culture

The popularization of this by Kass in the 1950s (Kass, 1957) laid the foundation for a major breakthrough in our understanding of urinary tract infection (UTI). It led to general agreement on diagnostic criteria and a huge surge of research interest in the 1960s and 70s. Today, quantitative urine culture, with proper interpretation of results, is essential for the successful management of patients with recurrent or persisting infection. It is now generally accepted that the demon-

stration of more than 100,000 (10^5) of the same organism/ml of urine indicates the establishment and multiplication of bacteria within the bladder and thus within the urinary tract. However, the results of quantitative urine culture must *not* be interpreted too rigidly. Pure growths in lower counts may also indicate bladder bacteriuria in patients who, by ingesting large amounts of fluid, are undergoing a water diuresis. If low counts of the same organism are repeatedly noted, and especially in symptomatic patients, urine for culture must be obtained by suprapubic aspiration (SPA) to establish or exclude the diagnosis of bladder bacteriuria. Bladder urine is normally sterile. If, in symptomatic patients, culture of urine samples obtained by SPA are repeatedly negative, including culture for fastidious organisms, they do not have UTI as a cause of their symptoms. SPA is a simple and non-traumatic procedure and used all too infrequently in difficult or doubtful cases.

As in 1926, the most common infecting organism is *E. coli* with occasional *Proteus*, *Klebsiella* or other enterobacteracea with one important addition – *Staphylococcus saprophyticus*. It is now clear that this particular subspecies of what used to be called *Staph. albus* is a common cause of urinary tract infection in young (15–25 year old), sexually active women and *not*, as was formerly taught, simply a urine contaminant.

Finally, it is now clear that pyuria is not always present in association with unequivocal bladder bacteriuria and its absence does not exclude infection. The significance of pyuria is that it indicates continuing inflammation from whatever cause – stones, papillary necrosis, tuberculosis and others – and is an especially important finding when present in the absence of bacteriuria or if it persists following eradication of bacteriuria.

Intravenous urography

Introduced in 1928, it was Hodson in the 1950s and 60s who exploited intravenous urography to great advantage in defining the natural history of urinary tract infection (Hodson, 1959). Overlapping in time with the popularization of quantitative urine culture, the

critical use of urography, then as now, was a major milestone in the understanding of urinary infection.

Natural history of urinary tract infection

It is now abundantly clear that UTI must not be considered a single entity but rather a condition which may present in different ways, has different significance in different individuals and differing management requirements dependent on the particular circumstances.

Presentation

UTI may present with the classical symptoms of frequency of micturition by day and by night, dysuria, suprapubic or loin pain, smelly urine, fever and possibly haematuria. Alternatively, the patient may admit to no symptoms and is diagnosed on routine urine culture. Finally, it may present with atypical symptoms such as abdominal or loin pain, fever, haematuria, etc., with no change in micturition. Conversely, it must also be realized that symptoms of frequency and/or dysuria are not synonymous with bladder bacteriuria, many alternative causes being recognized. For this reason, diagnosis in all cases must be based on quantitative urine culture.

Classification

It is convenient to subdivide UTI into single isolated, never or rarely repeated episodes on the one hand versus persistent or recurrent infection (Figure 1). The former, although often unpleasant for the patient, is rarely serious and readily treated. It is estimated that more than 50% of all women will at some time experience an acute attack of 'cystitis'. Happily, in the vast majority, it is an isolated event. Recurrent infection is much less common but very much more important. At best it can be the cause of great misery and disablement, while at worst it can cause progressive kidney damage and shorten life expectancy.

[%] represent approximate frequency

Figure 1 Classification of urinary tract infection.

Relapse vs reinfection

For conceptual and management reasons, it is helpful to subdivide recurrent infection into those patients with relapsing infection as opposed to those with reinfection. This is based on careful serial urine culture before, during and immediately (7–10 days) after treatment. By relapse is meant recurrence of bacteriuria with the same organism within 7–10 days of completion of antibacterial therapy. This is most conveniently identified by reference to species and antibiotic sensitivities. This implies a failure to eradicate infection from some nidus within the system and is most often associated with stones, papillary necrosis, scarred or cystic kidneys, diverticulae and prostatitis. Relapsing infection is uncommon. It must be distinguished from treatment failure in which 'on treatment' urine cultures remain positive despite appropriate antibacterial therapy. This occurs under few circumstances – a laboratory error in defining sensitivities, failure of the patient to take the drug or renal impairment of sufficient degree to prevent achievement of satisfactory antibacterial concentrations in the urine.

Reinfection accounts for some 80% of cases of recurrent infection in women. It is identified by recurrence of infection weeks or months after successful treatment due to the same or different organisms. It is no longer believed that in the absence of treatment, bacteria can readily 'hide' in some focus within the urinary tract for any length of time without the development of bladder bacteriuria, urine being such an excellent medium for the multiplication of germs. Exceptions to this are chronic bacterial infection of the prostate or, rarely, infection in an obstructed upper urinary tract. Interestingly, these current views were also held by Thomsom-Walker in 1926! The diagnosis of reinfection implies, not a failure to eradicate infection, but a propensity in that individual to reinvasion of the urinary tract.

'Cystitis' vs 'pyelonephritis'

It has been conventional to subdivide UTI into 'cystitis', in which there is a predominance of bladder symptoms and infection is believed to be confined to the lower urinary tract, and pyelitis or pyelonephritis, in which there is loin pain, fever and systemic upset believed due to ascent of infection to the pelvis or kidney. Several studies, in which the site of infection has been localized by one means or another, show that symptoms can be poor indicators of upper or lower UTI. Nevertheless, it is clinically acceptable to diagnose upper tract infection in the patient with bacteriuria who has severe loin pain and tenderness, fever and systemic upset.

Table I Classification of recurrent urinary tract infection into complicated *vs* uncomplicated.

<i>Uncomplicated</i>	<i>Significance of UTI</i>	<i>Complicated</i>
IVU normal	IVU normal or abnormal +	IVU abnormal
No associated disease	Associated disease Diabetes Analgesic abuse Sickle cell disease/trait	Stones Papillary necrosis Obstruction Vesico-ureteric reflux
Cause of misery Rarely kidney damage		Danger of progressive kidney damage or septicaemia

The significance of UTI – complicated *vs* uncomplicated disease

Prior to the radiological definition of chronic pyelonephritis and elucidation of its pathogenesis, it was commonly believed that recurrent infection of the upper urinary tract inevitably led to progressive kidney damage. This is now known to be untrue. In adults, in the absence of complicating factors, recurrent infection rarely, if ever, leads to serious chronic renal impairment. It is thus convenient in examining the significance of UTI in terms of kidney damage to subdivide it into complicated versus uncomplicated.

By *uncomplicated* is meant recurrent or persistent infection in patients with anatomically and functionally normal urinary tracts, as evidenced by a normal IVU, who do not have complicating associated disease (Table I). In such patients recurrent or persisting infection can be a source of great morbidity but does not generally lead to significant kidney damage. An exception are those patients, usually with *Proteus* infection, who may develop stones and become 'complicated'.

Complicated infection is defined as infection occurring in a structurally or functionally abnormal urinary tract or in a patient whose tract may or may not be normal but who also has associated disease such as diabetes, analgesic abuse or sickle cell trait.

The most important structural or functional abnormalities are stones, papillary necrosis, obstruction or vesico-ureteric reflux. Infection in association with these can undoubtedly lead to serious, sometimes rapidly progressive, kidney damage whether as a result of the growth of the stones or, more seriously, due to the combination of obstruction and infection – an obstructed pyonephrosis. This latter may also result in immediately life-threatening Gram-negative septicaemia and acute renal failure. Vesico-ureteric reflux plus infection, now clearly known to be the cause of 'chronic pyelonephritis' in infancy and childhood, is less common in adult life, reflux usually remitting at

puberty. The importance of continuing reflux and infection as a cause of progressive kidney damage in adult life is controversial but the acquisition of reflux and infection in adults has been reported to cause renal impairment (Williams *et al.*, 1971).

Diabetes, analgesic abuse and sickle cell trait or disease can all, of themselves, cause kidney damage due to interstitial nephritis and papillary necrosis. There is also suspicion – poorly documented – that coexistence of these with UTI is not only more difficult to treat but also associated with an increased potential for kidney damage.

In summary, patients with uncomplicated recurrent infection are unlikely ever to have serious kidney damage and should be told so. The level of medical surveillance and treatment then becomes a function of the extent to which the patient is disabled. By contrast, all patients with complicated infection must be warned of the potential danger of this to kidney function and every effort should be made to eradicate or control infection.

Pathogenesis of urinary tract infection

The successful management of recurrent infection and especially reinfection demands a clear understanding of current concepts of the pathogenesis of UTI.

Source of infection

With the exception of *Staph. saprophyticus*, the infecting organisms come from the patient's own gut. Transfer of organisms from the bowel to the urinary tract occurs via the bloodstream, via lymphatics, by direct extension, as in vesico-colic fistulae, or by the ascending transurethral route. Save possible blood-borne infection to obstructed or polycystic kidneys, the transurethral route is by far the commonest route of infection.

The possibility that patients with recurrent infection carried in their gut organisms of particular uropath-

Figure 2 Critical steps in ascending infection of bladder.

ogenicity was initially disproved by the work of Gruneberg *et al.* (1968) which showed that the spectrum of *E. coli* recovered from infected urine reflected the prevalence of these organisms in the faeces of normal women. More recently, interest in the importance of fimbriated or piliated bacteria as uropathogens has renewed interest in selective colonization of the gut in affected patients. Again, however, the same appears to apply – there are ample numbers of fimbriated organisms in the gut flora of all individuals.

Steps in ascending infection

Given a readily available supply of potentially pathogenic bacteria in the gut, the development of bladder bacteriuria – the first critical phase in the establishment of urinary tract infection – involves a series of steps (Figure 2). First, heavy colonization of the periurethral zone with pathogenic bacteria. Second, transfer of bacteria to the bladder via the urethra and, finally, the establishment and multiplication of bacteria within bladder urine.

Uro-epithelial adhesion of bacteria

There has been much interest in recent years in the capacity of *E. coli* recovered from infected urine to adhere to uro-epithelial cells by way of pili or fimbriae (Sobel & Kaye, 1984). Almost all *E. coli* contain Type 1 common pili which bind to mannitol-containing receptors on uro-epithelial and vaginal epithelial cells. There is now considerable evidence that this capacity for adherence may be an important factor in the heavy colonization of the periurethral area known to occur prior to ascending infection. Just why this should occur in some women and not in others is the subject of dispute. Stamey *et al.* (1971) claim a special biological predisposition to periurethral colonization in susceptible women. This has not been confirmed by others (Cattell *et al.*, 1974). Kunin, remarking on the well recognized tendency for one infection to predispose to another, has suggested that the initial infection predis-

poses to colonization of the periurethral zone (Kunin *et al.*, 1980). The controversy continues. There is little evidence that poor toilet habits are of significant importance and local cleansing has little to offer.

Transurethral passage

Transfer of bacteria along the short female urethra is not difficult to understand. The role of turbulent flow due to relative stenosis of the external urethral orifice is controversial and does not justify uncritical urethrotomy. There is considerable anecdotal and rather less scientific evidence to indicate that sexual intercourse facilitates transfer of bacteria to the bladder (Bran *et al.*, 1972; Buckley *et al.*, 1978; Kunin, 1978). In males, prostatic secretions are known to have bactericidal properties (Stamey *et al.*, 1968) which may play a part in the prevention of ascending infection. Whether women have similar secretions from periurethral glands remains conjectural.

Bladder infection

It would seem fairly clear that the most important step in the pathogenesis of ascending UTI is the establishment of bacteria within bladder urine. Conversely, the most important defence mechanisms against infection also lie here. Thus, while there is good evidence that bacteria may commonly enter the bladder whether after intercourse or not, this is usually only temporary colonization. Similarly, the deliberate installation of bacteria into healthy human bladders is followed by quite rapid elimination (Cox & Hinman, 1961). These observations in humans confirm much animal work which has shown the bladder to have a considerable potential for the elimination of bacteria. The precise details of the important defence mechanisms remain unclear but both hydrokinetic and mucosal factors would seem important.

Hydrokinetic clearance

There is good evidence from *in vivo* and *in vitro* studies (Cattell *et al.*, 1970; O'Grady *et al.*, 1968) that a high rate of urine flow with frequent complete bladder emptying facilitates the elimination of bacteria, while low flow rates and impaired emptying predispose to infection. Indeed, obstruction and reduced perfusion at any point in the urinary tract predisposes to infection.

Mucosal defences

The nature of the mucosal defence is much less clear. As already mentioned, there is considerable interest in the role of adhesion of bacteria to uroepithelial surfaces including the lining of the bladder. This has

been clearly demonstrated in animals (Parsons *et al.*, 1975) and indeed it is possible to enhance this by pretreatment of the bladder with dilute hydrochloric acid which strips off a surface mucopolysaccharide secreted by epithelial cells (Parsons *et al.*, 1979). Conversely, adhesion may be reduced by adding mannose to which Type 1 pili adhere, so blocking bacterial binding sites (Aronson *et al.*, 1979). Other possible mucosal defence mechanisms postulated include the production of antibacterial secretions by mucosal cells. Neither humoral nor cell-mediated immune mechanisms have yet been shown to play any part in bladder defence mechanisms.

Given these observations, we are left with the hypothesis that the establishment of bacteria in the bladder depends on entry of a sufficiently large inoculum of bacteria of special virulence, possibly due to adhesive properties, which can overwhelm normal or impaired defence mechanisms. This will be facilitated by a low urine flow rate and infrequent and incomplete voiding.

Kidney infection

The ascent of infection to the kidney is facilitated by vesico-ureteric reflux, atonic or dilated ureters, and bacterial virulence factors such as the presence of P fimbriae which bind to uroepithelial cells via globoseries glycolipid receptors (Leffler & Svanborg-Eden, 1981). These are different from the Type 1 pili which appear to play no part, or even oppose, upper tract infection. Other bacterial virulence factors such as the presence of K antigen or haemolysin production have also been postulated as important in renal infection. It is probable, however, that no one virulence factor is paramount, but rather there is a complex interplay between multiple virulence factors and host defence mechanisms.

Bacterial prostatitis

Recurrent ascending infection in males is commonly due to bacterial infection of the prostate. Uncommon, but very distressing, it is unclear, save following instrumentation or indwelling catheters, why initial infection takes place. It may be related to reduction in the normal antibacterial action of prostatic secretions and may relate to previous non-specific urethritis. Diagnosis of bacterial prostatitis can be difficult. Clinical indicators include perineal pain and, especially on ejaculation, epididymo-orchitis and/or a tender enlarged prostate. Diagnosis may be confirmed by the demonstration of clumps of pus cells in expressed prostatic secretion and, less commonly, the culture of bacteria from such samples. Commonly, diagnosis is based on symptoms, relapsing bacteriuria and a trial of appropriate antibacterial drugs (*vide infra*). Once

bacterial infection is established, this is a source of bacteria which may cause relapsing ascending infection.

Treatment

The principles of management are now fairly clearly defined.

Single isolated attacks

It is desirable but not mandatory that urine culture is carried out prior to treatment. If symptoms are predominantly bladder-related – frequency and dysuria – short 3–5 day courses of sulphafurazole 1 g t.d.s., ampicillin 500 mg t.d.s., amoxycillin 250 mg t.d.s., nitrofurantoin 50 mg t.d.s., co-trimoxazole 960 mg b.d. or trimethoprim 200 mg b.d., and a high fluid intake should be prescribed. An increasingly popular alternative is to give a single large dose of antibiotic – 3 g amoxycillin; 4 × 480 mg of co-trimoxazole or 2 g of sulphafurazole. Several studies show a very high cure rate in patients, who by various localization studies, have been shown to have infection confined to the bladder. In clinical practice, it is best restricted to patients whose symptoms began within 24–36 hours, who have no history of recurrent infection and have no loin pain or tenderness, fever or systemic upset. It is essential that post-treatment cultures be obtained. Failure to eradicate infection by single dose may indicate underlying renal disease. All patients, however treated, must be encouraged in prophylactic measures (*vide infra*) for some months to avoid recurrence.

Acute pyelonephritis

Where the patient is ill and febrile, with severe loin pain and tenderness, treatment must be more aggressive. Pending urine and blood culture results and sensitivities, it is best to start treatment with intravenous ampicillin or amoxycillin (1 g 6-hourly), switching to a regular oral dose with control of fever and reduction to loin tenderness. An alternative is to start with an intravenous aminoglycoside – gentamicin, tobramycin or netilmicin – in a dose of 1.5 mg/kg 8-hourly, switching to intramuscular treatment after 48 hours. The results of urine cultures, when available, may dictate alternative drugs. Maintaining a high urine output may require intravenous fluids. Treatment should be continued for 7 days but there is little evidence that more prolonged treatment is necessary. Failure to improve demands exclusion of urinary tract obstruction.

Recurrent infection

It is essential in such cases that urine be obtained before and 7–10 days after treatment, both to establish the diagnosis and to define whether recurrence is due to relapse or reinfection.

Relapsing infection In all cases a cause for relapse must be sought. Intravenous urography is essential and plain renal tomography may be required to exclude low density renal stones. In the presence of calculi, in which bacteria can 'hide', it is commonly impossible to eradicate infection unless the stones are removed. Where a cause for relapse cannot be eradicated, antibacterial therapy must be administered in large doses or prolonged courses in an attempt to eradicate the infection – 7 days' treatment with an aminoglycoside or 4–6 weeks' treatment with trimethoprim, co-trimoxazole, amoxycillin or cephadrine. If this fails, patients may be treated with long-term, low dose, suppressive treatment as used prophylactically in recurrent reinfection (*vide infra*).

Bacterial prostatitis is a common cause of relapsing infection in males. The choice of antibacterial drug is dictated by its ability to penetrate the prostate. Most success has been obtained with a prolonged 4–6 week course of co-trimoxazole (960 mg b.d.) or trimethoprim (200 mg b.d.). If this fails, prolonged, 6–12 month, courses of low dose treatment (100 mg of trimethoprim nightly) may be required to suppress reinfection pending eradication of infection by the host defences.

Recurrent reinfection Again, it is critical that urine cultures be obtained as soon as possible after the onset of symptoms to establish whether or not this is infection. Only in this way can patients with recurrent infection be separated from those with recurrent or persisting abacterial frequency/dysuria for whom antibacterial treatment is inappropriate. Culture of urine obtained by SPA may commonly be required.

If shown to be recurrently reinfected – more than two attacks in 6 months – all patients must have an IVU to exclude predisposing abnormality of the urinary tract and to separate patients with complicated versus uncomplicated disease. Initial treatment having been given as for a single attack, patients must be established on a self-help prophylactic regime – at least 2 litres of fluid daily; complete voiding at 2–3 hourly intervals by day, including double-micturition if intravenous urography suggests impaired bladder emptying; voiding before retiring at night and always after coitus. Constipation, which impairs bladder emptying, should be avoided. Bubblebaths or other chemicals in bath water should be avoided, as should vaginal deodorants. Chronic or recurrent vaginitis

must be treated. Large postmicturition bladder residues on IVU require urological assessment.

If, despite such measures, recurrences persist, patients should be established on a prolonged, 12-month, course of low dose prophylactic treatment using trimethoprim (100 mg), co-trimoxazole (480 mg) or nitrofurantoin (50–100 mg) taken last thing at night. Such regimes have been shown to be enormously successful (Cattell *et al.*, 1971; Stamm *et al.*, 1980). Many patients have no further trouble on completing this course but some may have recurrence and require indefinite prophylaxis. Occasionally, breakthrough infection with a resistant organism develops and should be treated as for a single attack, continuing thereafter with prophylaxis.

In women whose infections are clearly related to coitus, prescribing a single dose of trimethoprim (100 mg) or nitrofurantoin (100 mg) after intercourse may be as effective and involves less drug treatment than continuous prophylaxis.

Bacteriuria in pregnancy

Special mention must be made of asymptomatic bacteriuria in pregnant women. This must always be treated, with regular post-treatment cultures throughout pregnancy to ensure continuing abacteriuria because of the high incidence of severe pyelonephritis in such women and the possible risks of prematurity to the infant. Continuous prophylaxis may be required if infection is recurrent, when nitrofurantoin is the drug of choice.

When not to treat bacteriuria

In some patients – e.g. these with multiple inoperable calculi, neurogenic bladders or ileal conduits – it may be impossible to eradicate infection or prevent reinfection. In such patients heroic efforts at treatment may simply lead to infection with polyresistant organisms. Provided it is a low pressure system within the urinary tract these patients commonly tolerate bacteriuria remarkably well. It is thus best to reserve treatment for acute symptomatic episodes of loin pain, fever and systemic upset.

The future

While treatment regimens have become increasingly successful the major problem remains – prevention of reinfection. The solution to this must lie in increased understanding of bladder defence mechanisms and possible means to enhance these. Alternatively, methods must be found to reduce the uropathogenicity of bacteria, possibly by the development of vaccines

directed against bacterial pili to reduce their adhesiveness to uroepithelium. Should this last come about, we may have to turn the clock back and re-examine 'The

role of vaccine therapy in coliform infections of the urinary tract' reviewed by Benians in the first volume of the *Postgraduate Medical Journal* in 1926!

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