

Urinary Tract Infection in Women

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The last twenty years have seen an enormous amount of investigation into urinary tract infection, yet the central question why some women become infected, and particularly why some women become repeatedly infected, remains unanswered. It would certainly add considerably to rational management if there were a simple test, applicable in the clinic to the large number of women who present with urinary tract infection, which would select from among them those who are at particular risk from repeated infection, and therefore need to be followed, and those who require more intensive or more prolonged treatment than is necessary in the great majority of patients.

It is now generally conceded that the causative organisms reside in the patient's own bowel and that the first step in the genesis of infection is colonisation of the anterior urethra. The evidence that the organisms responsible for urinary infection are those of the normal bowel rests, in the case of the commonest organism causing infection, *Escherichia coli*, on the identity of the serotypes most commonly found in normal faeces with those most commonly responsible for urinary infection. This correspondence can be extended to the introitus, where it can again be shown that serotypes most commonly found colonising the anterior urethra are those found most commonly in infected urine.

Sequence of Infection

It is generally believed that the development of urinary tract infection is a sequential process in which colonisation of the anterior urethra is followed by transfer of the organisms to the bladder where they grow in the urine and, in some patients, by ascent of these organisms to the kidneys to cause pyelonephritis. Evidence for the sequential nature of this process is almost entirely derived from the studies of Stamey (1972), who has shown that in women examined at regular intervals a particular serotype appears first in the vaginal vestibule, then colonises the anterior urethra, and subsequently proves to be the serotype responsible for bladder infection. With present understanding of the overall genesis of the disease, two things would appear to follow naturally.

The first is that colonisation of the introitus should be an indication of the likelihood of subsequent infection. The second is that identification of the factors concerned in preventing colonisation of the anterior urethra and the growth of organisms in the bladder urine should make it possible to identify those women in whom the defensive factors are deficient and who are therefore at special risk.

In the event, the vigorous pursuit of these lines of enquiry has turned out to be somewhat disappointing in terms of clinical utility.

This is well illustrated by our own experience of the relationship between introital colonisation and the frequency of subsequent infections (Table 1). There

Table 1. Relationship between introital carriage of enterobacteria and frequency of urinary tract infection.

Carrier	No. of patients with urinary infections per annum	
	None	More than one
Persistent	3	11
Intermittent	19	19
Never	15	4

Data from O'Grady *et al.* (1970)

certainly is a relationship in that patients whose introitus was regularly colonised suffered infection more frequently over the subsequent year than those whose introitus was never colonised, but the correlation is not strong enough to be used as a test to identify women who are at special risk from infection.

Defence against Infection

Much the same thing has been true of the analysis of other factors likely to be involved in the control of the infection process. Unless urinary tract infection is very different from infection elsewhere in the body there are two opposing influences concerned: the constellation of properties in the organism that collectively constitute its uropathogenicity and the constellation of properties in the host that constitute the defence mechanism. This mechanism in various parts of the body is generally composed of mechanical, humoral and cellular elements. The humoral factors concerned, as elsewhere in the body, are part bactericidal substances and part antibody. The cellular factors are phagocytic activity of the uroepithelium itself and that of conventional phagocytes if the inflammatory process involves the bladder wall. The major mechanical defence of the bladder is that organisms multiplying in the bladder are diluted by the incoming sterile ureteric urine and the diluted culture is then discharged at the next micturition.

Efficacy of Mechanical Clearance

If the capacity of patients to wash away their own infection is examined by giving them copious amounts of water to drink and getting them to empty their bladders as completely as possible at regular intervals, the patients fall into several groups. There are those who are able to dilute their infecting organisms so satisfactorily that the concentration of bacteria in the urine falls below detectable levels, usually within four or five hours. In a small proportion of such patients the organisms do not return and they doubtless constitute the few who are able to bring about rapid spontaneous resolution of their disease by diuresis. In the second group of patients the early part of the response is similar in that there is a rapid decline in the concentration of organisms in the voided specimens of urine, but this is soon followed by a state in which the concentration of organisms hovers around 10^4 to 10^5 organisms per ml, and as soon as the patient stops drinking and emptying the bladder frequently—notably when she goes to bed—the organisms resume their original concentration. In the other groups of patients (mostly those with severe defects of the urinary tract like large residual volumes or grossly dilated upper tracts or renal stones) there is very little fall in the concentration of organisms in the urine on copious drinking and frequent micturition.

Prediction of Treatment Response

It seemed reasonable to expect that the capacity of patients to deal with their own infection in this way would be a useful indication of their likely response to treatment. Again, in the event, the application of these tests to patients turned out to be somewhat disappointing. In the patients who promptly reduced their urinary bladder bacteria to very low values, the response to treatment was good (with one exception) but in the patients who were able to exert very little effect on their bladder bacteria the response to treatment was very variable and there were certainly patients within this group who responded very satisfactorily to treatment despite the imperfections of their own mechanical defences (Table 2). One in-

Table 2. Patients' capacity to reduce the concentration of urinary bacteria by diuresis as an indicator of the response to treatment.

Effective therapy	No. of patients with fall in concentration of bacteria/ml to		
	$\leq 10^3$	$\leq 10^5$	$> 10^5$
Initial	8	27	30
Long-term—Low dose	0	15	16
High dose or surgery	1	3	14

Data from Cattell *et al.* (1972)

terpretation of this finding is that in these patients other defence mechanisms were of paramount importance, and that these mechanisms are likely to be of special importance in the clearance of organisms attached to the bladder epithelium. Incoming ureteric urine dilutes the organisms multiplying in the bladder urine, which are then discharged at the next micturition, but any

organisms attached to the uroepithelium remain *in situ* and continue to deliver their progeny into the urine, so that unless there is some other mechanism for their removal, infection will persist.

The importance of such adherent organisms has been shown by means of a mathematical model of the urinary tract (Mackintosh *et al.*, 1975) which compared the responses to regular micturition in the presence or absence of organisms growing on the surface of the bladder. Where there were attached bacteria the response followed the biphasic form (in which the concentration of bacteria in the voided specimens initially falls rapidly but subsequently remains at around 10^4 or 10^5 organisms per ml) which is very commonly shown by patients with bacterial cystitis. If this is the correct explanation for a response commonly observed in patients, then humoral and phagocytic processes directed against adherent organisms are likely to be major determinants of the patient's response, and we have at the present time no simple clinically applicable tests of the efficacy of these processes in patients. We therefore turned our attention to the possibility that patients at special risk or likely to present particular therapeutic problems could be identified from the other half of the host-organism interaction; that is to say by differential features in the organisms that they harbour.

Uropathogenicity

It has been known for a long time that certain differences exist between organisms present in normal faeces and those responsible for urinary tract infection. Notably, it is well established that haemolytic strains are commoner among *Escherichia* recovered from the urine than among organisms in normal faeces. This extends beyond a simple difference between faecal and urinary strains to a systematic increase in the proportion of haemolytic strains among those recovered from the faeces to those specifically identified as infecting the upper urinary tract (Table 3). Even among those organisms localised by direct catheterisation to the upper urinary tract, only 60 per cent were haemolytic. Plainly, the capacity to cause haemolysis is a common but not necessary requisite for strains producing infection of the urinary tract. This magnitude of difference turns out to be so common as to suggest the enunciation of a 'sixty per cent rule of urinary infection'.

Table 3. Proportion of haemolytic strains of *Escherichia coli* isolated from various sites.

Origin	No. tested	Haemolytic (%)
<i>Introitus</i>		
Normal subjects	45	9
Abacteriuric patients	75	21
<i>Urine</i>		
Infection confined to lower tract	29	27
Infection of upper tract	19	58

Data from Brooks (1976)

Large numbers of properties have been identified as possibly or actually correlating with the capacity to infect the urine. They can be divided into a number of groups. There are first of all properties that possibly facilitate the establishment of organisms; for example, the capacity to break down mucin and thus reach the uroepithelium beneath, or the possession of fimbriae that enable organisms to adhere to the epithelium. The specific identity of the organisms, either their biotype or serotype, has also been shown to be correlated. There are properties concerned with the capacity of the organism to grow in urine or to resist the inhibitory activity of substances found in urine such as spermine or urea. There is the capacity of the organism to elaborate toxins, for example haemolysin, and there is, of course, the capacity to resist the host's defences, such as phagocytosis or the bactericidal activity of normal serum. Thus, there is a long list of possible properties that may contribute to the uropathogenicity of *Escherichia coli*. The correlations shown with most of them are generally weak, but it is possible that the successful invader of the urinary tract requires not one or two of these properties but many of them and that it is a constellation of properties that constitutes uropathogenicity.

Combined Properties

This possibility was examined by taking the five properties correlated most strongly with urinary infection and giving each organism a score: thus, an organism which possessed all five properties scored 5 (Table 4).

Table 4. Proportion of *Escherichia coli* strains from various sources with low, intermediate and high scores for combined 'uropathogenic properties'.

Origin	Per cent strains with uropathogenicity score of		
	0/1	2/3	4/5
<i>Introitus</i>			
Normal	47	42	11
Patients	19	60	21
<i>Urine</i>			
Lower tract	17	69	14
Upper tract	16	37	47

Data from Brooks (1976)

Among strains recovered from the introitus of normal women who did not suffer from urinary infection, only about 10 per cent had high scores of 4 or 5. In contrast, of those strains that were identified as responsible for infection of the kidney, about half had scores of 4 or 5—a striking difference—but the proportion of strains with high scores did not even reach the 60 per cent rule. Subsequent formal cluster analysis of all the properties we have examined has not raised the correlation above that obtained by combining the most strongly correlated properties.

Ease of Treatment

So far, we have found no way of plainly identifying patients who are at special risk, either by an analysis of

host factors or by an analysis of the organisms that they harbour. We have, however, a very clear and simple way of identifying those patients who are easy to treat and that is by observing their response to minimal treatment. It has been apparent for some time that patients fall fairly distinctly into two groups: those who respond extremely readily to treatment and those who require much more extended therapy. If patients with the typical response to diuresis are given, when diuresis starts, a single dose of any agent to which the organism is sensitive, the urinary bacterial concentration falls below detectable levels—just as it does in patients who are able to eradicate their own infections—and although no more agent is given, organisms do not reappear for four or five days (Cattell *et al.*, 1968). These studies suggest that patients are ordinarily given far more drug than is necessary to eradicate their infection. There have now been a number of studies in which, for various reasons, usually therapeutic convenience, patients have been treated with single doses of drug and the results have generally been just as good as those obtained with conventional therapy. In a recent study by Bailey and Abbott (1977) the results were exceptionally good in patients receiving a single 2 g oral dose of amoxycillin. Most other studies have not enjoyed success of the same magnitude but there is a growing belief that patients will generally respond as well to extremely brief periods of treatment as they will to conventional treatment for one or two weeks in which the drug is given three or four times a day (Charlton *et al.*, 1976). Studies in our own mechanical model of the infected bladder have also strongly supported the likely efficacy of dosages much below those ordinarily employed (Greenwood and O'Grady, 1977).

Long-term Therapy

Conversely, it has been recognised for some time that those who fail to respond to a short period of treatment, and the period of effective treatment may be very short indeed, may require very prolonged therapy. At one time it was believed that patients with chronic urinary tract infection should be treated, like patients with sub-acute bacterial endocarditis, for six or eight weeks. Trials of such therapy were wholly unsuccessful and it emerged by chance that what were regarded as long periods of treatment were, in fact, nothing like long enough. Over ten years ago we were treating patients with chronic infection, very unsuccessfully, with long-term sulphonamides, and when trimethoprim became available it was natural to add that to the regimen. In the event, this proved to be so successful (O'Grady *et al.*, 1969) that many patients who had suffered from recurrent and distressing symptoms for many years refused to stop the drug, even after it had been administered for many weeks and subsequently for many months. It emerged that patients with chronic relapsing infection or frequent reinfection probably need to be treated for six months in order to prevent subsequent relapse or reinfection in a reasonable proportion of them, perhaps an indication of the very long period for which treatment must be continued in order to allow the defective intrinsic defences to recover (O'Grady *et al.*, 1973b).

Optimum regimens

We have therefore come to the interesting situation, largely by clinical experience rather than by the application of science, that short-term therapy has been too long and long-term therapy has been too short. This idea has been received with justifiable anxiety on two counts. The first is the danger of the emergence of resistance by too brief or too prolonged exposure to the drug and the second is the danger that renal infection will continue to smoulder and give rise in the long term to renal failure because of the inability of these forms of therapy to eradicate intra-renal organisms. It is hard to believe that the application of therapy which is conventional, except that it is greatly shortened in duration, can present a resistance hazard and our experience of very long usage of co-trimoxazole has suggested that, at least up to the present time, the emergence of resistance has not proved to be a limiting factor. That is not to say, of course, that it will not do so, and patients on long-term therapy must be closely followed for the possible emergence of resistance, of superinfection, and of chronic toxicity.

As far as the possibility of inadequate treatment of renal infection is concerned, there are those who believe in the existence of a disease in which infection persists in the kidney, where it can be responsible for progressive injury to the kidney and deterioration of renal function, without the presence of organisms in the urine. If we look at the natural history of patients with urinary tract infection (O'Grady *et al.*, 1973a) they can be divided into a number of groups. One of the most distinctive consists of those patients who suffer from classical symptomatic bacteriuria in which the only episodes they have are associated with both symptoms and significant bacteriuria. They do not suffer from asymptomatic bacteriuria and they do not suffer from symptoms in the absence of bacteriuria. If the urines of this group of sufferers are examined at frequent intervals we find episodes where they excrete excessive numbers of white cells unassociated with symptoms or bacteriuria.

Fairley and Butler (1971) have held that these episodes of pyuria indicate the presence of continuing infection in the kidney. We have argued in the past that this pyuria is a persisting response to extremely brief bladder bacteriuria, but the question remains open and there properly remains a great deal of interest in the possibility of identifying by some simple test those patients who have renal involvement. Numerous tests have been applied, including concentrating capacity and the presence of circulating antibody to the infecting organism. It is probably fair to say that these tests generally, at best, obey the 60 per cent rule. Even where direct ureteric catheterisation is carried out there remains the possibility that organisms shown to be present in the upper tract are, in fact, confined to the collecting system and that the patients are suffering from that classical, but long despised and disregarded disease, pyelitis.

In an area of such interest, importance and uncertainty, the advent of a new test has been received with enthusiasm. This is the presence of antibody-coated bacteria in the urine. If organisms are involved in tissue infection, as they are in the kidney, they are exposed to circulating antibodies with which they become coated,

and those coated bacteria can be demonstrated in the urine. There is no doubt that this is a simple enough non-invasive test and in the hands of a number of workers a very high degree of correlation has been shown between the presence of such antibody-coated bacteria in the urine and identified upper tract infection. However, Rumans and Vosti (1978) applied this test in the clinic to a mixed group of patients. Of those in whom they had good reason to believe that upper tract infection was present, 60 per cent were excreting antibody-coated bacteria. The 60 per cent rule was classically obeyed, which is not of much clinical help.

It appears, therefore, that the effort of two decades has yielded an enormous amount of valuable information about the genesis, limitation and resolution of urinary tract infection but has yet to produce a test that can be used in the clinic to identify, with a high degree of confidence, patients at special risk. On the other hand, there is now good reason to believe that the majority of patients will respond to amounts of drug much smaller than those customarily used, with all that this implies in reduced cost and possible adverse effects. Moreover, the majority of patients who fail to respond to short-term therapy (apart from those with gross abnormalities of the urinary tract or infection with polyresistant organisms) can be controlled or cured by long-term low-dose therapy.

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