

Urinary tract infection in women: A study from general practice

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ACUTE cystitis is a common condition of young and middle-aged women, but in the absence of gross anatomical abnormalities of the urinary tract its relationship to acute and chronic pyelonephritis is poorly defined. Even less is known of the natural history of asymptomatic bacteriuria and its relationship to cystitis and acute or chronic pyelonephritis in the non-pregnant woman. Since one of the main reasons for concern in the management of lower urinary tract infection is the possible development of acute or chronic pyelonephritis, any observations which can select those patients with the greatest risk of renal involvement are valuable.

This paper is a study of urinary infection in a practice of 5,500 patients in semi-rural Surrey where there is an obstetric-paediatric bias due to a high proportion of young married couples, and where social classes II, III and IV, predominate. There is an incubator in the surgery where bacteria can be cultured aerobically at 37° on standard media. The investigation is in three parts. The first comprised the establishment of a reliable method of detecting significant bacteriuria in clean catch urines collected in the patient's home. The second part was a three-month survey of urine specimens collected from all patients attending the surgery, in order to assess the pattern of infection in the community so that the groups with the highest risk of infection could be defined. These two parts of the project have been described elsewhere (Grob *et al* 1970). In this pilot survey, it was found that 80 per cent of urinary infections, irrespective of the presence or absence of symptoms, occurred in women between the ages of 16 and 65 years; further, significant bacteriuria was found in only three per cent of all urines examined regardless of age or sex, but that significant bacteriuria occurred in nine per cent of women aged 16 to 65 years. Hence the third part of the study is to follow this high risk group of women aged 16 to 65 years over the course of five years in order to investigate the inter-relationships of asymptomatic bacteriuria, cystitis, and acute or chronic pyelonephritis. At the time of writing, this part of the survey has been conducted for one year.

Cystitis is defined as frequency of micturition of sudden onset with or without dysuria and is called bacterial or non-bacterial cystitis according to whether significant bacteriuria is found or not. The diagnosis of acute pyelonephritis depends on loin pain and tenderness in association with general symptoms such as rigors, fever, headache, nausea and vomiting. Instances of cystitis with marked loin pain but no loin tenderness or general symptoms are called acute pyelitis and for the purposes of classification are included under acute pyelonephritis. The diagnosis of chronic pyelonephritis ultimately

depends on the characteristic IVP changes of clubbing of calyces due to destruction of pyramidal tissue in association with asymmetrical parenchymal scars.

Method

Women aged 16 to 65 years who attend the surgery for any reason are given a box holding two labelled universal containers, one empty and the other containing a dip inoculum spoon (Mackey and Sandys 1965, 1966).

Instructions on the collection of a clean catch early morning specimen of urine and immediate inoculation of the medium on the spoon are given in the box, which is returned to the surgery the same morning and incubated on the premises. The spoon was filled with MacConkey medium which did not inhibit the growth of *Streptococcus faecalis* or staphylococci and which was known to grow the usual urinary pathogens. Colony counts on the spoons were correlated with bacterial counts using layered pour plates and spread plates; the results of this comparison showed that when there were less than 10,000 bacteria per ml there were less than 20 colonies on the spoon, while when there were more than 100,000 bacteria per ml there was semiconfluent or confluent growth on the spoon.

The criteria of infection are based on those of Kass (1957), namely a pure growth of an organism at a concentration of more than 100,000 bacteria per ml in a clean catch early morning urine. Since a single urine specimen is liable to misinterpretation, a positive result should be reproducible on two further specimens when there will be a 96 per cent confidence rate compared with catheter specimens. When symptoms are severe and it is unreasonable to expect the patient to submit three morning specimens prior to receiving treatment, three consecutive urines are obtained irrespective of the time of day. A further criterion of infection is that the organism isolated should be a urinary tract pathogen of the type normally found in general practice; for all practical purposes this means *Escherichia coli*. A heavy growth of staphylococci, *Strep. faecalis*, or *Pseudomonas pyocyanea* were regarded as contaminants until proved otherwise by repeated specimens and correlation with symptoms.

Treatment is given to all women with severe or moderate symptoms of urinary tract infection, and is usually sulphadimidine 0.5 gm q.d.s. for one week if the diagnosis is cystitis, or ampicillin 0.5 gm q.d.s. for one week if the diagnosis is acute pyelonephritis. Patients with asymptomatic bacteriuria are left untreated except in pregnancy where the known high risk of developing acute pyelonephritis makes treatment mandatory. Apart from the first month following acute infection when urines are examined at weekly intervals, urines are obtained every three months from patients with a known episode of infection occurring during the study. Other women are asked to submit one urine each year.

Blood is taken from patients with bacteriuria for blood urea estimation and for serum antibody levels to the infecting organism which are tested according to the method of Percival *et al* (1964). Intra-venous pyelograms are performed if the patient has recurrent bacterial cystitis, acute pyelonephritis, asymptomatic bacteriuria of pregnancy, or if there is failure of eradication or rapid relapse (within six weeks of stopping treatment) of infection in a single episode of bacterial cystitis.

Positive spoon cultures were sub-cultured onto MacConkey media and single colonies were picked into peptone water for subsequent identification by the methods of Carpenter *et al* (1966).

Results

Urine specimens were obtained from 720 out of 1,410 women in the practice in the age-group 16 to 65 years. Symptoms of infection or asymptomatic bacteriuria occurred in 72 women; of these 11 had only non-bacterial cystitis. Hence 61 women (8.5 per cent) had significant bacteriuria. Asymptomatic bacteriuria was the presenting feature in 19 women, bacterial cystitis in 38, and four presented with acute pyelonephritis. The age of the patient at the time of this study and the nature of the presenting episode are shown in table I.

The past history of these infected patients was examined by reference to past notes and by direct questioning. The age of onset (table II) shows a shift towards youth largely because many of the patients detected in the survey had experienced cystitis or acute pyelonephritis some years previously. The overall numbers are increased because some patients had suffered more than one type of infection either in the past or during the time

TABLE I
DISTRIBUTION BY AGE OF THE PRESENTING FEATURE DURING SURVEY

<i>Years</i>	<i>15—24</i>	<i>25—34</i>	<i>35—44</i>	<i>54—54</i>	<i>55—64</i>	<i>Total</i>
Asympt. bacteriuria	1	3	3	6	6	19
Bact. cystitis	8	15	10	2	3	38
Ac. pyelonephritis	3	1	—	—	—	4
<i>No. of patients examined</i>	128	223	185	108	76	720

of the survey. The maximum incidence of cystitis is in the age-group 25 to 44 years. By comparison, asymptomatic bacteriuria was most often the presenting feature in women in the group 45 to 64 years, and acute pyelonephritis in the group 16 to 24 years. When the date of the first episode of symptoms is taken into account, the age distribution of cystitis is shifted to a maximum incidence in the group 16 to 34 years. In table II the age distribution of asymptomatic bacteriuria is more evenly spread due to the detection of episodes occurring during the follow-up of patients presenting in the survey with acute pyelonephritis. The group of cases with acute pyelonephritis is swollen by the addition of patients who, although presenting with asymptomatic bacteriuria or cystitis, either had a previous history of acute pyelonephritis or developed it during the period of follow-up, but the distribution remains restricted to the age-group 16 to 34 years.

TABLE II
DISTRIBUTION BY AGE OF ONSET OF EACH TYPE OF DISORDER BEFORE OR DURING SURVEY

<i>Years</i>	<i>15—24</i>	<i>25—34</i>	<i>35—44</i>	<i>54—54</i>	<i>55—64</i>	<i>Total</i>
Asympt. bacteriuria	4	4	4	5	5	22
Cystitis	11	14	10	2	2	39
Acute pyelonephritis	9	7	—	—	—	16

When the inter-relationships of the clinical syndromes are examined (table III) the high incidence of past, or the development of an acute attack during follow-up in patients with asymptomatic bacteriuria should be noted. Of the 19 cases, seven (37 per cent) had such a history, and only three had a history of cystitis. The symptoms of cystitis of two of these three had never been severe enough to consult their doctor; the third developed some frequency but no dysuria during follow-up.

When the 38 patients presenting with bacterial cystitis are similarly reviewed, three had a history of a single episode of acute pyelonephritis; however, in all three, the episode of acute pyelonephritis had preceded any symptoms of cystitis, and so these cases do not show the development of acute pyelonephritis in a patient already suffering from cystitis. None of the 38 developed acute pyelonephritis during the follow-up. By contrast, cystitis is often a recurring disorder, since ten patients had one or more episodes of cystitis per year for at least three preceding years, and another five had suffered cystitis at least once before. Further episodes of cystitis occurred in 13 patients during observation, the majority being in those already recognized as suffering from recurrent cystitis. In all 13 patients, clear urine specimens had been obtained between their episodes of

cystitis, and on three occasions had been negative as short a time as one week prior to the further episode.

Acute pyelonephritis occurred on eight occasions in seven patients and there were three episodes of acute pyelitis involving two patients during the study. Of these nine patients, three had episodes of acute pyelonephritis prior to the survey; in four the

TABLE III
HISTORY OF PATIENTS PRESENTING WITH ASYMPTOMATIC BACTERIURIA

	Number of patients 19	
	Past history	Developed on follow-up
Cystitis	2	1
Acute pyelonephritis	5	3

HISTORY OF PATIENTS PRESENTING WITH BACTERIAL CYSTITIS

	Number of patients 38	
	Past history	Developed on follow-up
Asymptomatic bacteriuria	1	2
Cystitis	15	13
Acute pyelonephritis	3	—

episode of acute pyelonephritis was their first urinary tract illness; acute pyelonephritis had been preceded by asymptomatic bacteriuria on three occasions (two of them in pregnancy). Radiological evidence of renal damage was found in four of these nine patients, in three being characteristic of chronic pyelonephritis.

Episodes of non-bacterial cystitis were seen on 18 occasions; five of these patients also had bacterial cystitis at other times, and two suffered from recurrent non-bacterial cystitis.

In 80 per cent of episodes of significant bacteriuria, a strain of *E. coli* sensitive to all the widely used drugs such as sulphonamides, nalidixic acid, nitrofurantoin, tetracycline, ampicillin and trimethoprim was isolated. A strain of *E. coli* resistant to one or two of these drugs was isolated on a further ten per cent of occasions, the drug to which resistance was most often found being sulphadimidine. Occasional isolates of *Proteus sp.*, *Klebsiella sp.*, or *Staphylococcus albus* made up the remainder.

The density of bacterial growth on the spoons was usually confluent in the patients with asymptomatic bacteriuria, whilst in patients with acute cystitis, colony counts varied from 20 to a semi-confluent growth, usually being more than 60 colonies; confluent growth was not often seen under these circumstances.

Intravenous pyelograms have been performed on 22 patients selected according to the criteria outlined previously. In six there were abnormalities of the pelvi-calyceal systems; of these three had changes characteristic of chronic pyelonephritis, and one had also a unilateral medullary sponge kidney; the remaining two had non-specific abnormalities. None of these six had ever had cystitis, two had presented with acute pyelitis, two with asymptomatic bacteriuria of pregnancy, and two with asymptomatic bacteriuria outside of pregnancy but also had a history of acute pyelonephritis.

One patient had a raised titre of serum antibody to the infecting organism (1:640); she was aged 60 years, had no previous or present history of urinary tract disorder and had a normal IVP.

The blood urea was normal in all cases except one woman of 49 who had recurrent acute pyelonephritis, asymptomatic bacteriuria, and is developing renal failure in association with DLE.

Discussion

There appears to be a positive relationship between asymptomatic bacteriuria on the one hand, and acute pyelonephritis on the other, since 37 per cent of patients with asymptomatic bacteriuria have a history of acute pyelonephritis. As four of the six patients with radiological abnormalities came from this group, asymptomatic bacteriuria may also be positively related to chronic pyelonephritis. The association between asymptomatic bacteriuria and acute or chronic pyelonephritis may be due either to ascending infection to the kidneys, especially likely during pregnancy, from a symptomless focus of infection in bladder urine, or may be due to seeding of the lower tract by bacteria persistently or intermittently released from a persistent focus of infection in the kidneys (descending infection). If the latter is the true explanation, infection may have originally reached the kidneys either from the bloodstream or by ascent from the lower tract. In infancy acute pyelonephritis is often associated with positive blood cultures, and there is a possibility that scarred kidneys begin with selective persistence of bacteria in a congenitally abnormally developed (dysplastic) area of the kidney following an episode of bacteraemia.

There is no apparent association between asymptomatic bacteriuria and acute cystitis, since at the most only 17 per cent of patients with asymptomatic bacteriuria had a history of cystitis. Of the 38 patients who presented with acute cystitis, two were later observed to have a transient episode of symptomless bacteriuria. The history of 100 randomly-questioned women who supplied negative urines showed that 48 per cent had suffered cystitis once or more in the past, and two per cent acute pyelonephritis. Hence the observed relationships between pyelonephritis and asymptomatic bacteriuria, and the lack of relationship between cystitis and either asymptomatic bacteriuria or acute pyelonephritis, are all the more striking.

That cystitis is frequently a recurring condition is shown by the high incidence of previous recurrent cystitis (26 per cent) and of further episodes of cystitis during the year of follow-up (34 per cent). Since five of the 16 patients with non-bacterial cystitis also had an episode of bacterial cystitis while under observation, it is possible that the two are associated conditions, the final diagnosis resting solely on the ability, or lack of it, of the infecting organism to extend from the urethra to assume such an established position in the bladder as to be able to multiply there. In the patient with dysuria and frequency it is important to separate the two disorders since the presence of an established infection in the bladder may be followed by reflux of urine and bacteria through an inflamed, and hence incompetent, ureterovesical junction to the upper urinary tract. No attempt was made in this survey to look for the aetiological agents of non-bacterial cystitis, such as viruses, mycoplasmas, trichomonads, or even esoteric bacterial infections such as tuberculosis or gonorrhoea; traumatic and chemical factors were not sought.

Both acute cystitis and acute pyelonephritis occur most often in women between the ages of 16 and 34; only three patients had experienced both conditions and in all, the episode of acute pyelonephritis had preceded that of cystitis. Renal damage on IVP had been found in four of the ten patients with asymptomatic bacteriuria in whom such an examination had been performed, and in six of 12 patients with a history of acute pyelonephritis; in contrast IVPS had been performed in ten women with either recurrent cystitis or a single infection in which eradication had proved difficult and evidence of renal damage was found in none. It has been suggested that failure of eradication of urinary infection, or its recurrence due to a similar organism within six weeks of stopping treatment, is an effective method of selecting patients for IVP who will show abnormalities; in our small series this criterion has not proved helpful.

Some points regarding bacteriological technique are pertinent. Some of the strains of *E. coli* isolated were late lactose fermenters under optimum conditions and, using standard methods of estimating such fermentative ability, could easily have been mislabelled paracolon organisms and hence perhaps be dismissed as contaminants. Furthermore, particular care in sensitivity testing is needed if some sulphonamide sensitive strains of *E. coli* are not to be called sulphonamide resistant. The presence of at least one per cent lysed blood is necessary in the media used for sensitivity plates.

A third point is the need for flexibility in applying the "100,000 bacteria per ml means infection" rule, since in the face of marked frequency and dysuria and the patient's self-administered high fluid intake, the effects of dilute urine rapidly emptied from the bladder in the presence of an acute local inflammatory response diminish the ability of bacteria to multiply in the bladder to reach the 100,000 bacteria per ml concentration. Under these circumstances a light (as little as 10 to 20 colonies on the spoon) but pure growth of *E. coli* in three successive urine specimens prior to treatment can be accepted as significant bacteriuria. The relative absence of contaminants in urines infected with *E. coli* is an as yet unexplained observation.

Conclusion

In order to explain some of these observations, the hypothesis is advanced that the presence of bacteria in the urinary tract may be revealed in one of two ways; first, in association with an acute inflammatory response in the bladder causing symptoms such as dysuria and frequency leading to the patient receiving chemotherapeutic or antibiotic drugs, and due to one or both of these antibacterial factors bacterial invasion is limited to bladder urine, excluded from the upper tract, and then eradicated until the next episode of cystitis occurs—the kidneys remain unharmed. Alternatively, an acute inflammatory response in the bladder does not occur—there are no severe symptoms and the patient does not usually receive specific treatment. In this group bacterial invasion of bladder urine continues without symptoms and there is a high incidence of renal involvement as either acute or chronic pyelonephritis, or both. Whether symptomless bladder urine infection precedes or follows renal involvement is a matter for conjecture, and on this point the controversy of ascending or descending infection of the urinary tract hinges.

The testing of this hypothesis will be conducted by a five-year study of the interrelationships of asymptomatic bacteriuria, cystitis, acute and chronic pyelonephritis. On the results of this study it should be possible to give guidance to the practitioner in selecting those patients who are at the highest risk of progressive renal damage due to bacterial invasion.

Acknowledgements

We are grateful to Dr G. T. Cook, of the Public Health Laboratory, Guildford, for the encouragement and facilities he has provided, and Dr J. S. Cameron, physician in charge of the renal unit at Guy's Hospital for his advice throughout this project.

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