The Central African
Journal of Medicine

Volume 18 OCTOBER, 1972. No. 10

The Modern Management of Bacterial Urinary Tract Infections

BY

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Urinary tract infections are common, and can now be managed very effectively. Management should not only have as its goal the removal of symptoms but also the elimination of the bacteriuria which may underline them, the detection and prevention of recurrences, and finally the identification of patients with abnormal or damaged urinary tracts.

Urine is a very good culture medium for bacteria, (Asscher *et al.*, 1966), as anyone who has left it around at room temperature will know, and the bladder urine is continually being contaminated from below, especially in the female. How is it that we do not all have bacteriuria or symptoms all the time? The defences of the bladder are twofold. First, there is the washout effect of voiding urine. Normally less than 1 ml. of urine is left in the bladder and, if infected, will be diluted with further urine flow. Second, the bladder wall has an ill-understood bactericidal action (Norden *et al.*, 1968) but only for bacteria in a film over it. IgA secreted by the urinary tract may also be important (Kaufman *et al.*, 1970) and prostatic fluid is bactericidal. These defence mechanisms emphasise the importance of residual urine in the maintenance of infection once it has gained a hold, since there will be a larger pool of urine in which the bacteria can grow, and the bacteria in the urine will be kept away from the bactericidal bladder wall. They also emphasise the importance of a high urine flow and bladder emptying during the treatment of urinary tract infections.

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Symptoms

Symptoms of urinary tract infection in general practice are very common. However, of patients who present in general practice with complaints of frequency, urgency, nocturia or difficulty in micturition, only half will show conventional bacterial pathogens, even on the most careful examination (Gallagher *et al.*, 1965; Mond *et al.*, 1965).

The remainder have what is usually called the "urethral syndrome", or else non-specific urethritis (BMJ 1971a) or gonorrhoea. The first may be a great nuisance, since it can be associated with sexual activity, and can be difficult to treat. Pyridium (phenazopyridine) may be used as a urinary analgesic.

The presence of these complaints of lower urinary tract inflammation indicate bacteriuria, but if there are in addition loin pain, fever or rigors, then infection is almost certainly present and involves the upper urinary tract and the kidney. The reverse, however, is *not* true; a patient with only symptoms of bladder irritation may well have kidney infection.

Symptomless Bacteriuria (Asscher, 1970)

For every patient who comes complaining of urinary tract symptoms there is at least one other who does not, but has bacterial infection of the urinary tract. This is usually called "symptomless" bacteriuria. On close questioning, many of these patients do in fact suffer from symptoms (Meadow *et al.*, 1969; Savage *et al.*, 1969) but they (or in children, their parents) have not thought these significant. This rather confusing situation must be borne carefully in mind, and is summarised in fig. 1.

It must also be remembered that in the very young and the very old, symptoms of urinary tract infection may be quite non-specific, and that septicaemia is common in both these groups, with shock and even jaundice the dominant features in severely ill patients (BMJ, 197 lb.)

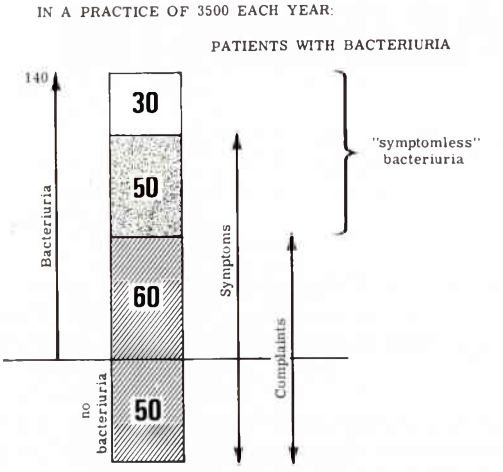
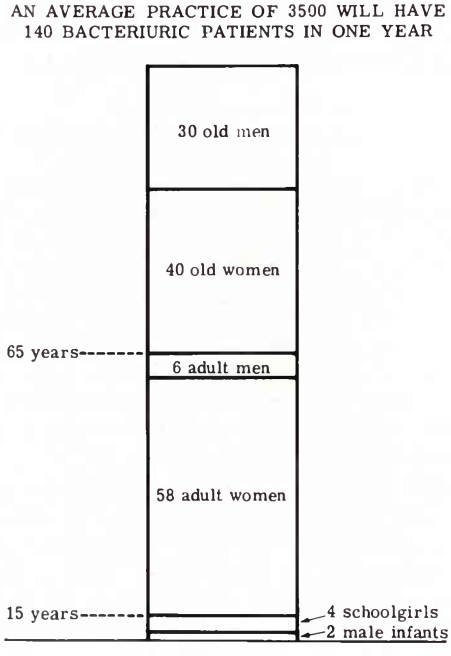


Fig. 1(a). — The distribution and numbers of patients with symptoms of urinary tract infection, and with bacteriuria, in a typical general practice of 3 500 patients (Gallagher *et al.*, 1965; Mond *et al.*, 1965 Steensberg *et al.*, 1970) 140 patients will be found to have bacteriuria, but less than half of these will come with complaints to their doctor. Conversely, of those that do come with complaints of dysuria and frequency, only half will show bacteriuria with current techniques.

Fig. 1(b). — The approximate distribution of these 140 bacteriuric patients by sex and age, based upon the data in Table 1.



INCIDENCE

Bacteriuria is common, and except in the neonatal period is much commoner in females than males. Table 1 summarises studies from European communities in several parts of the world:

Table 1

Prevalence of bacteriuria in the general population of Britain and Scandinavia.

	Age in years	Males %	Females %
Infants	0- 1	2, 5	0,3
Children	1-15	0,04	1,2
Adults	15-65	0, 5	5,0
Old People	65-70	3, 0	20,0
Old People	70+	20, 0	20,0
Old People institutions		50, 0	50-60

From Lincoln and Winberg (1954); Brocklehurst *et al.*, (1968); Kunin *et al.*, (1964); Meadow *et al.*, (1969); Savage *et al.*, (1969); Steensberg *et al.*, (1970); Sussman *et al.* (1969).

The very high incidence of urinary tract infection in old people (Brocklehurst *et al.*, 1968) deserves attention since the symptoms in this age group are often non-specific — for example, mental confusion, fever, refusal of food or weight loss.

The importance of symptomless bacteriuria in pregnant women has received much attention; this is present in about 7 per cent of pregnant women, and up to 40 per cent. of these infected will have overt urinary infections with symptoms later in pregnancy (Elder and Kass, 1967) which treatment can prevent. It is therefore worth while screening all pregnant women for bacteriuria at their first antenatal visit and treating those found. Whether there is an increase incidence of toxaemia, premature birth or foetal loss in symptomless bacteriuric women has been hotly debated (Kass, 1960; Little, 1966).

DIAGNOSIS

The diagnosis of bacterial urinary tract infection depends upon *quantitative* culture of *fresh* urine. Today, less than this is a waste of both the clinician's and the laboratory's time. Kass (1956) pointed out that using the clean catch mid-stream speciman of urine, contamination by urethral organisms could be distinguished from bacterial multiplication in bladder urine by culturing the urine within half an hour of voiding

(to minimise overgrowth of contaminating organisms) in a quantative fashion. Under these conditions, a growth of more than 10^5 organisms/ml of urine gave an 80 per cent. chance of true infection, and repeat culture at a similar level raised this chance to 95 per cent. Contamination usually gives 10^3 organisms/ml. Figures between 10^3-10^5 per ml must be repeated until they give an unequivocal result.

Most urinary tract infections are accompanied by an excess of leucocytes in the urine, but by no means all (Kass, 1956); for example in the school girls studied by Savage *et al.*, (1969) only 60 per cent. of bacteriuric girls had excess leucocytes in their urine. Conversely, in the school girls studied by Meadow *et al.*, (1969), of 96 girls showing pyuria on one occasion, only 61 showed this in the repeat sample, and only 10 were bacteriuric in quantitative culture. In Central Africa, the prevalence of *S. haematobium* infection must render the use of leucocyturia a very unreliable index of bacterial infection indeed. Where a microscope *is* useful is in revealing either motile bacteria in fresh specimens of unstained urine, or gram stained preparations of bacteria in the great majority of patients with more than 10^5 bacteria/ml in their culture.

Chemical testing might be thought to have advantages, but have so far proved disappointing. The nitrate test (Kahler and Guze, 1957) is positive in only 65 per cent. of cases; the TTC method (Simmons and Williams, 1967) has a much better performance, but of course gives neither the organism nor its sensitivities and is particularly poor at detecting *Ps. aeruginosa* infection. The method dependent upon the reduction by bacteria of the minute amounts of glucose in the urine (Scherstén *et al.*, 1968) suffers from the same problem, and in addition the "Uriglox" sticks incorporating this method can only be used on fasting early morning urines and in the absence of renal function impairment.

We return therefore to *quantitative culture of fresh urine*. If this is to be done in the laboratory multiplication of organisms can be prevented in transit by refrigeration at 4°C (adequate up to 24 hours, probably 48 hours) or more simply by adding 1.8 per cent boric acid to the urine (Porter and Brodie, 1969) which prevents multiplication, but does not kill the bacteria. However, the introduction of dip inoculation media as slides (Guttmann and Naylor, 1967) or spoons (Mackey and Sandys, 1965) seems the preferable method, which allows the practitioner to perform a quantitive culture himself at the bedside or in his clinic, to read the result and (if necessary) send off the slide through the post for further study or identification of the organism in the laboratory. A dip-slide, and its uses are described in detail in figure 2. At the time of writing these are not yet available in Central Africa but this should be remedied shortly.

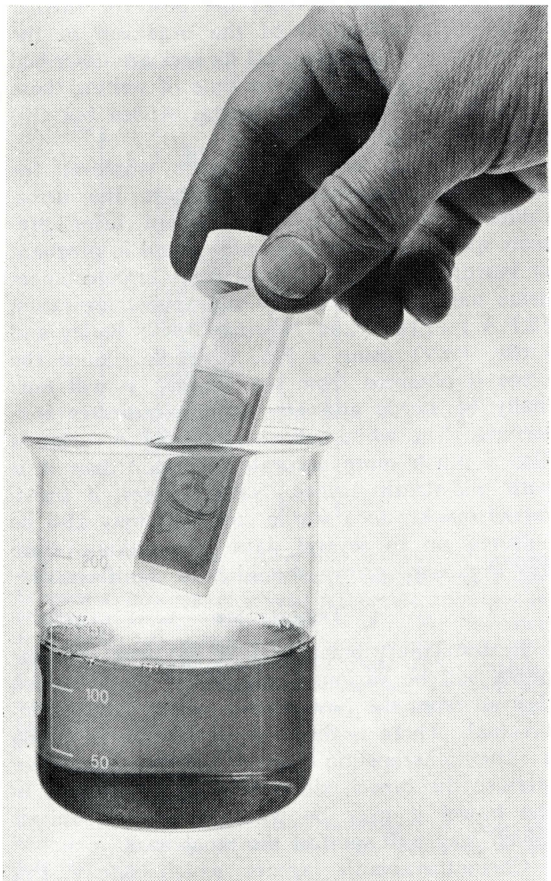
There is no longer any place whatever for diagnostic catheterisation to culture the urine. Collecting mid-stream specimens of urine presents special difficulties in infants and in pregnant or parturient women. Under these circumstances urine may be collected by suprapubic aspiration (S.P.A.) (Eykyn and Newman 1969; Bailey and Little, 1969) using a No. 1 needle. Since the urine is obtained from the bladder, it will normally be sterile and any growth indicates bacteriuria. The white cell count on S.P.A. urine is also a much more accurate indicator than it is with mid-stream urines. S.P.A. urines, if transferred quickly to a sterile container may also be cultured up to several days after taking, since any organisms grown should have significance.

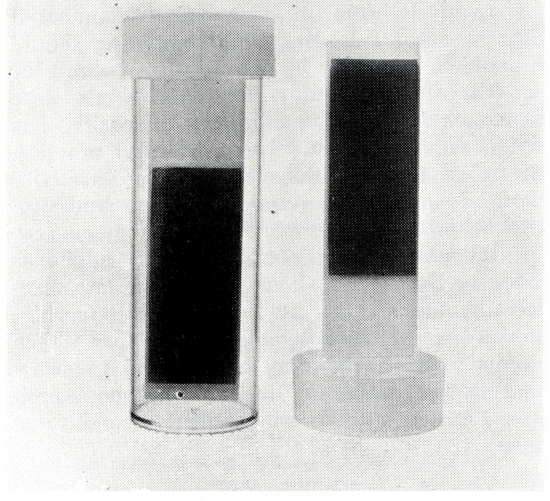
Treatment

In domiciliary practice 80-90 per cent. of organisms will be various serotypes of *E.coli* which derived from the bowel flora of the infected individual. There is therefore advantage in giving a chemotherapeutic agent which does *not* sterilise the bowel, since if re-growth occurs in the bowel it may be with resistant organisms which may well reinfect the renal tract.

Chemotherapeutic agents which satisfy this requirement include sulphonamides, nitrofurantoin and naladixic acid. Of these, by far the best variety of modern soluble sulphonamide such as sulphadimidine or sulphafurazole are much cheaper, equally effective (85 per cent of organisms are sensitive in most domiciliary practice) and relatively free of side effects compared with the other two drugs. Sulphadiazine should be avoided, especially in hot climates, because of the risk of crystalluria. The new single dose sulphonamide, sulphormethoxine (Fanasil), has obvious advantages in mission or rural practice, but has a higher incidence of acute sensitivity reactions in children, and is more expensive. Sulphonamides can be used safely in pregnancy.

If the patient does not respond to sulphonamides, or the culture shows one of the less common organisms such as *Proteus, Strep.faecalis, Staph.albus* or *Pseudomonas aeruginosa* then antibiotic sensitivities may be required to determine the best antibiotic. In the meantime, Ampicillin 250 mg. q.d.s. is an excellent second agent to use.





Throughout the treatment a high urine flow should be maintained, especially if the patient is febrile and in a hot climate such as in Central Africa. This has two effects: organisms multiply less readily in dilute uric (Asscher, *et al.*, 1966) and the maximum effect of washout is obtained. The slight dilution or urinary antibiotic concentration does not seem to matter. Alkalinisation of the urine also slows multiplication of *E.coli* and enhances sulphonamide excretion in the urine, but care must be taken with potassium-containing alkalies, if renal function is impaired.

Follow Up

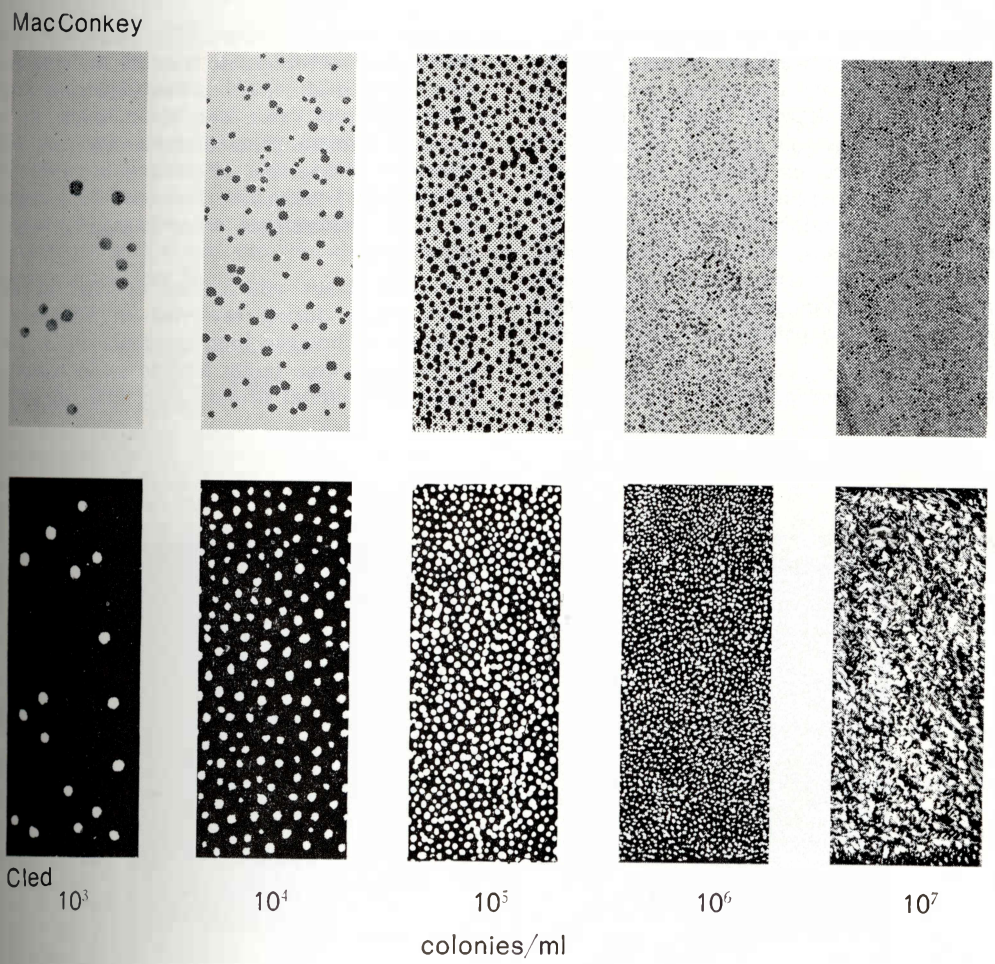
There is no evidence that courses of treatment longer than one week are more effective than the seven day treatment. In fact they may obscure the next phase of the managment, which is to see

Fig. 2. — The dip inoculation technique. The method shown here is the 'Uricult' dip-slide, obtainable from Lääketehedas Orion Oy, P.O. Box 10019, Helsinki 10, Finland.

Fig. 2(a). — The slide consists of a plate each side of which is coated with agar. One side has McConkey, the other Cled medium. The whole is prepared and packed sterile in a robust outer container. For use, a fresh clean catch midstream specimen of urine is obtained by the usual technique. In males, the glans is cleaned with plain soap and water or sterile saline and a swab. In females, the labia are separated and the introitus similarly cleaned from front to back three times. Disinfectants or antiseptics should *not* be used. Urine is then passed and a mid-stream specimen collected either in a sterile container or a freshly scalded domestic container. Sufficient should be collected to cover the agar part of the slide held vertically. The dip-slide is then removed from the container, dipped once into the urine to immerse the agar (2b) and removed. Holding the slide vertically the end should be blotted on to clean blotting paper, tissue or paper towel until no further excess urine comes off: usually two or three applications are enough. The slide is then replaced in its container. The container and slide may then be placed in a 37°C incubator for 16-24 hours, or placed in a warm situation such as a domestic airing cupboard or radiator (Arneil *et al.*, 1970). It can be sent direct to the laboratory for incubation on arrival. After incubation, the number of clones (colonies) on the slide is compared with the chart supplied 2(c) (the original is in colour). As a rough guide 10 colonies = 10^3 organisms/ml, 100 colonies = 10^4/ml/side and 1 000 = 10^5; 10^6 organisms/ml produces a near confluent, and 10^7/ml a confluent growth. Pictures of the actual slides are given in 2(b). Equivocal readings between 10^3 and 10^5/ml should be repeated.

S. Faecalis grows slowly or not at all on McConkey at room temperature, and infection with this organism cannot be excluded unless 24 hours incubation at 37°C is used. Gram negative rods, on the other hand, grow well, those lactose-fermenting appearing as pink colonies.

Subculture for sensitivities and identification of the organism can be performed direct from the colonies on the slide.



who among the patients will relapse with or without symptoms. Relapse or recurrence is frequent, bacteriuria recurring within six months in 50 per cent of patients. It is therefore very important to culture the urine again. One, three or six months are suitable times for detecting recurrent bacteriuria. If this is found there is presumptive evidence that the patient either has some defect in the defence mechanism or the urinary tract, or else some structural abnormality.

Infection is rare in males under the age of 40-50 years of age and correspondingly is associated in most instances with some urinary tract abnormality. *All* male children and young men should therefore be investigated even in the first attack of overt infection, or at the time bacteriuria is picked up on screening. With the much larger number of women showing bacteriuria, the position is more difficult since the great majority have normal urinary tracts and will do well. A rule of thumb is to investigate all those who show relapses, with or without symptoms, as outlined above. Some would wait for two relapses before moving, but it must be recognised that a few women and girls show damaged kidneys even in what clinically appears to be their first attack.

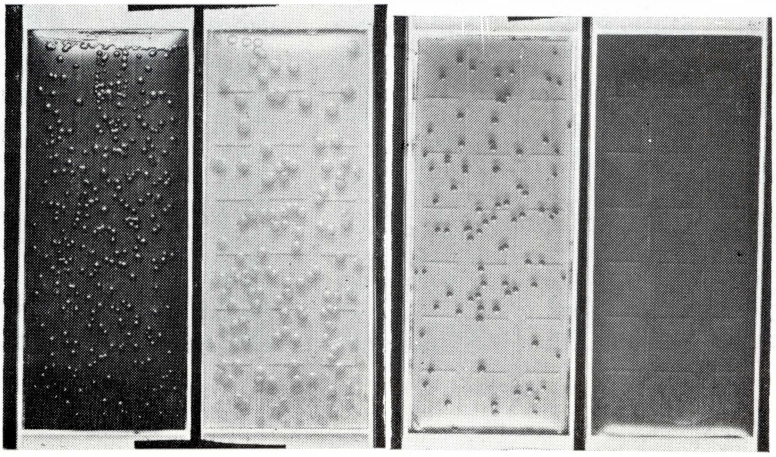
Investigation

Investigation of selected patients should at least consist of an IVP and some assessment of renal function, at the simplest a blood urea. Patients with abnormal IVPs should then have a micturating cystogram to see if there is either reflux of urine into the ureters during micturition or whether the outflow tract of the bladder is obstructed in any way. If this is the case then the help of a urological surgeon may be re-

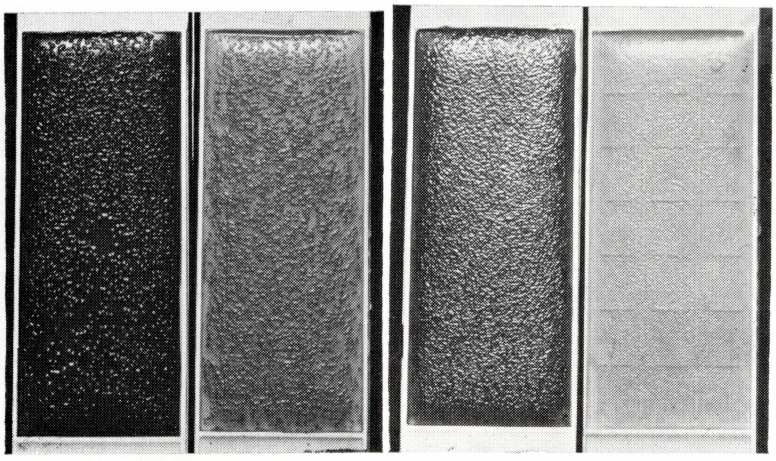
quired. Some reflux of urine is common especially during active infection, probably of little significance, and improves or disappears with time. Gross reflux with renal scarring, however, deserves attention. Detection of this type of abnormality is of great importance in children, since there is no doubt that some children can be saved from renal failure later in adolescence or adult life. Admittedly there are only a very small minority of these at risk, but long term chemotherapy, surgical correction of drainage problems, or both treatments in deserving patients can achieve remarkable results.

Long-term chemotherapy may be simple sulphonamides as before (Normand and Smellie, 1965), but considerable success is obtained in patients with abnormal urinary tracts and recurrent infections using one tablet a day or even less of a trimethoprim-sulphonamide combination (Bactrim or Septrin) (Cattell *et al.*, 1971). The low dosage is attractive in view of the high cost of these preparations when compared with sulphonamides.

One problem which was debated at almost every place during my visit to Rhodesia was whether or not the high incidence of *S. haematobium* infection, might lead to an increased incidence of bacterial urinary tract infection. Clearly



10^4 10^{3-4}



10^5 10^{6-7}

this is so when there is gross obstruction, pyonephrosis and septicaemia, but at the more subtle level of interference with ureteric motility it would be very interesting to know. Opinions both for and against the idea were vigorously expressed, but hard facts still seem to be lacking. We hope to organise an investigation into just this point, using 'Uricult' dip inoculation media, at Hararie in the near future.

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