Urinary tract infection – Some recent concepts

Ross R. Bailey, M.D. (N.Z.), CH.B., M.R.A.C.P., M.R.C.P. (U.K.),
London, Ont.

Diagnosis of urinary tract infection (UTI)

It cannot be denied that the diagnosis of UTI in women constitutes a problem in clinical practice. Furthermore there are difficulties in the management of these infections which make a careful follow-up of such patients essential. To enable this follow-up to be confined only to patients who really were infected, accurate diagnosis is essential. It is adequate to define UTI simply as a condition in which bacteria are multiplying within the urinary tract. The diagnosis therefore consists of demonstrating that this is occurring in some site other than the distal urethra which, particularly in women, is normally invaded by the perineal flora. Special problems such as infection of the urinary tract by viruses, the gonococcus and the tubercle bacillus will not be considered in this discussion.

There is no justification, except in unusual circumstances, for obtaining a catheter specimen of urine for culture. Although a specimen obtained in this manner rarely leads to false positive results it does introduce bacteria into the bladder, it is uncomfortable and also time-consuming.

The most widely used method of obtaining urine for culture is by the clean-catch mid-stream (MSU) technique. All of the many variations of this method suffer from the disadvantage that some contamination of the urine specimen is inevitable. As only 2% of normal women are able to void a completely sterile urine[1] it is necessary to quantitate the bacterial content of the MSU specimen. Kass[2] provided systematic statistical analyses of bacterial counts of urine in order to establish reliable criteria for separating contamination from true infection with gram-negative bacilli. No corresponding data were produced for infections with gram-positive cocci. These findings have been misinterpreted by many, even though Kass stressed that it was necessary to accept several basic principles when interpreting the results. A single MSU specimen from which can be cultured over 100,000 colonies per ml. represents only an 80% confidence level in diagnosing UTI. This means that one in five of positive cultures are false positives and represent gross contamination of the specimen. Such an error rate has been obtained under ideal conditions from populations of healthy, agile, co-operative young women attending special screening clinics.[3-5] To ensure more accuracy in diagnosis multiple cultures are necessary, although allowance must be made for the fact that some women with sterile bladder urine persistently produce heavily contaminated MSUs. Such women carry large numbers of enterobacterial organisms in the introital region.[6]

In general practice, in hospital practice and in the majority of outpatient clinics there is no preparation or supervision of patients prior to, or during, the collection of the urine samples and invariably an unacceptable delay in culturing the specimens. Special problems also exist in the collection of samples from infants, children, the elderly, bedridden or paraplegic patients, from women who are menstruating or who have a vaginal discharge, and from patients in the post-surgical or postpartum period. In infants and children the confidence limit for a single positive culture from an MSU or from a specimen collected in an adhesive bag is less than 40%[7] while in women in the puerperium, even with extremely careful urine collection, 30% of cultures have been demonstrated to give false positive results.[5] This high rate of false positive cultures is totally unacceptable.

Colony counting on MSUs is admittedly laborious but this has been simplified by the introduction of the many variations of the dip-inoculum method which are now commercially available and by the filter-paper method.[8] Chemical screening tests have proved generally unsatisfactory and are too crude for individual patient examination.

Symptomatic UTIs are usually accompanied by more than 10 leukocytes per c.mm. of uncentrifuged fresh urine, and if contamination of the specimen can be excluded, this is evidence of an inflammatory (not necessarily infective) process. The

From the Renal Unit, Victoria Hospital and Department of Medicine, University of Western Ontario, London, Ontario.
Reprint requests to: Dr. Ross R. Bailey, Renal Unit, Victoria Hospital, London, Ontario.

leukocyte concentration gives an accurate short-cut to the estimation of the leukocyte excretion rate.[9] Of women with asymptomatic UTI only one-half also have more than 10 leukocytes per c.mm. in the urine.[10] The presence of pyuria is therefore of no value as a screening procedure for detecting patients with bacteriuria. Screening populations for proteinuria is similarly valueless.[10] This point deserves emphasis because some laboratories, as well as leaving urinalysis to the most junior staff and refusing to perform quantitative cultures on MSUs, will not even culture the specimen unless proteinuria is detected or, worse still, unless leukocytes are seen in a non-quantitative assessment. In fact such an assessment gives little indication of the true leukocyte excretion rate.[9]

It is now well-recognized that many patients with UTI have bacterial counts in MSUs of less than 100,000 colonies per ml. and in some situations (e.g. marked frequency of micturition, high urine flow rate) less than 10,000 per ml.[1, 5, 7] This is especially so for infections with gram-positive cocci.[5]

The technique of suprapubic aspiration (S.P.A.)[11] of the distended bladder has made the diagnosis of UTI much more rapid, efficient and accurate. Contamination of the specimen is avoided and this eliminates the extra work required for multiple cultures and the need for quantitation, as any bacteria obtained by this technique can be regarded as significant. In most aspirated urine specimens bacteria can be seen microscopically in a drop of the unspun urine; such specimens can be considered as infected and prompt treatment instituted. The technique of S.P.A. is safe for all groups of patients including infants and children, simpler than a venepuncture, quicker than obtaining a careful MSU, readily acceptable to patients and easily performed by nurses. Also there is no urgency about transporting the specimen to the laboratory.[5, 11] The technique must be used in order to appreciate its simplicity and obvious advantages.

Host and bacteriological factors

Apart from during the first year of life and over the age of 60 years UTI is predominantly a problem involving the female. The entry of bacteria into the female bladder is facilitated by the short urethra and this probably explains, at least in part, the frequent observation that recurrent attacks of symptomatic UTI closely follow sexual intercourse. Women who suffer such recurrent attacks have been shown to have a higher number of enterobacterial organisms in the introital region than women who are non-bacteriuric and have no history of UTI.[12] The high number of introital organisms was not related to poor hygiene (e.g. frequency of bathing or showering) but it was not possible to evaluate the various techniques of perineal toilet.

The presence of residual urine is undoubtedly important in allowing an inoculum of bacteria to multiply within the urinary tract.[13] In many women this residual urine appears to stem simply from a bad bladder-emptying habit. The generation-time of a particular bacterial strain may be influenced by such factors as the urine pH, the urine osmolality, the concentration of urea, the amino-acid composition of the urine, the special properties of the urine in certain physiological situations such as pregnancy and the antibacterial properties of the urothelium.

It is well documented that complement, lysozyme and antibody play a role in the bacteriolysis of gram-negative bacteria. Recently, in a careful piece of analytical work, Taylor[14] demonstrated that in some patients with infection of the upper urinary tract the infecting gram-negative bacillus was sensitive to the bactericidal activity of normal serum but was not killed by the patients' own serum. In such patients, however, the serum was able to kill closely related bacterial strains. Taylor further showed that the serum contained an antibactericidal factor specific for the homologous strain, which was found to be a 7S globulin.

Infection due to two or more bacterial species or to more than one serotype of *Escherichia coli* is uncommon. Dugdale[15] has proposed theoretical reasons why, in a dynamic system, infections should be due to a single strain but Koutsaimanis and Roberts[16] have elegantly provided evidence for at least one possible circumstance where this may not be so.

Some strains or serotypes of *E. coli* involved in UTI invade the kidneys more commonly than others.[17] Furthermore, although strains of *E. coli* reach the bladder in proportion to their frequency in the fecal flora, strains rich in K antigen are more likely to succeed in subsequently invading the kidney. This has been suggested to be owing to the inhibitory action of K antigens on phagocytosis and on destruction by complement.[18]

E. coli remains the predominant urinary tract pathogen but as many as one-quarter of UTIs diagnosed by S.P.A. are due to gram-positive organisms, especially coagulase-negative staphylococci. This latter finding applies to both asymptomatic[10, 19] and symptomatic[20, 21] infections. In many earlier studies, and still in many centres, this organism is always regarded as a contaminant.

Table I

A suggested protocol for assessing patients with urinary tract infection

A. Clinical presentation	
1. Symptomatic	(a) upper—acute pyelonephritis (b) lower—cystitis (cf. urethral syndrome)
2. Asymptomatic	
B. Site of infection (localisation)	
1. Upper urinary tract	(a) unilateral (b) bilateral
2. Lower urinary tract	
C. Renal function tests and other indirect evidence	
1. Tubular function—especially concentrating ability	
2. G.F.R.	
3. Antibody titres	
4. Serum bactericidal activity	
D. Anatomy of urinary tract (radiology and cystoscopy)	
1. Normal	
2. Abnormal (e.g. chronic childhood pyelonephritis, VUR, significant residual urine)	

Assessment of patients with urinary tract infection

The author has found that the protocol presented in Table I provides a practical way to assess patients presenting with UTI.

A. *Clinical presentation*

A patient with UTI may present with an acute systemic illness with septicemia at one extreme of the

clinical spectrum or be totally asymptomatic at the other extreme.

1. *Symptomatic:* Symptoms may be referable to the lower urinary tract and include frequency, dysuria, urgency, strangury and hematuria. If bacteriuria is demonstrated this syndrome is referred to as *cystitis.* It has been well documented,[22] however, and it is also the author's experience, that one-half of women and also a large proportion of girls[23] suffering from such symptoms do not have coexistent bacteriuria. This has been termed the "urethral syndrome" and although in girls it has been attributed to a vulvitis, in mature women the etiological factors are still obscure. Subsequently the latter may develop UTI.[24]

Some patients present with loin pain, tender kidneys, fever, rigors and may have a positive blood culture. This clinical picture is regarded as *acute pyelonephritis.*

The urinary tract symptoms, especially those referable to the bladder and urethra, may not correlate with the site of infection when this is subsequently localized.[6, 25]

2. *Relatively asymptomatic* (Fig. 1): Patients are rarely completely asymptomatic when bacteriuria is present. Women regarded as asymptomatic frequently note an odour to the urine and on interrogation state that they are suspicious that there is something wrong with the urinary tract. These women rarely present to their practitioners, however, and only come to notice when the urine is cultured for some reason.

In a most meticulous study, Abbott[26] found that 1% of a series of 1460 neonates had asymptomatic bacteriuria. Eleven of the 14 infected children were males, and eight of the 14 were found to have vesico-ureteric reflux. In some instances the bacteriuria cleared spontaneously.[27]

In schoolgirls aged 6 to 18 years the prevalence of bacteriuria was 1.2% but only 0.03% in boys of the same age.[28] A prevalence rate of 1% was also found among a series of New Zealand girls who were leaving high school, starting university or starting preliminary training in a school of nursing. When these same girls returned for free contraceptive advice at a student health clinic the prevalence rate was almost 10%.[29] Sexually active women screened for UTI in many communities have all shown a prevalence rate of this order.[12, 30, 31] Of great interest is the superb study reported by Kunin and McCormack[32] who demonstrated a 1.6% prevalence rate of bacteriuria amongst 3304 nuns. Of these, 2212 were under 45 years of age and for them the prevalence rate was only 0.6%.

The earliest populations screened were pregnant women of whom usually 5 to 6% were found to have asymptomatic bacteriuria which was not necessarily associated with pyuria or with bladder mucosal inflammation.[3, 10, 33] The reported rates have varied from 2% in a private clinic in the United States[34] to 18.5% in a series of urbanised New Zealand Maori women screened by the author in a hospital obstetric clinic.[10] About one-quarter of these infected women developed acute pyelonephritis in the later stages of the pregnancy or the puerperium.[10, 33]

In some studies it has been shown that women with bacteriuria in pregnancy are at an increased risk of developing pre-eclampsia, a lowered fetal birth weight, a shortened gestation interval, congenital fetal defects, an increased perinatal mortality rate, infected amniotic fluid and transference of the infection to the infant. But these risks do not appear to be as serious as was initially thought.[10, 33, 35] In particular, Beard and Roberts[35] carefully analyzed the available evidence suggesting a relationship between bacteriuria and premature birth and concluded that UTI was unlikely to be a major causative factor in the condition. Furthermore, women with bacteriuria do not have infected amniotic fluid and there is no evidence that the infection is transmitted to the infant.[36]

Usually about 20% (18 to 51%) of women with asymptomatic bacteriuria in pregnancy have been found to have a radiological abnormality of the urinary tract which was frequently correctable surgically.[10, 37, 38] The incidence of urinary tract abnormalities is similar in women with asymptomatic bacteriuria who are not pregnant.[6, 31] There is no evidence that such bacteriuria has ever caused the lesions which have been demonstrated.

Although the prevalence of asymptomatic bacteriuria is fairly constant, in any given community the affected individuals are continually changing. The incidence of bacteriuria does not increase with age or parity[10, 33] and the prevalence in healthy postmenopausal women is of the order of 3%.[12, 31] Elderly, debilitated and bedridden women frequently have UTI but no convincing study of its prevalence rate has been performed in very elderly otherwise healthy women.

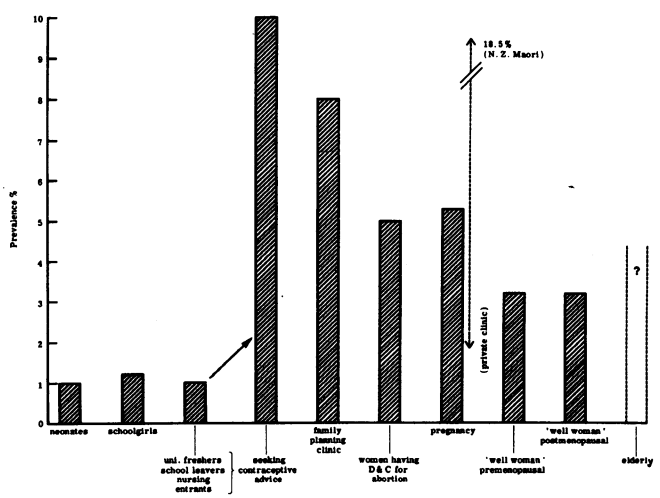

FIG. 1—Histogram depicting the prevalence of asymptomatic bacteriuria in a series of neonates and in various populations of females from childhood to old age (based on a variety of published and unpublished data[3, 10, 12, 26, 28-35])

B. *Site of infection*

In 50% of patients with asymptomatic[39] or symptomatic[25] UTI the infection is localised to the upper urinary tract. The simplest method for determining this localisation is with the neomycin bladder washout test described by Fairley and coworkers.[40] Only selective ureteric catheterisations will localise the side of an upper tract infection[41] and if unilateral infection is demonstrated this is an indication for more careful and in-

tensive investigation, treatment and subsequent follow-up.

Renal biopsy is of doubtful value because of the small sample of tissue obtained, the patchy nature of renal parenchymal infection, and the lack of accuracy of the diagnosis based on histological findings.

C. *Renal function tests and other indirect evidence*

In renal parenchymal infection the maximal concentrating ability of the kidneys is impaired and can be easily assessed by overnight dehydration, dehydration until a 3 to 5% reduction in the body weight is produced, or by the pitressin test. This defect, however, is non-specific as far as the cause of the renal damage is concerned and is reversible after the infection has been eliminated from the kidneys. A concentrating defect can usually be demonstrated in a kidney affected by chronic pyelonephritis as diagnosed radiologically. In some patients with acute pyelonephritis there is also a temporary reduction in the glomerular filtration rate (G.F.R.).

Antibody titres to the infecting organism as measured by the existing techniques (hemagglutination or direct bacterial agglutination using the patient's own strain as antigen) have unfortunately not fulfilled expectations in indicating in which patients there has been renal involvement by the infection. General correlations have been shown between these antibody titres and defects in concentrating ability but the results are variable and not sufficiently predictive to be of definitive value. The antibody titres do not show any firm correlation with the site of the infection.[25]

D. *Anatomy of the urinary tract*

The anatomy of the entire urinary tract can be studied adequately only by radiological techniques. The most important procedure is careful intravenous pyelography (IVP) performed with sufficient quantities of contrast medium (up to 2.2 ml. per kg. body weight) after thorough bowel preparation and overnight dehydration. The latter must be avoided if renal failure is present. Plain films should be taken before the contrast injection and a film taken immediately after the injection will reveal the nephrographic phase. The addition of tomography invariably gives further valuable information. Full length post-micturition films are essential and if urinary tract obstruction is suspected, then delayed films may be useful. Renal failure is not a contraindication to careful and adequate intravenous pyelography which has now greatly reduced the need for using potentially hazardous retrograde pyelography in excluding treatable extrarenal obstruction. Residual urine can be estimated from the IVP but is more accurately measured using a radioisotope technique.[42, 43]

Children and men with UTI should have their urinary tract investigated adequately at the time of the initial attack. In infants and children this should include micturating cystourethrography, as one-half of these patients will have some degree of vesico-ureteric reflux.[26, 44] It has been a common practice, however, not to investigate women until they have had two or more attacks, but the rationale for this has not been established. Recently the author investigated 204 consecutive women in the childbearing age group who presented to a London (U.K.) hospital casualty department with urinary tract symptoms or who were referred by their general practitioners to a urinary infection clinic because of recurrent attacks of urinary tract symptoms over many years. The results are summarized in Table II. The IVP findings were similar whether UTI was subsequently demonstrated or not (in some women bacteriuria was not demonstrated after referral although it had been well documented on some previous occasion). Nineteen (9.3%) of the 204 women investigated had major and 23 (11.3%) had minor radiological lesions. Only one woman in the series had an elevated blood urea or serum creatinine level. The author considered the radiological investigations justifiable and it was apparent that women presenting with their first attack were just as likely to have an abnormality on the IVP as women with a history extending over 30 years. It was also striking that the incidence and type of radiological changes were similar to what was observed in the same unit when 163 women with asymptomatic bacteriuria during pregnancy were subjected to intravenous pyelography six months to four years after delivery.[38]

At this stage it is appropriate to discuss the medical enigma of *chronic pyelonephritis*. The role of bacterial infection in the pathogenesis of chronic non-obstructive childhood pyelonephritis has been questioned.[45, 46] The diagnosis cannot be made clinically or by examination of the urine. A careful macroscopic study of the kidney will reveal both the patchy pelvi-calyceal and the parenchymal components of the disorder. On the contrary the microscopical appearances are non-specific[47] and are difficult to distinguish from the numerous other causes of "chronic interstitial nephritis."[48]

Nor is there conclusive evidence in man for an immunological mechanism in the pathogenesis of chronic

Table II

Intravenous pyelographic findings in 204 consecutive women in the childbearing age-group who were referred with urinary tract symptoms

Group of women	Major I.V.P. abnormalities (19)		Minor I.V.P. abnormalities (23)	
Urinary tract infection subsequently demonstrated (137)	Unilateral chronic pyelonephritis (4 with VUR still present)	6	Significant bladder residual	8
			Left duplex system	6
	Tubular ectasia	2	Calyceal cyst	1
	Renal calculus	1	Malrotation kidney	1
	Ureteric calculus	1	Dilatation sacral segment of ureter	1
	Medullary sponge kidney	1		
	Carcinoma kidney	1		
	Fused kidneys	1		
	Solitary renal cyst	1		
Urinary tract infection not subsequently demonstrated (67)	Renal calculus	2	Calyceal cyst	2
	Ureteric calculus	1	Significant bladder residual	2
	Analgesic nephropathy	1	Dilatation sacral segment of ureter	2
	Small ischemic kidney	1		

Figures in brackets indicate number of cases

pyelonephritis. Using an immunofluorescent technique, however, bacterial antigen has been detected in patients with histologically diagnosed chronic pyelonephritis whether or not UTI was or had been present.[49] No evidence of defective cell-mediated immunity has been demonstrated in women with radiologically diagnosed chronic pyelonephritis and UTI with *E. coli*. This was determined by studying the migration of their peripheral blood leukocytes into various suspensions of their own homologous infecting organism.[50]

The disorder of chronic pyelonephritis is recognized radiologically by demonstrating caliectasis and adjacent cortical scarring.[51] The condition may be difficult at times to differentiate radiologically from the lesion of analgesic nephropathy and many women with this common form of renal disease have in the past incorrectly received the diagnosis of chronic pyelonephritis. It has now become clear from the superb studies of Rolleston, Utley and Shannon[44] that the lesion which is recognized radiologically as chronic pyelonephritis develops in infancy or childhood and only when the more severe degrees of vesicoureteric reflux (VUR) are present. What is of even greater significance is that progressive lesions have been demonstrated in children only when this VUR persisted. Some children have shown such progression in the continued absence of UTI. There is increasingly compelling evidence that the high pressure transmitted to the upper urinary tract in children with gross VUR may be sufficient by itself to lead to an arrest of renal growth and the radiological appearance of obstructive atrophy. These children with VUR are undoubtedly prone to UTI and it may be the addition of renal parenchymal infection which leads to the development of localised cortical scar formation. However, there is very little evidence in man, if any, to document either the development or the course of these scars in relation to the clinical and bacteriological evidence for UTI.[48] Satisfactory correction of gross VUR will allow renal growth to recommence. Further reports from the Christchurch group of workers[44] are awaited with world-wide interest. In view of this and additional evidence it is the opinion of some prominent workers in the field that it may be more beneficial to screen neonates and infants for VUR than for bacteriuria.[29, 52] This suggestion is of even greater significance in view of a recent preliminary report by Heale that VUR may be inherited as an autosomal dominant of variable expression and as an autosomal recessive.[53]

Of very significant recent interest is the report of three infants who, after severe gastroenteritis, developed renal tubular necrosis and extensive papillary necrosis diagnosed radiologically. Though these infants are now well, renal damage has occurred and preliminary follow-up studies have shown that this damage has given rise to radiological features indistinguishable from those of chronic pyelonephritis.[54]

In *adults* without VUR there is no evidence that either a single attack of acute pyelonephritis or repeated symptomatic or asymptomatic episodes of UTI ever result in cortical scarring and caliectasis. An acute parenchymal infection, however, may lead to a loss of overall renal mass.[55, 56] Such an exception occurs if VUR develops after the acquisition of a neurogenic defect (e.g. paraplegia) or following surgical damage to the vesico-ureteric junction. In these patients cortical scarring and caliectasis may develop.

If chronic childhood pyelonephritis is not diagnosed until adulthood, as is frequently the case, the VUR may have disappeared or be greatly diminished. This is because the natural history of VUR is that it becomes less marked with age or disappears completely.[44] Many of these patients have never had a history of UTI[53] but frequently present with hypertension. Not infrequently women with radiological evidence of chronic pyelonephritis and also having UTI have the infection localised to the bladder.[6, 50] The majority of such patients with chronic childhood pyelonephritis reaching adulthood invariably have a normal G.F.R. and this tends to persist unless there is a complicating factor present, of which the most significant is hypertension. The relationships between UTI, chronic pyelonephritis and hypertension are extraordinarily complex and beyond the scope of this review. This important subject has been critically evaluated by Freedman.[48] Of lesser importance as complicating factors are persisting gross VUR, a high analgesic intake, an element of urinary tract obstruction, a neurogenic bladder defect, diabetes mellitus, sickle hemoglobin or occasionally repeated severe attacks of acute pyelonephritis. Certainly uncomplicated chronic childhood pyelonephritis is not a major cause of renal failure in adults.[57] Similarly it has been commonly thought that women who develop recurrent attacks of UTI and who are otherwise completely normal may go on to renal failure and hypertension but this rarely if ever occurs.[6, 57]

Treatment

1. *Acute attack* It is not difficult to relieve lower urinary tract symptoms and these frequently (and the bacteriuria occasionally) disappear within a few days even if no antibacterial treatment is given. The traditional treatment of a large fluid intake is a useful adjunct to antimicrobial drugs principally because it results in more frequent bladder emptying. A more rational basis for this time-honoured clinical practice in parenchymal infection may be because it results in a lowered osmolality of the medulla and renal papilla. The urinary concentration of the administered drug will be lowered by the induced diuresis but this is rarely of practical importance. The still frequent prescription of "Mist. pot. cit." is to be condemned because it does not eradicate bacteriuria although it may temporarily alleviate the lower urinary tract symptoms; if renal failure is present the patient may develop dangerous hyperkalemia. In some special circumstances it may be useful to adjust the urine pH (e.g. acidification is essential for the effect of mandelamine; alkalinization enhances the effects of sulphonamides and considerably potentiates the action of kanamycin and gentamicin).

Antibacterial therapy is the mainstay of the management and can usually be administered orally. A seven to ten day course of an appropriate drug is adequate for the initial treatment although in some patients with bladder bacteriuria the infection may be successfully eradicated by as little as a single dose.[6] If the patient is acutely ill or vomiting parenteral therapy is indicated.

It is now the experience of some workers that the penicillins (e.g. ampicillin, carbenicillin) and the cephalosporins (e.g. cephalexin) all of which inhibit bacterial cell wall synthesis, only give approximately a 60% cure rate as evidenced by a sterile urine seven to 14 days after the treat-

ment has been terminated.[58-61] This disappointing figure is true even for women with a normal urinary tract and normal renal function.[61] The possible reasons for this may be, in a proportion at least, the formation of protoplasts and bacterial variants or the persistence of bacteria which have substantial amounts of cell wall remaining but which are metabolically dormant at the time of the exposure to the antibiotic. This unsatisfactory cure rate with the penicillins and cephalosporins has also been the author's experience and for this reason he does not generally use these antibiotics as the initial treatment agent. The preferred drugs are nitrofurantoin (50 mg. 6- or 8-hourly), the sulphonamides or the trimethoprim-sulphamethoxazole combinations and nalidixic acid (500 mg. 6- or 8-hourly) according to the results of sensitivity testing. These agents lead to eradication of the infecting organism in over 85% of uncomplicated cases. Unfortunately the latter drug is usually ineffective against gram-positive organisms. It will be noted that the effective doses of nitrofurantoin and nalidixic acid are considerably lower than those recommended by their respective manufacturers. The common side effects frequently seen with these two agents when the "full" dosage is used are thereby virtually eliminated.

The author has recently used nitrofurantoin 50 mg. 6- or 8-hourly for seven days to treat 65 women with UTI. The infecting pathogens were all sensitive to this agent on *in vitro* testing. A 94% cure rate was obtained (Table III). The cure rate was the same whether the patients took a total of 150 or 200 mg. of nitrofurantoin daily. All these women had normal renal function and a radiologically normal urinary tract.

When parenteral treatment is indicated gentamicin, kanamycin, colistin, cephaloridine and ampicillin appear preferable. These drugs should only be used in hospital.

2. *When renal impairment is present* The above discussion applies only to patients with normal renal function. When renal functional impairment is present the pharmacology of the agent intended for use must be known. Nitrofurantoin,[62] the majority of common sulphonamides except sulphadimidine[63, 64] and the tetracyclines except doxycycline[65, 66] should never be used. Nalidixic acid,[67] ampicillin, cephalexin[68] and carbenicillin[69] are all excreted in renal failure and the concentrations obtained in the urine may be considerably in excess of the minimal inhibitory concentration for the infecting pathogen. Dosage modifications will generally be necessary. Carbenicillin can now be administered orally as the indanyl ester which is acid-stable.[61, 69]

Gentamicin, colistin and kanamycin are not contraindicated in the treatment of UTI in the presence of renal failure. The first agent is particularly useful and also highly effective against *Pseudomonas aeruginosa* which is a problem only in patients with renal failure, an abnormal urinary tract (e.g. calculus, urethral catheter, ileal conduit, nephrostomy tube) or following frequent instrumentation of the urinary tract. The peak serum level after a single dose of these agents is related to body weight and not G.F.R. and therefore a full loading dose should be used. Afterwards, modification of the dosage for varying degrees of renal impairment should be effected by altering the interval between doses. Dosage schedules for most of these drugs have been produced and are discussed in the excellent review by Linton and Lawson.[70] The initial course of treatment in these patients should be for a minium period of seven to 10 days.

3. *Follow-up* A careful bacteriological follow-up is essential after treatment of the UTI because a further infection occurs in one-half of the patients within six months and in 75% within 18 months. Much has been written about attempting to distinguish a relapse from a reinfection of bacteriuria, but this is difficult and ignores the possiblity that a "relapse" may be just a reinfection with the same organism or the same serotype of *E. coli* which is predominant in the fecal flora. The early (e.g. within 24 to 48 hours) reappearance of the identical organism, however, should suggest a failure of eradication, point to the likelihood of an upper tract infection, and certainly lead to prompt investigation of the urinary tract.

After treatment is completed, ideally the urine should be cultured at one week, six weeks and then at increasing intervals for a total period of 12 to 18 months. This plan will prevent many symptomatic recurrences but as there is little evidence that these infections cause any deterioration in renal function, such a detailed follow-up is hard to justify.

A full pelvic assessment is mandatory for all patients, while cystoscopy and urethroscopy are sometimes necessary to exclude lower urinary tract pathology. The popular urological practice of dilating the female urethra at intervals is unnecessary and unjustified, as significant urethral stenosis is rare. Prompt surgical handling of urological lesions, including gross VUR in infants or children, should be practised.

4. *Recurrent attacks* The management of recurrent sexual intercourse-induced acute urinary tract symptoms with bacteriuria is frequently difficult. If these women have a normal urinary tract and normal renal function, the great majority can be kept free of attacks by taking a single 50 mg. tablet of nitrofurantoin each night, after voiding and before going to bed. Bailey and co-workers[21] have shown that this form of low dose medication is safe when taken for long periods, effective, and very acceptable to the many patients whose life has become intolerable. After 6 to 12 months of such management there should be a trial period without treatment. A single 500 mg. dose of nalidixic acid is also effective[6] and has the added benefit of being excreted in renal failure. It is possible that any antibacterial agent given as a single low dose in this manner will prevent recurrent UTI's. This is a field for further investigation. The impressive results with nitrofurantoin, however, may be because this drug

Table III

Women with urinary tract infection (diagnosed by suprapubic aspiration), normal renal function and a radiologically normal urinary tract treated with nitrofurantoin 50 mg. 6- or 8-hourly for 7 days

	Sterile urine 14 days after treatment		Side effects	
No. treated	No.	%	No.	%
65	61	94	10 (8 mild nausea)	15

does not cause any change in the fecal flora (in comparison to sulphonamides) of patients and also because the development of resistant bacterial strains during its administration is virtually unknown.

Some patients with recurrent UTIs have remained free of attacks by regularly practising double micturition, postcoital micturition, or especially by the very useful practice of applying an antiseptic cream such as cetrimide B.P. 0.5% w/w (Savlon) to the periurethral area prior to sexual intercourse.[6]

Occasionally patients present with an upper tract infection which is not eliminated by one or more conventional courses of oral antibacterial therapy. It has been found worth while to give such patients a supervised seven to 21-day course of a parenteral antibiotic. Most of these patients have gross urological abnormalities as well as a degree of renal functional impairment and in some situations (e.g. a child with a meningomyelocele or an ileal conduit, or a woman with a staghorn calculus) it may be almost impossible to eradicate the UTI. If this is the case, suppressive (as opposed to curative or prophylactic) treatment with a suitable antibacterial agent may become necessary. Nalidixic acid and trimethoprim-sulphamethoxazole combinations are useful agents in the author's experience.

5. *Asymptomatic bacteriuria in pregnancy* The initial treatment should be with a conventional short course of drugs. If bacteriuria returns following treatment the patients can usually be successfully controlled by giving a 50 mg. dose of nitrofurantoin nightly until the puerperium. It is these latter patients that are more likely to have a radiological abnormality of the urinary tract.

6. *Special problems in men* In the absence of urinary tract obstruction, men with recurrent bacteriuria frequently carry the infecting organism in their prostatic fluid. Careful segmental urine cultures are essential in making this diagnosis.[1] Normal men secrete a potent antibacterial substance in their prostatic fluid but in patients with persistent bacterial prostatitis the gland seems incapable of eradicating the infection. At present there is no antimicrobial agent that can effectively cross non-inflamed prostatic epithelium from plasma into prostatic fluid, but long term, low-dose therapy (e.g. nitrofurantoin, nalidixic acid) may prevent the prostatic bacteria from initiating a bacteriuria.

The future

Infants and children with severe VUR have a high incidence of renal damage when first seen, are prone to an arrest of renal growth, to progressive renal damage and, in the majority of cases, to recurrent attacks of UTI. Children and adults with lesser degrees or no VUR do not appear to develop renal damage even if recurrent UTI occurs. Although screening children and adults for bacteriuria leads to the diagnosis of a wide spectrum of radiological lesions in the urinary tract, it would seem that the most rewarding screening procedure would be for the detection of VUR in infancy or early childhood and in particular to examine the children of affected individuals. Until a simple and safe form of population screening becomes available, this suggestion would at present seem impractical.

Summary

The subject of urinary tract infection is reviewed with particular emphasis on the necessity for making a completely accurate bacteriological diagnosis. The obvious advantages of obtaining urine for culture by the simple technique of suprapubic bladder aspiration are discussed.

Certain host and bacteriological factors are considered, including the observation that at the present time as many as one-quarter of urinary tract infections are due to gram-positive cocci, and that up to one-half of women presenting with lower urinary tract symptoms have sterile urine.

A practical protocol for assessing patients with urinary tract infection is proposed.

The medical enigma of chronic childhood pyelonephritis and its relationship to vesico-ureteric reflux are examined. In the management of patients with urinary tract infection special consideration is given to the use of antibacterial agents in curative, preventive and occasionally suppressive regimens.

It is suggested that to prevent progressive renal damage it may be beneficial to screen populations of neonates, infants or children for the presence of vesico-ureteric reflux. This will require development of a simple, safe, non-radiological screening procedure.

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Résumé:

L'infection de l'appareil urinaire: quelques principes récents

L'auteur passe en revue le sujet de l'infection des voies urinaires et insiste particulièrement sur la nécessité de disposer d'un diagnostic bactériologique très précis. Il expose également les avantages incontestables d'obtenir un échantillon d'urine prélevé par la technique d'aspiration vésicale directe, par voie suprapubienne.

L'article étudie les facteurs bactériologiques et certaines particularités de l'hôte. Il fait remarquer qu'actuellement près d'un quart des infections urinaires sont causées par des coques gram-positifs et que, chez une grande partie des femmes — en fait la moitié — qui présentent des symptômes d'infection des voies urinaires inférieures, l'urine est stérile.

L'auteur propose une protocol pratique des malades souffrant d'infections urinaires.

Il se penche sur l'énigme médicale qu'est la pyélonéphrite chronique de l'enfance et considère sa relation possible avec un reflux vésical via les uretères. Il étudie le rôle joué par les agents antibactériens dans les régimes curatifs, préventifs et, parfois suppressifs.

Enfin, il estime que, pour prévenir une lésion rénale progressive, il peut être avantageux de procéder à un dépistage massif des cas de reflux vésical-uretérien dans des populations de nouveau-nés, de nourrissons et d'enfants. Ce qui exigerait la mise au point d'une méthode de dépistage simple, efficace, sans danger et qui ne serait pas radiologique.

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Retrospect

Some hospitalization problems — hospital standardization

We have arrived at a time of perfecting organization in all activities of life. The day of communalism and cooperation is here, when men and women desire to work together to produce better results by cooperative effort. In all cases the results obtained depend on the kind of service rendered. Indeed, we must frequently take stock of ourselves in terms of service. The keynote of get-together meetings or conventions such as this is service and better service. Corporations, hotels, railroads and other commercial organizations aim today at high-class service. I have just crossed the continent and had occasion to acquaint myself with the service on six different railroads and some five or six important hotels. I particularly noticed the efforts made to give their patrons service. Railroads today are catering to their patrons by supplying all their wants and comforts, and as the traveller crosses the continent he sits in comfort and luxury enjoying almost all the privileges of life, so complete is the service now being given. If commercial and business organizations believe that in their success they must regard service as fundamental, how much more essential is it that hospitals must likewise so believe, dealing as they constantly do not with dollars and cents, but with human lives and life and death? Indeed, hospitals must regard service as the very ground on which they stake their right to exist. — Malcom T. MacEachern: Can Med Assoc J *12: 520, 1922.*