Current Practice

URINARY TRACT DISEASES

Infections of the Urinary Tract II—Management

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The aim of treatment of infections of the urinary tract is not only to procure symptomatic relief of the acute attack, but also to prevent recurrences and to preserve renal function. Infections are sometimes associated with a structural abnormality which may be amenable to surgery. Investigation is required to detect these abnormalities.

It is not difficult to relieve symptoms in the typical attack of acute cystitis, and in fact these often disappear within a few days even if no antimicrobial agent is given. Since in these cases bacteriuria may persist after the symptoms have gone it is important that cure should be confirmed bacteriologically.

Patients who have had an attack of acute symptomatic urinary tract infection are very likely to get a recurrence. Bacteriuria recurs within six months in half, and by the end of 18 months in three-quarters of patients. Though relapses due to the same organism mostly occur within three months, reinfections due to a new organism are acquired at a slower rate, mostly within eighteen months. In the case of recurrences of infections with *Escherichia coli* it is possible to distinguish relapses from reinfections only if sero-typing is used. Differentiation between relapse and reinfection is helpful in localizing the infection since 80% of relapses are associated with upper tract bacteriuria, while 70% of reinfections occur in patients with bladder bacteriuria. Of those with bacteriuric recurrences about one-quarter will have a symptomatic attack during the year. Following the initial cure about a quarter will not have a bacteriuric recurrence, and it is said that recurrences are less common among Negro patients.

It is difficult to exclude the possibility that patients in whom bacteriuria has recurred are suffering continuing asymptomatic renal damage. Those centres where some technique for the localization of the infection is available have found that about half of those patients with frequently recurring bacteriuria have evidence of upper tract involvement. In some children radiological studies have shown that long term prophylaxis to eradicate bacteriuria has prevented or diminished renal damage. In adults with recurring urinary tract infections, on the other hand, though treatment may prevent repeated illnesses, it has not yet been proved that it may stop progressive renal damage.

These considerations emphasize that the management of infections of the urinary tract requires bacteriological follow-up in order to confirm cures and to detect recurrences. It is hoped that modern methods for transmitting samples to the laboratory (see previous article) will make this available in domiciliary practice.

Treatment of the Acute Attack

Domiciliary Infections

About 80 to 90% of domiciliary infections are caused by *E. coli* of a serotype which can be found in the intestinal tract of the patient. *Proteus mirabilis*, *Streptococcus faecalis*, *Kleb-*

siella aerogenes, and *Staphylococcus albus* are all encountered much less frequently. The strains of *E. coli* involved are usually sensitive to most antibiotics, and a week's course of any sulphonamide results in a sterile urine in 80 to 90% of these patients. It may be convenient to give the week's treatment as a single dose (for example, 2 g. of sulphamethoxine) in ambulant patients. Nevertheless because of reports of sensitivity reactions, including the Stevens-Johnson syndrome long-acting sulphonamides should not be given to children. Ampicillin is widely prescribed as primary treatment and is as effective as sulphonamides. It is much more expensive, however, and there is a high incidence of rashes. These may be due to impurities, but once such hypersensitivity has occurred further use of penicillins is inhibited. If an initial course of a sulphonamide does not eradicate bacteriuria a second course of a different drug should be given. Choice will be guided by sensitivity tests, but will usually lie between ampicillin, nitrofurantoin, trimethoprim-sulphamethoxazole, or tetracycline.

Hospital Infections

Infections occurring in hospital are due to a wider range of organisms, some of which may be resistant to the more commonly used antibiotics. Resistant strains of *E. coli* are encountered because cross infection alters the flora of the gut in patients in hospital. *P. mirabilis* and *Pseudomonas pyocyanea* appear to be isolated with increasing frequency in hospital infections. If treatment must be initiated before the results of sensitivity tests are known trimethoprim-sulphamethoxazole or ampicillin is advised.

Some factors affecting the choice of antibiotics are summarized in the Table. Choice will often be dictated by bacteriological considerations, but both the side effects of the drugs and the level of renal function in the individual patient must also be considered, as must the economic implications of the prescription. More important than the correct choice of antibiotic is the organization of follow-up to detect failures in treatment.

Asymptomatic Bacteriuria

The treatment of asymptomatic bacteriuria does not differ essentially from the treatment of the acute symptomatic attack. As discussed in the first article, treatment is indicated in bacteriuria of pregnancy and in children with vesicoureteric reflux, but its necessity in other contexts is not established. Whether or not it is decided to treat the patient, careful bacteriological follow-up is mandatory.

Fluid Intake

Traditionally the patient who has an infection in the urinary tract is advised to take a large fluid intake. This is a useful adjunct to antimicrobial drugs, for the growth rate of *E. coli* is reduced if the urine is very dilute (less than 200 m.osmol/kg.). A high fluid intake and frequent emptying

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of the bladder result, because of the "washout" effect, in an appreciable reduction in the bacterial count of bladder urine. Diminished osmolarity of the renal medulla also makes the development of protoplast forms less likely. The antibacterial effect of commonly used drugs is potentiated despite some reduction in the concentration of drug in the urine. Furthermore, any risk of sulphonamide crystalluria is diminished.

Urinary pH

Adjustment of the pH of the urine affects the growth of urinary pathogens and the effectiveness of some antimicrobial agents. Optimal growth of *E. coli* occurs in urine at pH 6.0 to 7.0, while at pH values less than 5.5 and above 7.5 growth is inhibited. The administration of methionine produces a highly acid urine and has reduced bacterial counts in the

Antibiotics Used for The Treatment of Infections of the Urinary Tract

Antibiotic	Administration	Dose	Spectrum and Usage	Side Effects	Use in Renal Failure	Cost to N.H.S. of One Week's Treatment (in £s)	
						Hospital Pharmacy	Retail Chemist
1. Primary Treatment							
Sulphadimidine	Oral	1 g. 6 hourly	Spectrum excludes <i>Kl. aerogenes</i> and <i>S. faecalis</i> , Domiciliary infections with <i>E. coli</i> usually sensitive. Resistance common in hospital infections.	Rare with short courses.	Unchanged dosage	0.05	0.22
Sulphafurazole	Oral	1 g. 6 hourly		Hypersensitivity, nausea and vomiting, crystalluria, blood dyscrasias.		0.27	0.60
Sulphamethizole	Oral	200 mg. 6 hourly		Stevens-Johnson syndrome		0.09	0.23
Sulphormethoxine	Oral	2 g. once				0.09	0.23
Ampicillin	Oral (or Intramuscular or Intravenous)	500 mg. 6 hourly	Spectrum excludes <i>Kl. aerogenes</i> and <i>Ps. pyocyanea</i> .	Skin rashes, sensitivity	Unchanged dosage	1.59	2.15
Tetracycline	Oral (or Intramuscular, or Intravenous)	250 mg. 6 hourly	Broad spectrum, but <i>P. mirabilis</i> and <i>Ps. Pyocyanea</i> resistant.	Raises blood urea. Nausea and vomiting. Tetany.	Best avoided. M.D. every 3-4 days in severe cases, every 1-2 days in moderate cases. Fixed ratio combined tablets prevent adjustment of trimethoprim in renal failure.	0.13	0.57
Trimethoprim-sulphamethoxazole (T-S)	Oral	2 tabs. 12 hourly	Broad spectrum	As for sulphona-mides.	Not good urinary concentrations	1.04	1.35
Nitrofurantoin	Oral (after meals)	100 mg. 8 hourly	Spectrum excludes <i>Ps.pyocyanea</i> and <i>P. mirabilis</i>	Nausea. Peripheral neuropathy in renal failure.	Not good urinary concentrations	0.18	1.17
Nalidixic Acid	Oral	1 g. 6 hourly	Broad spectrum but excludes <i>Ps.pyocyanea</i> , <i>S. faecalis</i> and <i>Staphylococci</i> .	Nausea. Phototoxic skin rashes.	Not good urinary concentrations	2.22	2.59
2. Resistant and Chronic Infections							
Phenoxymethyl Penicillin	Oral	250 mg. 6 hourly	Broad spectrum at concentrations achieved in urine, excluding <i>Kl. aerogenes</i> and <i>Ps. pyocyanea</i> .	Sensitivity	Unchanged dosage	0.12	0.41
Phenethicillin	Oral	250 mg. hourly				0.55	0.76
Cephaloridine	Intramuscular or Intravenous	1 g. 12 hourly	Broad spectrum, excluding <i>Ps. pyocyanea</i> . May be useful when the patient is sensitive to penicillins and the organism resistant to T-S.	Nephrotoxicity reported in patients with renal damage hypovolaemia	M.D. 24 hourly in severe cases	17.36	20.18
Cephalothin		2 g. 12 hourly			Unchanged dosage in moderate cases.	33.84	36.84
Cephalexin	Oral	500 mg. 6 hourly					12.60
Methenamine (mandelate)	Oral	1 g. 8 hourly	Useful for chronic bacteriuria. Urine must be acid.	Non-toxic	Patient may be acidotic.	0.07	2.54
Cycloserine	Oral	250 mg. 8 hourly or, alternate nights	Useful for chronic bacteriuria and when <i>E. coli</i> resistant to sulphonamides. Inactive against <i>P. mirabilis</i> .	Acute mental disturbances (related to blood levels).	Blood levels should be measured.	0.88	1.51
3. Septicaemic States							
Gentamicin	Intramuscular or Intravenous	80 mg. 6 hourly	Broad spectrum, synergistic with carbenicillin against <i>Ps. pyocyanea</i> . Good urinary concentrations. Alkalinize urine. Broad spectrum excluding <i>Ps. pyocyanea</i> . Active against <i>Ps. pyocyanea</i> , <i>Kl. aerogenes</i> , and <i>E. coli</i> . Treatment of <i>Ps. pyocyanea</i> Septicaemia may need 20 to 40 g./day if renal function good. May be forced to use it where modern broad spectrum antibiotics are not available.	Ototoxic	Blood level estimation is advised. Otherwise, M.D. every 3-4 days in severe cases, every 1-2 days in moderate cases.	54.32	
Streptomycin	Intramuscular	1 g. 12 hourly		Ototoxic Ototoxic Nephrotoxic neurological symptoms.		0.67	
Kanamycin	Intramuscular	1 g. 24 hourly				8.31	
Colistin	Intramuscular (painful)	120 mg. 8 hourly				15.43	
Carbenicillin	Intramuscular (painful)	1 g. 6 hourly (for U.T.I. 40 g./day		As for penicillins	Good urinary concentrations.	15.97	
Chloramphenicol	Oral Intramuscular or Intravenous	250 mg. 6 hourly		Marrow aplasia. "Grey syndrome" of infants.	Not good urinary concentrations.	0.21	

Renal failure: "Severe" = anuria, oliguria, GFR < 10 ml./min., Serum creatinine > 8 mg./100 ml.; "moderate" = recovery in acute tubular necrosis, Serum creatinine > 3 mg./100 ml. Cost: The cost to the N.H.S. of a prescription dispensed by a retail chemist is inclusive of his professional fees. Hospital Pharmacy costs are lower owing to bulk purchase. M.D. = maintenance dose.

urine of patients with chronic infections of the urinary tract. Acidification enhances the effect of tetracycline and cycloserine and is essential for the effect of the urinary antiseptic mandelamine. It may be impossible to maintain the urine acid in the presence of urea-splitting organisms using a single agent, so that in addition to methionine ammonium chloride may be used. Alkalinization of the urine enhances the effect of sulphonamides and penicillins, and considerably potentiates the aminoglycosides, streptomycin, kanamycin, and gentamicin. Care must be taken in prescribing potassium citrate to a patient whose level of renal function is not known because of the risk of hyperkalaemia. Sodium bicarbonate or sodium citrate may be used if the patient's kidneys can handle the sodium load. The action of ampicillin and nitrofurantoin is not materially affected by change in urinary pH.

Pyelonephritis

If the symptoms point to an infection of the renal parenchyma or there are bacteriological reasons for diagnosing infection in the upper urinary tract, it seems reasonable to choose an antibiotic which achieves good concentrations in the tissues and blood as well as in the urine. But this point of view has been challenged. Good results have unquestionably been obtained using nitrofurantoin and nalidixic acid, which have been thought to achieve an effective antibacterial level only in the urine.

In domiciliary practice, where most attacks of acute pyelonephritis are encountered, the infecting organism is likely to be *E. coli*. Initial treatment with either ampicillin (which may be given intramuscularly), tetracycline, or trimethoprim-sulphamethoxazole usually proves effective. Opinions vary about the length of treatment for a single attack of acute pyelonephritis. Symptomatic and bacteriological cure may be achieved within a few days, but histological evidence compatible with acute pyelonephritis has been found in biopsies performed many weeks later. The damaged kidney is vulnerable to reinfection, and some authors suggest that treatment should be given for as long as six months since recurrences are so common. The value of this length of treatment is not established. At present it seems best to advise that antibiotics should be given for a minimum of three weeks, and longer if loin tenderness persists. Follow-up is essential.

The resistant organisms encountered in hospitals frequently dictate a choice between ampicillin, trimethoprim-sulphamethoxazole, and the cephalosporins. The last have a wide spectrum of antibacterial action and achieve good urinary concentrations even in the presence of renal failure. Cephaloridine and cephalothin require parenteral administration, but cephalixin can be given by mouth. Unfortunately, there have been a few reports of nephrotoxicity with cephaloridine and cephalothin. If severe kidney disease is accompanied by hypovolaemia and shock it appears particularly important to avoid exceeding the usual daily dose, and it may be wisest to avoid giving these drugs to patients with renal disease if an alternative antibiotic is available. The choice of antibiotic most likely to prove effective in initial therapy should be made in collaboration with the bacteriologist, who will know the pattern of resistance of the particular organisms occurring in his hospital.

Bacteraemia in hospital practice is frequently due to Gram-negative rods, whose portal of entry has been the urinary tract, and requires urgent antibiotic treatment before the results of sensitivity tests are known. If gentamicin, kanamycin, or colistin are indicated their dose must be adjusted to the level of renal function and when renal failure is present it is advisable to monitor blood levels if possible. Though carbenicillin may be used in septicaemia due to *Ps. pyocyanea*, resistant strains have begun to appear and it is important that good clinical and bacteriological indications

are present before this antibiotic is used. If renal function is good carbenicillin may need to be given in very high dosage (30 to 40 g. per day). A synergistic action with gentamicin has been described.

Antibiotics in Renal Failure

Therapy in patients with renal failure poses special problems. Antibiotics whose excretion is related to glomerular filtration rate have an increased serum half life and may not reach the urine in good concentration when renal failure is present. It is always safe to give the usual loading dose of the antibiotic which is indicated. The frequency of maintenance dosage must be adjusted according to the excretion of the drug in the individual patient, preferably by monitoring blood levels. (When this is not possible the rules outlined in the Table must be followed.)

Tetracycline should not be given to patients with renal failure. Apart from the nausea, diarrhoea, and vomiting and the precipitation of tetany due to the formation of chelates with calcium, the blood urea may be further raised by the anti-anabolic effect of the drug. Nitrofurantoin nalidixic acid take several days to reach therapeutic urinary concentrations in patients with renal failure. At high blood levels nitrofurantoin may cause peripheral neuropathy and is therefore contraindicated in renal failure. Erythromycin and chloramphenicol are metabolized by extrarenal routes and do not reach the urine in therapeutic concentrations. Ototoxic aminoglycosides such as gentamicin, kanamycin, and streptomycin, and the nephrotoxic drugs colistin and polymixin B should not be withheld if there is proper bacteriological indication for their use, but the dosage must be appropriately adjusted (see Table).

The penicillins can be used with safety provided massive intravenous doses and the potassium salts are avoided. The clearance of sulphonamides bears no relation to glomerular filtration rate and good urinary concentrations are achieved in renal failure. The clearance of trimethoprim falls when renal function is impaired. The combined trimethoprim-sulphamethoxazole tablets at present available do not permit the independent manipulation of dosages which may be required in patients with renal failure to achieve the optimum ratio of the drugs in the urine. The renal handling of these two drugs also differs in respect of urinary pH; trimethoprim excretion is enhanced in acid urine, that of sulphonamide in alkaline urine.

The difficulty of achieving effective antibacterial concentrations of antibiotics in the urine when renal excretion is impaired may be one of the reasons for the tendency of infections to recur in patients with localized renal damage. If unilateral renal disease or a smaller area of nephron damage is present the urine formed at that site will have lower urinary antibiotic concentrations.

Need for Investigation

Catheterization

The most important preventable cause of urinary tract infection is catheterization and instrumentation. If these are unavoidable, intermittent catheterization rather than an indwelling catheter is preferred and the instillation of a urinary antiseptic, such as neomycin or noxytiolin, reduces the incidence of subsequent bacteriuria.

Predisposing Factors

Host resistance is influenced by anatomical and other factors. Urinary tract infections are ten times more frequent in women than in men. The female urethra is short and more

likely to be exposed to contamination with faecal organisms and to the mechanical effect of coitus. Human prostatic fluid has recently been shown to contain an antibacterial substance, which may be partly responsible for the different incidence in males; moreover, the prostatic fluid of patients previously treated for chronic bacterial prostatitis did not appear to possess bactericidal activity. The usual pH and osmolality of female urine favours bacterial growth more than male urine. Because of the vulnerability of the female lower urinary tract isolated infections in women do not require exhaustive investigation.

Urinary tract infections in children may have serious long-term results and hence investigation is important. In elderly patients bacteriuria is very common, but does not often assume serious importance.

A careful history is required to exclude analgesic abuse, and biochemical investigation to exclude hypokalaemia, hypercalcaemia, and hyperuricaemia. Recurrent infections and those which prove difficult to eradicate are found to be associated with a high percentage of cases in which there is evidence of renal involvement.

Radiology

An intravenous pyelogram should be carried out in all patients who have had an attack of acute pyelonephritis. In many patients structural defects, congenital abnormalities, calculi, and evidence of childhood pyelonephritis will be discovered. Some of these, especially urinary tract obstruction, will be amenable to surgical attack. A large volume of residual bladder urine may be due to an enlarged prostate, a cystocele, bladder neck obstruction, urethral stricture, or neurological bladder disease.

Micturating cystourethrography demonstrates vesico-urethral reflux, which is found more commonly in young children. If the reflux is gross, with filling and dilatation of the renal pelvices and ureters, and if there is a long history of recurrent infections and pyelonephritic scarring is found on pyelography then the reflux should be corrected by surgery. If reflux is less severe its presence emphasizes the vulnerability of the upper urinary tract and the necessity for careful follow-up. If bacteriuria is successfully eradicated there is a reasonable hope that mild vesico-ureteric reflux in children will be cured without surgery.

Recurrent Infections

Hard and fast rules cannot be laid down for managing the difficult problem of recurrent urinary tract infection. Each patient requires individual assessment taking into account predisposing factors, evidence of renal involvement, and the frequency of bacteriological relapse or reinfection. The success of treatment depends on investigation to discover removable predisposing factors and, above all, on careful follow-up of all patients.

Bacteriological relapse with the same organism suggests a focus of renal involvement. High dose antibiotic therapy is usually given. Though many authors recommend a prolonged course, others have failed to find any advantage in giving the antibiotic for six as opposed to two weeks. Some of the relapses may be due to the persistence of protoplast forms of bacteria in the hypertonic renal medulla, and it is not known whether treatment should be directed against these forms—which are resistant to antibiotics acting on cell walls such as the penicillins, but are susceptible to tetracycline and erythromycin.

Reinfections with different organisms suggest that the infection may be limited to the bladder. In the treatment of recurrent infections the choice must be made between intermittent therapy for symptoms only, intermittent therapy for symptoms and asymptomatic bacteriuria, or long-term continuous therapy. After four or five recurrences it is usual to consider some form of prophylaxis. If recurrences are related to sexual intercourse, the patient should be instructed to empty her bladder after intercourse and to take a single tablet of an antibiotic at the same time. One tablet of nitrofurantoin taken at night has been found useful for long-term prophylaxis. Recent results with trimethoprim-sulphamethoxazole in low dosage (one tablet per day) have been encouraging. Continuous therapy reduces the frequency of symptomatic recurrences, but there is no evidence that it preserves renal function. After a successful period of six months or one year on continuous therapy, it is reasonable to change to intermittent therapy. Patients are supplied with a course of antibiotics which they take if a symptomatic recurrence occurs, or, if it is decided to treat asymptomatic bacteriuria as well, when this is discovered at follow-up. The frequency of bacteriological follow-up need not be limited to clinic attendances. Patients can be trained to prepare dip inocula at home, which they can then post to the laboratory.

Summary of Management

Management of infections of the urinary tract depends on a close integration of the physician and the bacteriologist. Radiological assessment and surgical intervention are often essential. Choice of antibiotics is influenced not only by the sensitivity of the organism isolated, but also by the level of renal function present. Recurrent infections are common, therefore careful follow-up and bacteriological surveillance is necessary. The prevention of progressive renal destruction is better documented in children than in adults.

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