EDITORIAL

MANAGEMENT OF CHRONIC URINARY TRACT INFECTION

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Introduction

In the management of a patient with chronic urinary tract infection (UTI), the clinician should take note of two salient features. The first is that clinical improvement does not equate with bacteriologic eradication and the second, follow-up urine cultures are necessary to ensure a cure. The first will determine the choice of antibiotics and the duration of treatment, and the second will help the clinician decide when to do follow-up urine cultures and sensitivity. In this paper on chronic UTI, I shall be constantly emphasising on the problem of relapse or recurrence in each of the conditions elaborated upon.

Relapsing recurrences due to urologic abnormalities

One should always consider three common causes: renal stone disease, vesicoureteric reflux and prostatitis. A relapse often occurs about two weeks after an infection. In a female, she should receive another 6-week course of treatment and in a male, another 12 weeks. These 6 weeks would ensure proper eradication of UTI due to vesicoureteric reflux and 12 weeks for chronic prostatitis[1]. Relapse occurs because the bacteria are deep-seated within the stone, the prostate or within the kidney tissue in the case of reflux nephropathy. A short course of antibiotic will kill the organism but those within the stone or organ will still survive and cause a relapse if not properly eradicated.

Reinfections

Patients with frequent reinfections will have altered bacteria flora, reflecting faecal bacterial reservoir and impact of antibiotics. Sulphonamides, penicillin and cephalosporins will eradicate gram negative organisms in the gastrointestinal tract (GIT) but they are replaced by *enterobacteraceae* or *pseudomonas* species[2]. The next "infection" usually occurs within 2 to 4 weeks and would be resistant to the above antibiotics. The choice of antibiotics would depend on the results of culture and sensitivity. Nitrofurantoin, trimethoprim and quinolones (nalidixic acid, norfloxacin) less commonly select resistant organisms in the GIT[2].

Prophylaxis

Prophylaxis of symptomatic lower tract infection in women is effective. Women with 2 or more symptomatic upper tract infections in a year should have prophylaxis. Nitrofurantoin 50 mg, cotrimoxazole 240 mg or 1/2 tablet, nalidixic acid 500 mg following sexual intercourse is effective. If the patient continues to have recurrent infection the antibiotic can be prescribed thrice weekly or even nightly if necessary. In males, there are no definitive studies regarding the value of preventing asymptomatic infection to reduce occurrence of acute pyelonephritis. For patients with vesicoureteric reflux, prophylaxis prevents infection of kidneys, protects or preserves renal function and in a growing child, allows resumption of normal renal growth[3].

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Continuous suppression

Permanent suppression is recommended in patients with frequent relapses (3 or more episodes a year) or for those where the source of infection cannot be removed, like stones, vesicoureteric reflux, prostatitis or obstructive uropathy.

The suppressive regimen consists of nightly, twice daily or full dose suppressive therapy with nitrofurantoin, cotrimoxazole or nalidixic acid. For example, a patient with chronic prostatitis, after treatment of the infection for 6 to 12 weeks with antibiotics can be put on cotrimoxazole one tablet (480 mg) nightly for years with no infection. It is important to review the patient every 3 to 4 months with urine culture and sensitivity. In the event of a breakthrough infection occurring, a new antibiotic is prescribed to treat the infection. After that, the patient is put on suppressive antibiotics again. Cotrimoxazole can still be used as the suppressive agent once the infection is eradicated. After 2 years on suppressive therapy, in the absence of infection, the antibiotic can be stopped to see if infection recurs. If it does, the patient will require treatment followed by further suppressive therapy.

Patient with renal impairment

Aminoglycosides like gentamicin and amikacin should be avoided if possible. If they have to be used, the dose should be reduced and serum creatinine and antibiotic levels monitored. Nitrofurantoin is contraindicated because it is of no use since it is poorly concentrated in the failing kidney. But more importantly, it causes very severe and painful peripheral neuropathy in patients with renal impairment[4].

Penicillins can be used. The newer ones with a broader spectrum of activity like piperacillin, mezlocillin and azlocillin are also active against most strains or *pseudomonas* and *strep faecalis*[5]. They are preferred over the third generation cephalosporins like ceftriazone and ceftazidime if either of these are infecting pathogens. The first generation cephalosporins are nephrotoxic but the second generation is less so and the third generation are safe but dosage has to be reduced in renal failure. Cotrimoxazole consists of trimethoprim which is not nephrotoxic but sulphamethoxazole is. In mild renal impairment only half the usual dose of cotrimoxazole (480 mg) twice daily should be used. Quinolones are safe drugs to use in renal failure.

Causes of recurrent UTI

Recurrent UTI could be due to or associated with the following: obstruction of the urinary tract, vesicoureteric reflux, renal calculi, diabetes mellitus, analgesic nephropathy, polycystic kidneys, cystitis, prostatitis, pregnancy, neurogenic bladder, urinary catheterisation, benign prostatic hypertrophy and uterovaginal prolapse among the elderly.

Obstruction of the urinary tract

Obstruction at all levels, from renal tubules to urethral meatus, is the most important factor predisposing to infection. Stasis compromises bladder and renal defence to sepsis. In patients with renal cortical scars as in reflux nephropathy, there is no increased susceptibility to infection. However in those with renal papillary scars (analgesic nephropathy, diabetic papillary necrosis) there is an increased susceptibility to infection because of intratubular obstruction.

Causes of obstruction could be due to congenital lesions (valves, bands stenosis, bladder neck obstruction), extrinsic compression of the ureters (tumours, retroperitoneal fibrosis), localised intrarenal obstruction to urinary flow (nephrocalcinosis, uric acid nephropathy, polycystic kidney and analgesic nephropathy).

Vesicoureteric Reflux (VUR)

This is a common cause of UTI. In patients with VUR, bladder infection may induce reflux because the inflamed intramural portion of the ureter is rendered a rigid plastic tube by the inflammation thus allowing reflux when the bladder contracts during micturition. Reflux disappears once infection is controlled. This is therefore a vicious cycle. Infection produces reflux or aggravates it, which in turn maintains the infection by producing residual urine which predisposes to infection because of urinary stasis.

If urinary infection is controlled, reflux tends to diminish as a result of the ureteral and bladder wall growing thicker with age. Prophylactic antibiotics are useful in preventing infection. About 20% of children not on prophylaxis develop new scars compared to those on prophylaxis[6-8].

Infection and nephrolithiasis

Damage to renal papillae produced by infection can cause calcified foci which with time become renal stones. The renal stones then cause UTI, incidence varying from 2% to as high as 47%[9]. About 50% of infections are due to *proteus mirabilis*. UTI with urea splitting organism causes triple phosphate (struvite) stones. There is a 25% mortality over 5 years in patients with stones induced by bilateral renal infection[10]. The risk of stone recurrence after surgery is 40% to 60%. The rate of persistent UTI is 40% because bacteria survive deep inside the stone[10]. In the management of such patients it is important to continue suppressive antibiotic therapy to prevent infected stones.

Diabetes mellitus

Diabetes mellitus is said to be associated with an increased frequency of UTI. However, this is based on evidence from uncontrolled or poorly controlled studies. A diabetic with no neurological complication affecting the bladder and has not undergone instrumentation is not at greater risk of developing UTI. However, following urinary catheterisation or in the presence of an autonomic bladder the incidence of ascending infection is frequent and severe. Underlying nephrosclerosis in a diabetic kidney also increases the possibility of papillary necrosis which predisposes to infection.

Analgesic nephropathy

This condition is associated with recurrent or asymptomatic UTI. UTI occurs in 15% to 60% of patients with analgesic nephropathy[11]. In a patient with analgesic nephropathy associated with UTI and deteriorating renal function, one has to exclude urinary tract obstruction and septicemia. The cause of urinary obstruction in a patient with analgesic nephropathy could be the result of a sloughed papilla, a calcified papilla or renal stones, transitional cell carcinoma in the renal pelvis or ureter and lastly, pyonephrosis. Analgesic nephropathy is one of the causes of sterile pyuria.

Cystitis

Acute cystitis or urethritis is common in women. An infection is termed a relapse if it occurs within 3 weeks of cessation of treatment. Reinfection accounts for about 80% of recurrent UTI. The organism is often from the perineal flora. Other foci of infection are the kidneys, prostate or the presence of any urologic abnormality. Nuns have an annual incidence of 0.4% cystitis compared to 1.6% in women aged 13 to 54 years[12]. This is because during sexual intercourse, bacteria is massaged into the urinary bladder through the anterior urethra.

E coli causes 79% of cystitis, *Staph saprophyticus* 11%, *Klebsiella* 3%, mixed organisms 3%, *Proteus mirabilis* 2%, *enterococcus* 2% and other bacteria 2%[13]. Uropathogenetic *E coli* has virulent features like increased adherence to cells, resistance to bactericidal human serum and K capsular antigen which is anti-phagocytic and causes persistent infection in a certain proportion of women with recurrent cystitis[13].

In men, prostatic fluid itself inhibits bacterial growth and the mucus in the bladder has anti-mannose activity which discourages bacterial growth[12]. Some females are prone to UTI because of a defect in local defence which makes them vulnerable to periurethral colonisation. This defect may be due to a lack in a particular antibody. Another reason may be the virulence of the particular strain of bacteria. Once infected, the bacteria persist[14].

Treatment of cystitis

The principle is to use the least toxic and least expensive antibiotic like nalidixic acid, ampicillin and nitrofurantoin. The patient should be encouraged to drink plenty of water to promote a good flow of urine to prevent urinary stasis which encourages bacterial growth. In recent years, ampicillin has been found to be less effective because of resistant strains of *E coli*. Fifty percent of *Staph saprophyticus* and all *Klebsiella* species are now ampicillin resistant[13]. However, augmentin which is a combination of ampicillin and clavulinic acid is effective. The clavulinic acid destroys penicillinase produced by the bacteria and allows the ampicillin component to act on the cell wall of the bacteria.

Nitrofurantoin is highly effective but 40% of patients experience nausea[15]. Cotrimoxazole has a propensity to cause gastrointestinal upset and rash. It is also effective against *Chlamydia trachomatis*. The quinolones (norfloxacin, pefloxacin) are related to nalidixic acid and cinoxin. They are also highly effective against *C. trachomatis*.

If a patient has symptoms of acute dysuria, suggestive of cystitis, she should be treated for UTI though the urine culture shows $<10^5$ colony counts of bacteria growth as one-third of patients with UTI has negative urine cultures[16].

Cystitis and urethritis

Females are 50 times more likely to have UTI than males. About 20% of females aged 24 to 60 years have at least one episode of UTI per year. After the age of 60 years the frequency is equal in both sexes.

One-third of patients with cystitis have gross haematuria. Some of these progress to upper UTI. About 40% of those with symptoms of UTI would have less than 10^5 colony counts of bacteria in the urine culture. They should still be treated as for cystitis. Fifty percent of patients with the "acute urethral syndrome" with negative cultures subsequently develop significant bacteriuria on follow-up[16].

If urine cultures are negative for bacteria and the patient has symptoms of dysuria suggesting the urethral syndrome,

one should consider *C. trachomatis, N. gonorrhoea, Herpes simplex, Mycoplasma and Ureaplasma.* These are organisms which cause the acute urethral syndrome. Sometimes a complaint of "dysuria" is actually due to pain caused by urine flowing over the inflamed vagina as in *Candida vaginitis.*

Relapsing lower tract infection

In a woman with relapsing lower tract infection one should suspect an upper tract infection (pyelonephritis) and in the case of a man one should suspect prostatitis. In both sexes, a structural abnormality, stones, diverticulae should also be considered.

A patient who relapses after a week of treatment should be treated for another 2 weeks, cotrimoxazole is the best choice. If there is another relapse the patient should receive a 6-week course of treatment and an intravenous pyelogram (IVP) should be performed. Thereafter the patient should be followed up with repeat urine cultures at 2 weeks, 4 weeks, 12 weeks and 6 months to ensure eradication of the infection.

In the case of patients with chronic prostatitis they should be treated with antibiotics like cotrimoxazole, erythromycin, oleandomycin and ciprofloxacin[17]. With these antibiotics, adequate therapeutic levels can be achieved within the prostate. Treatment should be for at least 12 weeks in chronic prostatitis to ensure eradication of the infection.

Recurrent urinary tract infection in the females

Two groups of women should be considered. Those with structural or functional abnormality of the urinary tract and those with normal IVP who have lower tract infection. In some, there may be a relationship to sex or use of diaphragm but in the majority there is often no apparent cause. Infection tends to cluster in time, that is, it tends to occur more and more frequently with shorter intervals in between and then it will go off for long periods without a recurrence.

Patients should be given advice regarding sexual hygiene like voiding of the urine within 15 minutes of sexual intercourse, prolonging the period of foreplay to ensure adequate lubrication, drinking enough fluids to pass more urine to reduce urinary stasis at night and wiping from front to back to avoid introduction of perianal flora into the urethral opening.

Women with frequent lower UTI should have prophylactic antibiotics post coitally if infections are related to sex. Nitrofurantoin one tablet post coitally is a useful prophylactic agent. Others are trimethoprim or cotrimoxazole (1/2 tablet or 240 mg) and nalidixic acid 500 mg. Women who suffer 2 or more infections a year could be taught the use of self administered single dose therapy, 4 x 480 mg of cotrimoxazole orally or 3 gm of amoxycillin orally as a single dose therapy[18]. For those who still continue to suffer recurrent UTI with prophylactic nightly antibiotics, we would prescribe suppressive therapy, either nitrofurantoin 50 mg tds, nalidixic acid 500 mg qid or cotrimoxazole 480 mg bd. This should continue for 2 years and thereafter antibiotics stopped and reinfections monitored. If reinfection occurs, it should be treated with a course of antibiotics and the suppressive regimen continued for another 2 years and then reviewed again.

Prostatitis

E coli is the commonest organism responsible for prostatitis. Others are *Proteus, Klebsiella, Enterobacter, Pseudomonas* and *Serratia*[17]. The route of infection is (i) by ascending urethral infection, (ii) reflux of infected urine into the prostatic duct and into the prostate, (iii) invasion by rectal bacteria, and (iv) hematogenous route.

During sexual intercourse a man can be infected by gonococcal urethritis through sexual contact with an infected female partner harbouring the gonococci in the cervix. Reflux of infected urine is another route. The presence of an indwelling catheter would enable bacteria to directly infect prostatic ducts by peri-urethral extension along the catheter. In acute prostatitis, a rectal examination will reveal a tender prostate. Prostatic massage or instrumentation like cystoscopy should not be performed during acute prostatitis.

In a patient with prostatitis one should exclude prostatic calculi, cancer of the prostate, prostatomegaly due to benign hyperplasia and chronic prostatitis. If epididymitis is present the patient is likely to have chronic prostatitis[17]. Urethral discharge in a male could be due to urethritis, urethro-prostatitis, or prostatorrhoea (very often the result of infrequent ejaculation). Chronic bacterial prostatitis is a common cause of relapsing UTI in a male with normal IVP. If a patient has a large residual urine volume, an enlarged prostate is often the cause. In a male with positive urine cultures from mid-stream urine with no symptom of UTI, a diagnosis of prostatitis is very likely. Under these circumstances a prostatic massage should be performed. Four specimens should be obtained: void bladder urine (VB1) when urine is passed before the mid-stream urine (MSU), the mid-stream urine (VB2), expressed prostatic secretion (EPS) resulting from the massage and the fourth specimen which is the urine passed following the massage (VB3)[19,20].

Relapsing urinary tract infection due to prostatitis

Infection should be by the same pathogen with symptoms of dysuria, urgency, frequency of micturition, nocturia, suprapubic, perianal, scrotal, penile pain or hemospermia. Once treatment is stopped, symptoms recur soon after in a patient with a relapse.

Acute prostatitis should be treated for 4 to 6 weeks to prevent chronicity. Cotrimoxazole 2 tablets twice daily is a useful agent. Alternatively, one could start off with injection gentamicin plus intravenous ampicillin for a week followed by oral cotrimoxazole once cultures confirm the sensitivity of the bacteria to the antibiotic. Other agents like erythromycin, doxycycline, cephalosporin and quinolones could be used in acute prostatitis. In acute prostatitis most antibiotics can penetrate the inflamed prostate gland because of the acute inflammation of the gland.

For chronic prostatitis treatment should be with trimethoprim, erythromycin, oleandomycin or ciprofloxacin for 12 weeks[17]. If there is no cure after 12 weeks and relapse still occurs, the infection should be treated and thereafter the patient should receive suppressive therapy with trimethoprim one tablet daily or twice daily on a long term basis for 2 years, and thereafter stopped to see if there is a relapse. If so, the patient should continue to receive therapy for another 2 years.

Non bacterial prostatitis

This is caused by the same organisms causing non gonococcal urethritis (NGU); apart from fungus and anaerobes. Organisms causing NGU are *C. trachomatis, Ureaplasma, Mycoplasma, Trichomonads, H. simplex and Cytomegalovirus (CMV). C trachomatis* causes 40% to 50% of NGU and Ureaplasma causes another 25%[21]. These organisms also cause the dysuria-pyuria syndrome where patients present with dysuria and frequency. Urine cultures should be performed to exclude gonococci and special cultures performed for *C. trachomatis* and *Ureaplasma.*

Treatment for NGU consists of either erythromycin or tetracycline for 2 weeks. But in the case of non bacterial prostatitis resulting from organisms causing NGU, treatment should be for 12 weeks. Trimethoprim and ciprofloxacin could also be used. During therapy the patient should abstain from sex and

alcohol. The sexual partner should also be treated. Relapse could be due to the organism becoming resistant to the antibiotic, poor patient compliance, *H. simplex* infection which would require therapy with iodoxyuridine or it could mean that the sexual partner has not been or has been inadequately treated.

Pregnancy

Asymptomatic bacteriuria occurs in 4% to 7% of pregnant women. About one-third of these women run the risk of developing acute pyelonephritis in the later stages of pregnancy[22].

Screening is important as this will reduce the incidence of pyelonephritis to less than 5% in 75% of patients[22]. This will prevent the foetal morbidity due to prematurity.

In pregnancy, estrogen and progesterone induce dilatation of ureters and the renal pelvis. This will increase progressively towards term. The bladder capacity also doubles and the bladder becomes distorted due to compression by the gravid uterus.

The following antibiotics are safe in pregnancy: short acting sulphonamides, ampicillin, nitrofurantoin and cephalosporin[23].

Upper urinary tract infection and neurogenic bladder

Patients with spinal cord injury require either continuous or intermittent urethral catheterisation. Renal infection is secondary to chronic upper tract infection and many patients form stones[24].

In the past decade the use of non-sterile intermittent self catheterisation has been introduced[25]. The patients were not treated with routine prophylactic antibiotics so as to reduce incidence of emergence of resistant strains of organisms. However, others employ low dose prophylactic antibiotics with cotrimoxazole to prevent infection[25]. Continuous long term suppression with antibiotics has been used to prevent recurrent symptoms. Antibiotics used include cotrimoxazole, amoxycillin and cephalosporins.

Infection by *proteus* must always be suppressed as such infections predispose to stone formation which are difficult to eradicate as the bacteria lie within the stone. Some advocate treatment only for symptomatic infection. They argue against suppressive antibiotic therapy as it selects multiresistant organisms.

Catheter associated urinary tract infection

This constitutes 35% to 40% of all hospital acquired infections[26]. It is the most common source of gram negative bacteremia. Bacteria gain entry in the following ways:

(i) at time of catheterisation,
(ii) they enter around catheter in the urethral mucus (periurethral route),
(iii) via contaimination of the collecting system; bacteria ascend through the lumen of the catheter, hence the importance of using a closed drainage system.

Antecedent rectal or periurethral colonisation also plays an important role as it does in females with cystitis. After a single in-out catheterisation, bacteriuria occurs in 1% of healthy persons compared to 3% to 20% among the pregnant, the elderly, debilitated and those patients with urologic abnormalities[26].

About 50% of females and males who are catheterised for 2 weeks become bacteriuric[26]. The overall incidence increases with the duration of catheter in place and is related to the patient's condition.

Prevention of catheter urinary tract infection

The following have been advocated:

(i) Closed drainage system. This prevents bacteriuria up to 10 days.
(ii) Twice daily application of polyantimicrobial cream to urethral meatus.
(iii) Systemic antibiotics in the short term not long term because this will predispose to infection with resistant strains.
(iv) Lubricating gels for catheter.

Treatment of catheter urinary tract infection

The infected catheter should be removed, antibiotic therapy initiated and a new catheter reintroduced together with a new closed drainage system. If the patient has fever and loin pain, parenteral antibiotics should be initiated immediately and therapy continued for a week. Resistant bacteria and fungi (*Candida, Torulopsis*) are frequently isolated in patients on multiple courses of antibiotics. The choice of a suitable antifungal agent is guided by results of sensitivity tests.

Lower tract fungaria (cystitis) usually responds to amphotericin B bladder washout. First, empty the bladder of urine by means of a urinary catheter. Amphotericin B is then introduced in a dosage of 15 mg in 100 ml of distilled water through the urinary catheter. The catheter is then removed. The amphotericin will stay in the bladder and is passed out together with the urine after a few hours. Lower tract fungaria causing cystitis should respond after an amphotericin bladder wash out. After one week the urine culture should be negative for fungus. If fungus persists, it would mean that the infection is in the upper tract (pyelonephritis). If that is the case then, the patient should be treated as for an upper tract fungal infection as for systemic candidiasis (if *candida* is the organism grown). Intravenous amphotericin is administered following a test dose and then progressively increased until a total dosage of about 1 gm has been given, usually over a period of 6 weeks or more. Alternatively, if the organism is sensitive to 5-fluorocytosine, it could be administered intravenously for the first 2 weeks and then oral therapy given for the remaining period. This has the advantage of early discharge of the patient from hospital.

Urinary tract infection and the elderly

Ageing is associated with an increased prevalence of bacteriuria. It is about 10% in males and 20% in females over the age of 65 years[27]. Young female adults have 30 times greater prevalence of bacteriuria compared to young male adults.

The following causes account for an increased prevalence of UTI in the elderly:

(i) Obstructive uropathy
(ii) Loss of bactericidal activity of prostatic secretion
(iii) Poor bladder emptying due to utero-vaginal prolapse, cystocele and prostatomegaly
(iv) Soiling of perineum from faeces
(v) Increased bladder catheterisation

Conclusion

Every episode of a UTI has the potential to become a recurrent or chronic disease. Patient education is a very important aspect of the management as in many diseases which have the propensity to become chronic. Patients should be taught to anticipate subsequent episodes by teaching them to look out for early symptoms. They must understand the reasons for recurrence in order to avoid infection.

It is equally important too that the attending physician should be aware of certain aspects of the management to minimise the possibility of relapse, recurrence and chronicity. Clinical improvement does not equate bacteriologic eradication. Follow-up urine cultures are necessary to ensure cure. Depending on the circumstances of the case, whether it is a lower tract infection due to cystitis (1 week treatment), upper tract infection (2 weeks) or prostatitis (6 to 12 weeks), the physician would have to prescribe an antibiotic for varying dura-

tion. The choice of the antibiotic will depend on whether one is treating a simple recurrent cystitis in a female with normal IVP, or a patient with acute or chronic prostatitis. The choice of an antibiotic will also depend on whether it is prescribed for the current infection or for prophylactic or suppressive therapy because the emergence of multiresistant organism has to be considered. Therapy has to be accompanied by follow-up cultures and sensitivity performed at the right time and the correct periodic interval; 1 week, 2 weeks, 4 weeks, 12 weeks and 6 months to detect asymptomatic bacteriuria and at any time when the patient has a breakthrough infection.

Managed properly, the patient is likely to have a marked reduction in the incidence of relapses and recurrences, apart from the possibility of preventing a relapse or recurrence in a patient with a first or new infection. Even so, for many patients who have had a UTI, they would be prone to relapses and recurrences, often requiring long term prophylactic or suppressive antibiotics.

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