

Urinary Tract Infection: Key Points in Management

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NATURAL HISTORY OF BACTERIURIA

Urinary tract infection is the most common of all infections affecting humans throughout their lifespan. It occurs in all populations—from neonates to geriatric patients—but it has a particular impact on females of all ages (especially during pregnancy), males at the two extreme of ages, kidney transplant recipients and anyone with functional or structural abnormalities. It can produce ranges of clinical syndromes including pyelonephritis with gram-negative sepsis, asymptomatic bacteriuria and even the so-called symptomatic bacteriuria. While managing urinary tract infection (UTI), three issues are to be kept in the mind:

1. What is the pathogenesis and how can such pathogenesis be interrupted?
2. How does one best diagnose, prevent, and treat the infection?
3. What are the contributions of UTI to the development of chronic renal disease, hypertension, or both; its effect on longevity and effect on outcome of pregnancy?

Bacteriology of Urinary Tract Infection

There exists an incomplete correlation between the clinical symptoms and urinary tract infection and the presence of UTI, so objective evidence of the presence and type of infection is of great importance. There is frequently great difficulty in obtaining a spontaneously voided urine specimen that is uncontaminated by the normal flora of the distal urethra, vagina or skin. Therefore certain guidelines are necessary for evaluating the results of urine culture:

1. Obtaining a positive urine culture and correlating its importance for the treatment.

2. Search for fastidious organisms, e.g. *Ureaplasma urealyticum* and *Mycoplasma hominis* as cause of UTI which may not be justified.

In women, 5-20% may harbour gram-negative bacilli at the site of urethra in the absence of UTI. In more than 95% of true infection, a single bacterial species is responsible for the infection. True polymicrobial UTI occurs uncommonly and is observed in very few clinical situations, either with long-term catheter or a foreign body (e.g. calculus, necrotic tumour) in place of stagnant pool of urine where repeated procedures are being done.

The major criteria for the validity of culture is based on the quantification of the number of colony forming units (CFUS) in the urine and one should demonstrate significant bacteriuria with at 10^5 CFU/ml. Others having less than this (insignificant bacteriuria) had a high probability of being free of infection. Still, there could be patients having symptoms with colony count of as little as 10^2 CFU/ml. Hence, new criterions have been established to ensure adequate sensitivity and specificity:

- a. Women having symptoms of UTI (acute uncomplicated) with dysuria, frequency, suprapubic discomfort, are thought to be true even with colony count of 10^3 CFU/ml of a single species.
- b. Symptoms of acute uncomplicated pyelonephritis (fever, rigor, flank pain, with or without dysuria or frequency) the cut-off is at least 10^4 CFU/ml.

Fungal Pathogens

Candida species is the commonest fungal infection of the urinary tract. Most such infections occur in patients with indwelling. Foley's catheters who have been receiving broad-spectrum anti-bacterial therapy particularly in immuno-compromised hosts. Most of

Table 1: Common pathogens and contaminants in UTI

| Common pathogens of UTI | | Common bacterial contaminants |
|---|-------|-------------------------------------|
| <i>Escherichia coli</i> | 89.2% | <i>Staphylococcus epidermidis</i> ; |
| <i>Proteus mirabilis</i> | 3.2 | <i>Corynebacterium</i> ; |
| <i>Klebsiella pneumoniae</i> ; <i>Enterococci</i> ; <i>Enterobacter aerogenes</i> ; | 2.4 | <i>Lactobacillus</i> ; |
| <i>Pseudomonas aeruginosa</i> | | <i>Gardnella</i> |
| <i>Proteus</i> | 2.4 | <i>vaginalis</i> ; Anaerobic |
| <i>Serratia marcescens</i> | 3.3 | bacteria |
| <i>Staphylococcus epidermidis</i> | 1.6 | |
| <i>Staphylococcus aureus</i> | 0.7 | |

these infections clear-off after removal of the catheter; however, in 10% patients it remains the source of candidaemia in those patients where urinary tract manipulation occurs, or in obstructive uropathy. In transplant patients and other immunocompromised patients it can lead to systemic dissemination. The commonest species which are highly invasive are *Candida albicans* and *Candida tropicalis* in non-diabetic, non-pregnant, and non-catheterized individuals. Other species are less invasive but can cause catheter related UTI, focal pyelonephritis or disseminated infection. Hematogenous infection to kidney and urinary tract can occur in any systemic fungal infection particularly in coccidiomycosis and blastomycosis. Cryptococcal infection can occur in immuno-compromised hosts and may cause prostatitis, renal papillary necrosis, pyelonephritis, and pyuria akin to tuberculosis.

Chlamydia, mycoplasma are other rare organisms alongwith viruses like adenovirus papovavirus and cytomegalovirus may also lead to UTI in immuno-compromised patients.

Frequency and Epidemiology of Urinary Tract Infection

Approximately one per cent of the neonates are bacteriuric, with a two-fold to four-fold higher frequency among boys which could be associated with urogenital congenital anomaly in male infants. An equal rise may be seen in infants (2.9%) who are premature and may have vesico-ureteric reflux. Uncircumcised male infants are at increased risk of UTI and pyelonephritis in the neonatal period and this may continue to adulthood. The preputial space may act as a reservoir, and after circumcision the incidence may fall drastically. After infancy and until age 55 years when prostatic hypertrophy starts becoming apparent in men, UTI is predominantly a female disease. From infancy until age 10 years, the frequency of UTI in girls is about 1.2% with,

one-third of these infections being asymptomatic. After an initial episode of bacteriuria, approximately 80% of school girls have one or more recurrences; 8% of these recurrences are due to reinfections rather than relapses of sequestered deep infections. 5 to 6% of school girls have at least one episode of UTI between the age of 5 and 18 years, and 20% of school girls with bacteriuria have demonstrable vesico-utereitic reflux.

Bacteriuria may reappear shortly after marriage or pregnancy and 63.8% women in active sexual age group may suffer with pregnancy associated urinary tract infection. Amongst adult women the incidence and prevalence of bacteriuria are related to age, degree of sexual activity and form of contraception employed. Approximately 1 to 3% women between the ages of 15 to 24 years have bacteriuria; the incidence increases by 1 to 2% for each decade, thereafter upto a level of about 10 to 15% by the 6th or 7th decades, and 40 to 50% women will experience at least one episode of UTI in their lifetime. Dysuria may present in at least in 20% women between age of 24 and 64 years and one-third may have acute urethral syndrome and two-third may have significant bacteriuria in association with clinical symptoms referable to the urinary tract. Asymptomatic or clinically overt bacteriuria is quite uncommon in male patients till they reach their 50s, in the absence of instrumentation or obstructive uropathy. The incidence in school boys is at little as 0.04 to 0.14% and the first episode may be delayed till the age of 10 years. During adolescence the heterosexual transmission may be an important factor depending upon cultural behavior and lifestyle in younger and middle-aged people and by 70 years of age frequency of bacteriuria may reach level of 3.5% in otherwise healthy men, and 15% in hospitalized patients. With the onset of chronic, debilitating illness and long-term institutionalization bacteriuria in both sexes may reach to 25 to 50% with slightly higher frequency in women than men.

TREATMENT

General Principles of Antimicrobial Therapy

The rationale of treatment is based upon the need to eradicate the infection by a drug which can reach the lumen of the tract as well as in the deeper tissues where bacteria might be harbouring and multiplying. The goals of treatment are to prevent systemic sepsis, to relieve symptoms, to eradicate sequestered infection, to eliminate uropathogenic bacterial strains from faecal and vaginal reservoirs, and to prevent long-term sequelae with minimum side-effects and with the least selection of antibiotic resistant bacterial flora.

SPECIFIC RECOMMENDATIONS

Acute Uncomplicated Cystitis in Young Women

Women in their reproductive age and having acute symptoms of dysuria, frequency, urgency, nocturia, and suprapubic discomfort in the absence of signs and symptoms of vaginitis, e.g. vaginal discharge or odour, pruritus, dyspareunia and vulvovaginitis should be approached with two objectives:

1. Eradication of superficial mucosal infection of the lower urinary tract.
2. Eradication of uropathogenic clones from the vagina and lower gastrointestinal tract.

In the last two decades the treatment of choice has been short course chemotherapy with trimethoprim-sulphamethaxazole or a fluoroquinolone; both of them are superior to β -lactam in the treatment of simple UTI. These drugs attain higher concentration in vaginal secretions that are more than sufficient to eradicate the usual *E. coli* and other major uropathogens. These drugs do not harm the normal anaerobic flora and micro-aerophylic vaginal flora which provides colonization resistance against the major uropathogens. In contrast β -lactam drugs such as amoxicillin appear to promote vaginal colonization with uropathogenic *E. coli*. Due to emergence of co-trimoxazole resistant uropathogens, in more than 50% younger women, the use of fluoroquinolones has increased; however, it must be emphasized that monitoring of resistant strains to this class of drugs will be important. And, it is likely that resistance, will slowly develop to these drugs as well.

There are two forms of short course chemotherapy:

- a. Single dose therapy
- b. Three days course therapy.

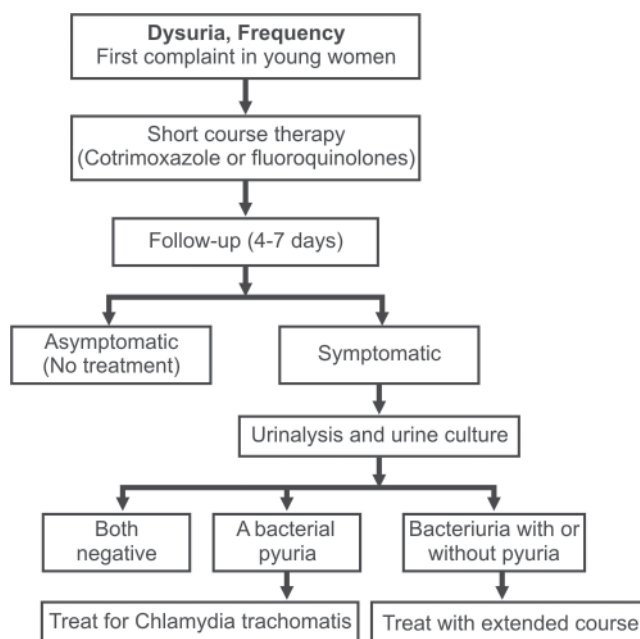
There are compelling evidences that 3 days course therapy is superior to a single dose, with either trimethoprim-sulphamethoxazole or a fluoroquinolone, provided the infective organism is susceptible. Both forms of short course therapy are probably equally efficacious in eradicating bladder infection in women. However, single dose therapy is not as effective in eradicating the uropathogenic clones from the vaginal or intestinal reservoir as 3 days course therapy. As a result, early recurrence, predominantly resulting from reinfection from these reservoirs is significantly more common with single dose therapy.

The short course therapy is specifically designed for the treatment of superficial mucosal infection and to

serve as a guide for those with unsuspected deep tissue infection who would benefit from a more extended course of therapy (e.g. women with occult pyelonephritis). Short course therapy should never be recommended in the following categories of patients:

1. Anyone with overt pyelonephritis.
2. Patients with deep tissue invasion, e.g. prostate.
3. Patients having symptoms of more than seven days.
4. Patients with underlying structural or functional defects.
5. Immuno-suppressed individuals.
6. Patients with indwelling catheter or recent instrumentation.
7. Infection with a probability of antibiotics-resistant organisms.

Acute uncomplicated UTI in otherwise healthy women is so common, the range of organism causing the infection is so well defined, the susceptibility of these organisms to the anti-microbial agents recommended is so uniform, and the efficacy and lack of side-effects of short course therapy are now so well established that all have combined to lead a cost-effective approach that minimizes both laboratory studies and the need for visits to the physicians. The critical practitioner-patient interaction comes after the completion of therapy: if the patient is asymptomatic, nothing further needs to be done.



If the patient is still symptomatic, both urinalysis and urine culture are necessary. If the patient has a negative urinalysis and bacterial culture, no clear microbial etiologic agent is present; one must analyze the associated trauma, personal hygiene, allergy to clothing dyes, or primary gynecological conditions. If the patient is pyuric but not bacteriuric, the possibility of *C. trachomatis* urethritis should be considered, particularly in sexually active women with multiple partners. The treatment should be given for a 7-14 days duration with either tetracycline or sulphonamide to both partners. Alternatively, a more prolonged course of treatment should be considered with a fluoroquinolone or co-trimoxazole treatment.

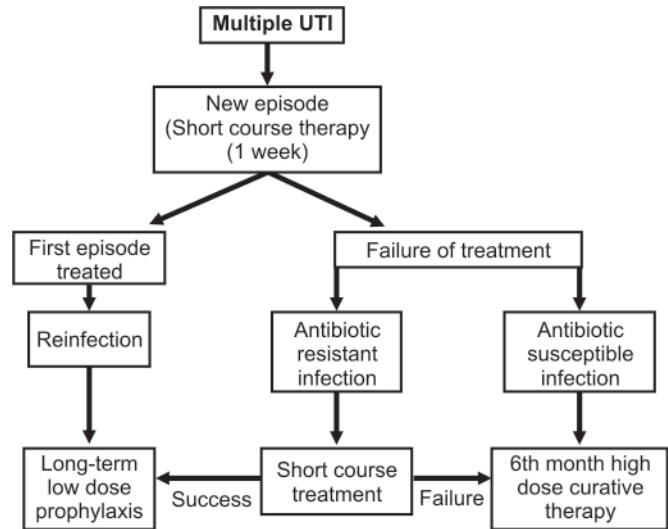
Recurrent Urinary Tract Infection in Young Women

Approximately 20% of young women with a first episode of UTI will have recurrent infection. Various regimens have been designed to prevent repeated reinfections, which accounts for more than 90% of UTI recurrences. Women should be careful about sexual hygiene, voiding after sexual intercourse, and should change the contraceptive device they are using which may be a predisposing factor to prevent reinfection. The urine should be acidified with the use of either methanamine mandelate or methylamine hippurate plus ascorbic acid, which results in release of formaldehyde when the urine pH is maintained at pH of 5.5 or lower. Low dose of TMP with sulphamethoxazole can also be tried in these women for a prolonged period. Use of nitrofurantoin 50 or 100 mg at bed-time could be equally effective and does not alter the gut flora, however its prolonged use can result into chronic interstitial pneumonitis, acute pulmonary hypersensitivity reactions, liver damage, blood dyscrasias, skin reactions, and neuropathy. In addition, nitrofurantoin should not be used in patients with renal failure. A low dose of co-trimoxazole as little as half tablet (TMP 40 mg, sulphamethaxazole 200 mg) three times a week at bed-time can reduce the frequency of less than 0.2 per patient per year. The fluoroquinolones can also be used in low dose prophylaxis.

The duration of prophylaxis should continue for a period of 6 months and then discontinued. If infection recurs, prophylaxis should continue for 1-2 years or even longer. A low dose of sulphonamide or co-trimoxazole should be continued with strict monitoring of the cardiovascular system.

Acute Uncomplicated Cystitis in Elderly Women

Post-menopausal women face special problems in treatment of cystitis. The frequency of both symptomatic



and asymptomatic bacteriuria is considerably higher than in younger age groups, probably as a result of the following factors:

- i. Due to loss of pelvic tone of muscles many women have residual urine in their bladder.
- ii. The lack of estrogen makes bladder and vaginal epithelium more susceptible for uropathogens due to change in vaginal flora.

In these women, oral or local replacement of estrogen in the form of a vaginal cream may restore the bacterial flora and atrophic genitourinary tract mucosa. Regular intakes of a cranberry juice have been found to be effective in both bacteriuric and pyuric elderly women.

Acute Uncomplicated Pyelonephritis in Women

In women having uncomplicated pyelonephritis, the choice of an antibiotic is based on the principle that it should be able to reach in the deep tissue infection as well as in the lumen of the urinary tract. Following strategies should be adopted in formulating the principle of treatment:

- i. A combination of parental antibiotic with oral drug should be preferred. One can start with parenteral antibiotics for immediate control of sepsis for 2 to 3 days followed by or with oral agents.
- ii. Ampicillin, amoxicillin, or first generation of cephalosporines should be used first, depending upon the sensitivity range, as initial therapy in the form of intravenous treatment followed by oral co-trimoxazole or quinolone.
- iii. Alternatively, a single large dose of gentamicin (10 mg/kg) followed by oral ciprofloxacin could be a

much cost-effective regimen for many such patients once antimicrobial sensitivity is being awaited.

If possible, one may start by doing a Gram staining of the urinary deposit. If gram-positive cocci are present intravenous ampicillin, vancomycin plus gentamicin should be the initial prescription to cover both enteropathogens and gram-negative uropathogens. If only gram-negative bacilli are seen then one can consider parenteral administration of co-trimoxazole and fluoroquinolones and gentamicin; such broad spectrum cephalosporin as ceftriaxone, azotrenane, ampicillin, salbactam piperacillin-tazobactam and impapanemucilastatin. The last agents should be reserved for those patients who have more complicated histories, previous episodes of pyelonephritis and recurrent urinary tract infection.

Urinary Tract Infection in Pregnancy

Women having pregnancy with uncomplicated UTI should be screened in the similar way as acute in complicated infection with urine analysis and culture sensitivity. Once culture has been sent, they may be started with three day regimen with those drugs which are non-toxic to the growing fetus. The principle should be to use adequate dose and interpose follow-up with the institution of prophylaxis for the duration of pregnancy.

Sulphonamides, nitrofurantoin ampicillin and cephalixin have been considered relatively safe for use in early pregnancy. However, sulphonamides are to be avoided near the term because of possible role of kernicterus. Trimethoprim has toxic effect on fetus in experimental animal, but no report has yet appeared in human beings. Fluoroquinolones can affect the development of fetal cartilage hence needs to be avoided. Therefore, safe drugs are nitrofurantoin, ampicillin or cephalosporins. In pregnant women with overt pyelonephritis, a short course of parenteral treatment with β -lactam drugs, aminoglycosides or both are the cornerstone for treatment provided there is strict monitoring of renal function.

Urinary Tract Infection in Men

Though UTI is uncommon in men younger than 50 years, it can occur in following conditions:

- i. Homosexual men
- ii. Infected partner
- iii. Men having immunocompromised state with a CD4 count less than 200/mm³.

Such individuals should never be treated with short course chemotherapy. They should be treated for a minimum period of 10-14 days with either co-trimoxazole or fluoroquinolones unless antimicrobial intolerance or uropathogen requires an alternative approach. In men older than 50 years age with UTI, tissue invasion of prostate, the kidneys, or both should be assumed, even in the absence of overt signs of infection at these sites. Because of the inflammation usually present, acute bacterial prostatitis initially responds well to the same array of antimicrobial agents as used to treat UTIs in other populations. If relapse occurs or there is recrudescence one should take the following precautions:

- i. Choose an antibiotic which is secreted in the racemose gland of the prostate and in prostatic fluid.
- ii. Exclude the presence of prostatic calculi, as it may require intervention.
- iii. An enlarged prostate may cause bladder outlet obstruction, and if there is significant residual volume (postvoid) and does not respond to medical therapy, surgical intervention is necessary.

Due to these factors, intensive antimicrobial therapy of four to six weeks is required and even may be extended to 12 weeks if pyuria/bacteriuria or symptoms persist. If co-trimoxazole or fluoroquinolone therapy fails, the patients should be subjected to ultrasonography, pyelographic or cystoscopic studies to exclude obstructive uropathy. If relapse occurs, a choice has to be made amongst the following three therapeutic approaches:

- i. Long-term antimicrobial suppression.
- ii. Repeated treatment for each relapse.
- iii. Surgical removal of infected prostate gland.

Treatment of Childhood Urinary Tract Infection

In pediatric age group there is always difficulty in obtaining urinary samples for culture. Hence, all precautions should be taken to obtain the sample during spontaneous void and to prevent the contamination. A parenteral therapy should be started if suspecting pyelonephritis by broad-spectrum antimicrobial till the culture report is available; subsequently, a narrow-spectrum antibiotic should be selected having least toxicity. The parenteral therapy should be continued till baby becomes afebrile and it should be followed with oral therapy for a period of one to three months. The children having uncomplicated UTI, 7 to 14 days therapy

is sufficient with the exception of adolescent girls where the compliance of short course therapy is difficult to achieve and personal hygiene is to be counselled. The major difference in children is the use of quinolones which is to be avoided as it may interfere with the development of cartilage.

Recurrent UTI in children particularly in those having scar and demonstrable vesico-urinary reflux is dealt with by long-term prophylaxis with co-trimoxazole (2 mg/kg trimethoprim, 10 mg/kg sulphamethoxazole) or nitrofurantoin 2 mg/kg/day. Some of these children can have associated constipation which is to be treated if associated with incontinence. Surgical correction of VUR should only be considered if child fails to respond to 2-4 year prophylactic medical treatment.

Complicated Urinary Tract Infection

This encompasses a heterogeneous group of patients with a wide variety of structural and functional abnormalities of the urinary tract and kidney. The organism invading the genitourinary tract is much broader with a high percentage of these organisms being resistant to one or more of the microbial agents frequently used in other population of patients with UTI. The following general principles have been recommended in approaching patients with complicated UTI:

1. Primarily symptomatic treatment should be started first. All patients must receive antimicrobial therapy empirically or according to culture sensitivity before any instrumentation or catheterization as a preventive measure for a period of three to seven days.
2. A broad-spectrum antibiotic should be selected first such as, ampicillin plus gentamicin, impenamciclastin and piperacilline-tazobactam. In a patient who is more sub-acutely ill, co-trimexazole can be started till sensitivity pattern is available.
3. Effort should be made to correct the underlying pathology, whenever possible in conjunction with anti-microbial therapy. If this is possible, 4 to 6 weeks curative course of therapy in conjunction with surgical manipulation is appropriate. If such correction is not possible, shorter course of therapy (7 to 14 days) aimed at controlling the symptoms appears to be more appropriate. Frequent symptomatic relapses are worth an attempt at long-term suppressive therapy. Patients with neurogenic bladders secondary to spinal cord injury should be advised for intermittent self-catheterization with methanamine prophylaxis.

Table 2: Prevention of catheter associated infection

1. Use catheter only when necessary and remove promptly.
2. Only trained person should introduce catheter.
3. Ensure obstruction has been taken care of and closed drainage system should be followed.
4. Urine culture should be obtained immediately after insertion of catheter.
5. Downhill unobstructed flow should be maintained and bag should be emptied frequency.
6. Replace catheter if sign of rupture or obstruction is present.
7. Preferably, patients of UTI are isolated from immune compromised patients.

Catheter Associated Urinary Tract Infection

Nosocomial urinary tract infections are more common in patients on indwelling catheters in hospital acquired infection. Although bacteriuria is inevitable with long-term catheterization, guidelines have been employed to delay the onset of such infections and to minimize the rate of acquisition of antibiotic resistant pathogens (Table 2). Sterile insertion technique, use of closed drainage system and prompt removal and isolation of patients with catheter associated infection will decrease the incidence and the spread of infection to others. Various methods have been suggested to decrease the incidence, e.g. topical use of povidone-iodine solution at meatus before insertion and use of disinfectants in collection bags.

In any patient who is symptomatic (e.g. fever, chills, dyspnea and hypotension) empirical antibiotic therapy should be started without delay. However, in an asymptomatic patient, no therapy is indicated. Patients on long-term catheter rarely become symptomatic unless the catheter is obstructed or gets eroded through bladder mucosa. Those who become symptomatic inspite of antibiotics, a change of catheter or drainage system should be adopted.

In catheter associated candidial infection, the old catheter should be replaced with a three-way catheter and infusion of an amphotericin rinse for 3 to 5 days is recommended taking care of other associated factors like hyperglycemia, corticosteroid therapy and antibiotics. Treatment with Amphotericin B may have high incidence of bacteriuria, hence may require fluconazole 200-400 mg/day for 10 to 14 days. Oral flucanazole therapy is as effective as local amphotenicin especially in immuno-compromised host and renal transplant patients.

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