

Review Article

Management of urinary tract infections in adults: An overview

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Introduction

Urinary tract infections (UTIs) remain one of the most common infections observed in community and hospital based practice. They result in significant morbidity and mortality while consuming large amounts of national resources. It is estimated that 7 million episodes of cystitis occur annually in the United States and the cost of caring for such infections exceeds \$1 billion [1]. Although most adult (UTIs) are uncomplicated and respond rapidly to antimicrobial therapy, they occasionally cause serious and permanent renal damage. Due to the anatomical continuity of the system infection may extend throughout part or all of the urinary tract, and more rarely, may involve the perinephric spaces[2]. The incidence of (UTIs) in women is 10 times that in men and amounts to an annual general practice consultation rate of 62.5 per 1000 [3,4]. In institutionalised elderly patients the prevalence of asymptomatic bacteruria approaches 20-50% in women and 5-20% in men [5]. Clearly on the basis of their prevalence alone (UTIs) warrant careful consideration by clinicians.

The emergence of the newer antibiotic classes, including the second and third generation cephalosporins and the fluoroquinolones, has provided the clinician with agents that offer a broad spectrum of activity, good patient acceptance, a well tolerated safety profile, and convenient dosage regimens due to their unique pharmacokinetic profiles [6].

Unfortunately (UTIs) remain a problem because of the poor clinical application of the measures currently available.

Renal tuberculosis will not be discussed in this review.

Definitions

Significant bacteruria

Normal bladder urine is sterile. Kass in 1956 defined significant bacteruria as the presence of 10^5 or more colony forming units per millilitre of a midstream sample of urine. Occasionally counts of 10^4 bacteria/ml should be taken into consideration as possible (UTI), particularly in diabetic patients and those who are immuno-compromised. Such counts may also be relevant with complicated infections as a pure growth of 10^4 of a given Gram negative organism cannot be discounted. Contamination becomes more likely if there is a mixed growth of bacteria. Where it is possible to obtain uncontaminated samples, or in symptomatic patients with low bacterial counts, bladder bacteruria is diagnosed by the culture of urine obtained by suprapubic aspiration. Pyuria is defined as 10 or greater leucocytes per high-power field in centrifuged urine [7]. It is supportive evidence of the presence of a clinically important (UTI), but pus can be present in "sterile" urine, where it may indicate a fastidious organism such as mycobacteria or recent treatment with antibiotics [4]. The leucocyte esterase test on dipstick urinalysis is a rapid screen for the presence of pyuria and a positive test correlates with a minimum of 8-10 leucocytes per high-power field [8]. Specimens need to be transported to the laboratory for culture without delay, and if stored for a few hours should be kept at 4°C to prevent bacterial proliferation artificially increasing the count. Pure growths in lower counts may also indicate bladder bacteruria in patients who are undergoing a water diuresis by ingesting large amounts of fluid [9].

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Recurrent attacks: Relapse or reinfection ?

Recurrent infection is a problem for both the clinician and the patient. Relapsing infection is a recurrence of bacteruria with the same organism within three weeks of completing treatment which, during treatment, rendered the urine sterile. It most often occurs in association with renal scars, stones, cystic disease, prostatitis, in patients with chronic interstitial nephritis or in those who are immunocompromised. Patients who relapse should undergo detailed investigation.

Reinfection is much more common than relapse and accounts for 80% of recurrent infections. It is defined as eradication of bacteruria by appropriate treatment, followed by infection by a different organism after 7-10 days. Unlike relapse, reinfection does not represent failure to eradicate infection from the urinary tract, but is due to reinvasion of the system. Prophylactic measures must be initiated. Women with recurrent (UTI) are more likely to be non-secretory of blood group antigens [10]. A bio-chemical fingerprinting system has been designed for subtyping of *Eschereschia coli* and is suitable for screening large numbers of bacterial strains in patients with non-obstructive pyelonephritis renal scarring and recurrent (UTIs). This helps to determine whether recurrent infections are relapses or reinfections [11].

Complicated vs uncomplicated (UTI)

Persistent or recurrent infection in adults with anatomically and functionally normal urinary tracts rarely lead to significant kidney damage.

Complicated infection is defined as infection occurring in a structurally and functionally abnormal urinary tract, or in a patient whose tract may or may not be normal but also has associated disease such as diabetes, analgesic abuse or sickle cell trait. Obstruction, stones or vesico-ureteric reflux predispose to kidney damage, perinephric abscess, septicaemia or a combination of the above. Such complicating factors also determine treatment strategies [2].

Natural defence mechanisms of the urinary tract

These can be conveniently classified into non-specific resistance mechanisms which protect against microbial invasion in general, and specific immunologically-based mechanisms which are directed against particular micro-organisms [12]. The washout effect of urine flow, vaginal normal flora, phagocytosis, bladder glycosaminoglycan and Tamm-Horsfall glycoproteins all combine to have an inhibiting effect against uropathogens. Specific immunological mechanisms include lower and upper urinary tract secretory IgA supported by circulating

IgM and IgG. In the experimental animal, T-cell infiltration occurs in the kidney and transiently in the bladder in ascending infection, and the prominence of T-cell infiltrate correlates with the chronicity of renal infection [13]. The persistence of renal infection has been associated with enhanced suppressor T-cell activity [14]. The outcome following the entrance of micro-organisms into the urinary tract is a result of competing forces which consist of local urinary defence mechanisms, the initial numbers of micro-organisms contaminating the urinary tract and microbial virulence factors. (UTI) is facilitated by a low urine flow rate and infrequent and incomplete voiding.

In adults, women are 30 times more likely than men to develop (UTI) [7]. Women who are sexually active and especially if they use a diaphragm and spermicide for contraception [1]. In one study spermicide-coated condoms were responsible for 42% of the (UTIs) among women who were exposed to these products [15]. The presumed mechanism is colonisation of the vaginal and urethral mucosa with intercourse facilitating migration of the organisms into the bladder.

Diagnosis

Urine frequency, dysuria and suprapubic discomfort are the characteristic symptoms of cystitis. Pain and burning may occur at the onset, during, or just after urination. Physical examination is unremarkable in most patients with lower (UTI). The diagnosis should always be considered in patients with pyrexia of uncertain origin. In uncomplicated pyelonephritis the onset is commonly acute and may or may not be preceded by bladder symptoms. Many patients will give a history of cystitis within the previous 6 months [2]. Absence of bacteruria, despite symptoms of frequency, urgency or dysuria, suggests acute urethral syndrome or urethritis, or possibly vaginitis. Severe renal infection may produce chills, rigors, high fever and systemic symptoms of anorexia, nausea, vomiting and generalised myalgia. Blood and urine cultures have positive results and Gram-negative shock may occur. Patients with diabetes mellitus, or those who are immunosuppressed may have renal infection with minimal localising symptoms and signs. Renal abscess is suggested by fever, rigors, loin pain and tenderness with leucocytosis. Mid-stream urine may be sterile but blood cultures are often positive. An ultrasound scan will readily detect the perinephric collection and also demonstrate a dilated renal pelvis of a pyonephrosis. Diagnosis of prostatic infection is most often made on the basis of symptoms such as frequency, dysuria, perineal or groin pain, and the finding of an enlarged tender prostate [2]. In the absence of positive urine culture, prostatic massage and repeat of culture may increase the yield.

Micro-organisms

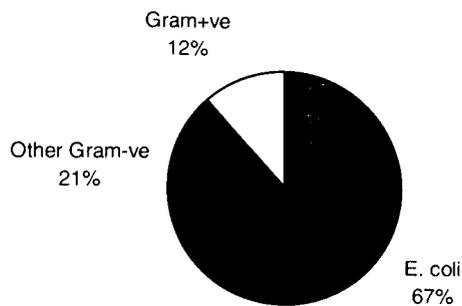
Dipstick tests can be used for rapid urine analysis. Evidence of nitrate reduction to nitrite reflects the presence of a Gram-negative organism, with the exception of *Pseudomonas aeruginosa*, which does not often convert nitrate to nitrite [16]. Gram-positive (UTIs) also do not convert nitrate to nitrite. Evidence of leucocyte esterase in a urine specimen likewise correlates with significant pyuria, reflecting a (UTI). If either or both of dipstick tests are positive, urine culture may be appropriate. However, if both are negative, a more complete microscopic analysis and culture can be avoided [16].

Although (UTI) may occasionally be caused by viruses and fungi, the overwhelming majority are caused by bacteria. Most acute community-acquired (UTI) in otherwise normal women is caused by Gram-negative bacilli, usually by *Eschereschia coli* derived from the bowel flora of the patient. Less frequently other organisms are involved such as *Klebsiella*, *Enterobacter*, *Streptococci*, and particularly in young sexually active women *Staphylococcus saprophyticus* [17]. There is evidence to suggest that virulence is associated with the presence of filamentous appendages (fimbriae or pili) on uropathic strains of *Eschereschia coli*. These fimbriae are of two main types that can be distinguished by their haemagglutination properties. They attach to

receptors on the uroepithelium, urinary mucus and Tamm-Horsfall glycoprotein. The genes of fimbriae are located on the bacterial chromosome [12]. Adherence of bacteria to uroepithelial cells is a prerequisite for colonisation, persistence and infection, particularly in a system of continuous urinary flow including the powerful effect of micturition.

Eschereschia coli strains isolated from (UTI) belong to a restricted range of O-serotypes particularly O1, O2, O4, O6, O7 and O75. These O-serotypes are also found in the faeces of patients and can frequently be isolated from their faeces before the onset of (UTI) [18]. The endotoxin activity of lipopolysaccharide induces shedding of bladder epithelial cells [19], reduces ureteric peristalsis and may contribute to renal parenchymal damage by granulocyte activation. As with O-antigens a limited number of K-antigens is found on *E.coli* strains associated with (UTI) [20] but there appears to be no difference in the frequency with which these are found in upper and lower (UTI). *E. coli* produces α -haemolysin, which is secreted and present in culture supernatants, and β -haemolysin, which is cell-associated [2]. The association between haemolysin production and virulence is now well established. Figure 1 shows the frequency of different community acquired (UTI) pathogens in the authors' hospital in 1997.

Community-acquired UTI pathogens in authors' Hospital-1997



Radiological investigations of (UTIs)

The extent to which an individual patient should be investigated varies tremendously. A plain abdominal film is valuable in assessing the size of the kidneys, localising mal-positioned kidneys, and in detecting calculi or renal calcification. Intravenous urography (IVU) has been an important diagnostic tool in selected patients (Table 1). Ultrasonography is useful in the detection and percutaneous drainage of

hydronephrosis, particularly when an intravenous urogram is not possible due to renal functional impairment.

The investigation of vesico-ureteric reflux requires a voiding cysturethrogram [21] or an indirect radiopaque cystogram which has the advantages of reduced radiation dosage and avoiding bladder catheterisation. Dimercaptosuccinic acid (DMSA) scan is helpful in detecting ectopic kidneys and cortical scars.

Table 1. Indications for an IVU

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- All males.
 - Recurrent infections in women.
 - Persistent haematuria.
 - Failure to respond to treatment.
 - History of childhood UTIs.
 - Persisting sterile pyuria.
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Anti-microbial agents: dose and duration

The effect of an anti-microbial on the faecal and vaginal flora is an important property that influences long term care. Treatment choices include single dose, 3-day, 7-day and two weeks regimens. The single dose has lost favour because of increased recurrence and fewer cure rates [7]. Amoxycillin resistance is rising and therefore it is no longer the first line antibiotic of choice. Resistance to trimethoprim alone or in combination with sulphamethoxazole is 5-15% while resistance to fluoroquinolones is less than 5% [22]. Trimethoprim and trimethoprim-sulphamethoxazole are the optimal choices for empirical 3 days therapy of uncomplicated (UTI) as the fluoroquinolones are more expensive. The oral cephalosporins are excreted in active form in high concentration in the urine but have no special advantage as first line drugs. Post-treatment cultures are not routinely indicated.

Patients with mild acute pyelonephritis may be treated in the community especially in the absence of nausea and vomiting. Trimethoprim-sulphamethoxazole or ciprofloxacin may be given for 10-14 days. Patients with moderate or severe illness require hospitalisation and treatment with parenteral antibiotics such as ceftriaxone or ciprofloxacin until the fever is gone and then oral antibiotics for 14 days [22]. Urological consultation and evaluation of the upper urinary tract should be considered if the patient remains febrile after 72 hours of treatment to rule out the presence of nephrolithiasis, renal or perirenal abscesses or other complications of pyelonephritis. All patients require a post treatment culture after two weeks of treatment [23].

Patients with acute bacterial prostatitis presenting with voiding difficulty require hospital admission. Treatment should be continued for 4-6 weeks and urethral catheterisation should be avoided. Suprapubic drainage may be used to treat retention.

Asymptomatic bacteruria

The diagnosis implies absence of symptoms and pyuria in urine analysis. Urine culture must demonstrate bacterial growth of greater than 10^5 colony forming units/ml from two separate clean-catch midstream specimens. Patients who may benefit from

antibiotic treatment are those with clean intermittent catheterisation, those with abnormal urinary tracts such as congenital polycystic kidneys and medullary sponge kidney, those with acquired abnormalities such as obstruction and renal calculi, and those planning to have urinary tract instrumentation. Antibiotic therapy is also appropriate for patients with diabetes mellitus, mechanical prosthesis, immuno-suppression, renal transplants and pre-existing renal dysfunction. Treatment protocols suggest single-dose therapy such as trimethoprim-sulphamethoxazole if the organism is susceptible. A repeat culture should be done at two weeks post-treatment [7].

Infection in pregnancy

Asymptomatic bacteruria occurs in up to 7% of pregnant women, and of those, about 30% develop acute pyelonephritis if not treated [24]. Diminished ureteral peristalsis and a change in urinary pH contribute to the increased risk. Amoxycillin is effective in up to two third of cases; other choices include cephalixin, nitrofurantoin, and sulpho-namides (except in the third trimester). Seven day course appears to have better cure rates than shorter courses of therapy [25]. A urine culture one week later is advised to document cure, and repeated every 4 to 6 weeks until delivery [24].

Catheter-related infections

Indwelling bladder catheters are implicated in 40-75% of all hospital-acquired (UTI). Even with the best methods of aseptic closed drainage, colonisation of bladder urine will occur in half the patients within 10 days to 2 weeks. For catheters in place for up to 14 days, the use of prophylactic antibiotics within 48 hours prior to catheter removal reduces the risk of bacteruria fivefold [26]. In longterm catheterised patients, systemic antibiotics should be used only when signs and symptoms strongly suggest a urinary tract origin. Treatment is directed to more resistant organisms, especially in hospital acquired infections. Infections complicated by bacteraemia should be treated for 10-14 days, but if no bacteraemia is present, a shorter course (3 to 5 days) usually clears the bacteraemia and does not select out more resistant organisms [27].

Candidal infection

The presence of yeast in the urine is most often due to colonisation of the bladder by *Candida albicans* or other *Candida* species. Positive urine cultures may be the first sign of systemic candidal infection. Risk factors for the development of candiduria include the use of broad spectrum antibiotics, corticosteroids and

indwelling bladder catheters, diabetes mellitus, urological abnormalities and haematological malignancies [28]. Discontinuing any unnecessary steroid or antibiotic therapy may be helpful. Amphotericin bladder irrigation for 5 days (50 mg/l sterile water every 24 hours) has been used successfully [27]. Alternative treatments include oral fluconazole 50-100 mg daily for 7 days or a single dose of intravenous amphotericin B [28].

Prophylaxis

Continuous low dose suppression is effective at reducing the recurrent rates for (UTI) by 95% among sexually active women. Trimethoprim (100mg), trimethoprim-sulphamethoxazole (960mg), and nitrofurantoin (50-100mg) have all been shown to be very effective [29]. These drugs have to be given last thing at night as a high fluid intake and frequent voiding could maintain bacterial clearance by day. Side effects and the emergence of resistant strains are unusual. Most authorities recommend a 6 month to 2 year trial of prophylaxis, but as long as 5 years has been reported to be effective and well tolerated [30] (Table 2).

Table 2. Indications for prophylaxis

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- Women with recurrent infections.
 - After acute pyelonephritis in pregnancy.
 - Pregnancy with history of childhood infections.
 - Persistent or relapsing infections in patients with renal stones, scars or prostatitis.
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