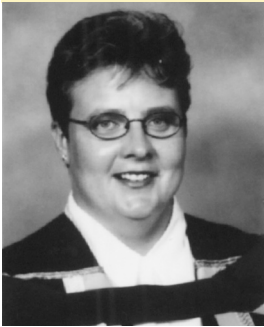


URINARY TRACT INFECTION IN ADULTS

Urinary tract infection in adults is common and may be complicated or uncomplicated.



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Infection of the urinary tract (UTI) is frequently encountered in clinical practice — in the USA these infections account for approximately 7 million office visits annually. The reported incidence in women is 11% per year and approximately 50% of all women have at least one UTI in their lifetime.^{1,2} UTI accounts for 40% of nosocomial infections and catheter use is the leading cause.³ Up to 25% of hospitalised patients undergo catheterisation and the incidence of bacteriuria is 5% per day.⁴

Symptomatic UTI exists when clinical symptoms are attributable to bacteria in the normally sterile urinary tract. Symptoms vary depending on the site of infection (lower or upper tract).

- Uncomplicated UTI describes infection where the urinary tract is entirely normal.
- Complicated UTI occurs where the urinary tract is compromised, either structurally, functionally, metabolically or immunologically.

Asymptomatic UTI is identified when organisms can be isolated in appropriate numbers from urine in the absence of symptoms.

Adult patients with UTI can be categorised according to different clinical syndromes (Fig. 1).

DEFINITIONS AND DIAGNOSTIC TESTS^{1,5}

Bacterial invasion of the urinary tract causes an inflammatory response resulting in bacteriuria and pyuria. Indirect dipstick tests and/or direct microscopy of urine should be performed in all patients suspected of having a UTI.

Indirect dipstick tests

Dipstick nitrite is used as a surrogate marker for bacteriuria. Infection due to uropathogens which do not reduce nitrate to nitrite (e.g. Gram-positive cocci) may be responsible for false-negative results.

The dipstick leukocyte esterase test is a rapid, convenient and cheap screening tool for detecting pyuria.

However, neither is diagnostic of significant bacteriuria, and urine microscopy and culture are required for confirmation.

Microscopic urinalysis and culture

Pyuria is the presence of white blood cells (WBC) in the urine and is indicative of urothelial inflammation. This is a nonspecific finding, but the vast majority of symptomatic patients have pyuria. In a random clean-catch urine specimen ≥ 10 WBC/mm³ will be consistent with infection. WBC casts in the presence of symptoms is strong evidence for pyelonephritis. Sterile pyuria warrants investigations for other conditions such as tuberculosis, calculi or urinary tract malignancy.

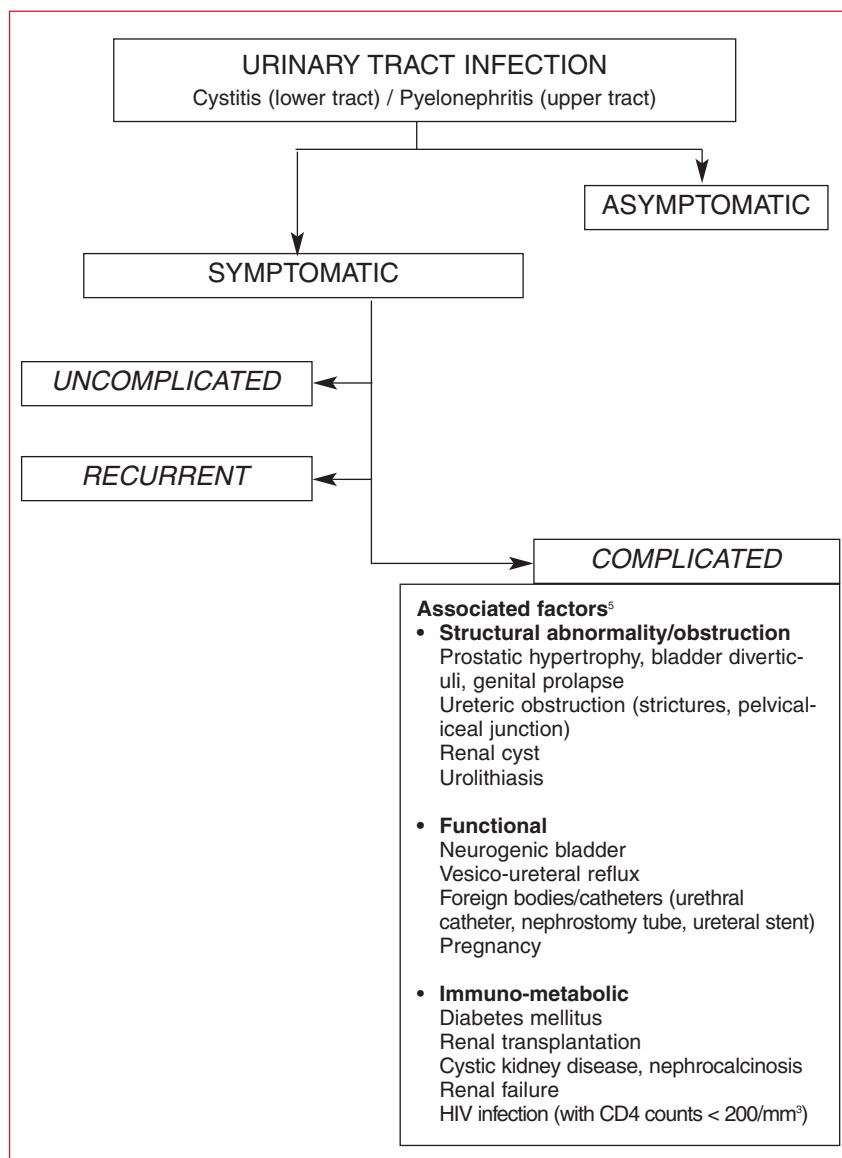


Fig. 1. Classification of UTI.

Bacteriuria is the presence of bacteria in normally sterile urine. It implies that micro-organisms are from the urinary tract and not contaminants from the distal urethra, vagina or skin. Bacteriuria without pyuria indicates bacterial colonisation rather than infection. Significant bacteriuria is defined as $\geq 10^5$ organisms/ml of voided urine (i.e. the number of bacteria that exceed the number usually due to urethral contamination). The possibility of contamination is inversely proportional to the reliability of the collection technique. Acceptable collection methods include:

- segmented voided urine specimens or midstream clean catch
- catheterisation
- suprapubic aspiration.

Collecting urine specimens

- The clean-catch method is preferred for routine collection, as it avoids the risk of infection associated with invasive methods. With proper collection voided urine usually contains $< 10^4$ organisms/ml. In asymptomatic patients $10^4 - 10^5$ organisms/ml represents contamination 95% of the time. In patients with symptoms of UTI, a titre of $\geq 10^5$ organisms/ml carries a 95% probability of true bacteriuria and even counts as low as 10^2 organisms/ml confirm the diagnosis.
- Catheterisation performed under scrupulous aseptic technique may be necessary in those who are unable to void for neurological or

urological reasons, or those with an altered sensorium. In non-infected patients samples obtained in this manner are less likely to be contaminated enough to demonstrate 10^5 organisms/ml. With careful technique numbers as low as 10^2 organisms/ml are highly indicative of infection.

- Suprapubic aspiration is particularly useful in adults with paraplegia. This invasive procedure is unpleasant for the patient but, when performed properly, is not dangerous. Bladder urine obtained this way is either sterile or contains significant growth, even if bacterial numbers are $< 10^5$ /ml.

PATHOGENESIS

Urinary tract invasion occurs in different ways:

- **Ascending.** Most pathogens are intestinal, and enter the urinary tract through the urethra into the bladder. In women vaginal colonisation is an important factor. Once in the bladder, bacteria may multiply and ascend via the ureters to the renal pelvis and parenchyma.
- **Haematogenous.** This is uncommon in normal individuals, but blood-borne organisms can infect the kidneys in patients with staphylococcal bacteraemia from infective endocarditis or infected oral sites. Secondary renal infection has also been described with *Candida* fungaemia.

Once colonisation and invasion has taken place, host-parasite interaction becomes important in the development of UTI. Strong host resistance needs to be overcome by increased bacterial virulence factors. Conversely, less virulent bacteria are able to infect patients who are compromised. Normal antibacterial defences of the urinary system include high osmolality, low pH and presence of organic acids in urine, urine flow and micturition, specific inhibitors of bacterial adhesion, the inflammatory response (neutrophils, cytokines) and the immune system.

CLINICAL SYNDROMES — MICROBIOLOGY, MANIFESTATIONS, AND MANAGEMENT

Uncomplicated UTI

A relatively narrow spectrum of uropathogens cause UTI in patients with normal urinary tracts. *Escherichia coli* is the main organism isolated, followed by *Staphylococcus saprophyticus*. Enterococci and other Gram-negative enterobacteriaceae such as *Klebsiella*, *Enterobacter* and *Proteus* species infrequently cause infection in this group.⁶

Acute cystitis and uncomplicated pyelonephritis are common problems in women, particularly sexually active women from 20 - 40 years of age, and in the postmenopausal population.

In healthy adult men between the ages of 15 and 50 years, cystitis is very uncommon and uncomplicated pyelonephritis hardly ever occurs.

Uncomplicated cystitis

In women, sexual intercourse, diaphragm and/or spermicide use, delayed postcoital micturition and a history of a recent UTI all increase the risk of infection. In postmenopausal women, oestrogen deficiency with atrophic vaginitis, and less abundant protective lactobacilli is another contributing factor.^{1,2,5} Reasons for infection in men are not always clear, but risk factors include intercourse with an infected partner, anal intercourse and lack of circumcision.²

Cystitis is typically diagnosed clinically. In women, symptoms include dysuria with frequency and urgency, but no fever or constitutional symptoms. Suprapubic pain and tenderness

are only found in about 20% of patients. Major differential diagnoses are outlined in Table I.

In men, cystitis presents with irritative voiding symptoms, but in some patients may mimic urethritis. Major differential diagnoses are outlined in Table II.

In women, uncomplicated cystitis rarely progresses to symptomatic upper UTI, and does not have long-term negative effects with respect to renal function or mortality. The causative organisms are predictable, as are their antimicrobial susceptibility profiles. This means that women generally require only an abbreviated workup and empirical therapy. Uncomplicated cystitis rarely occurs in men, so pre-treatment urine culture is recommended and clinicians should have a low threshold for urology referral and investigation.

Table I. **Differential diagnosis of uncomplicated cystitis in women**

Condition	Clinical findings in addition to dysuria and pyuria	Common aetiology
Urethritis or vaginitis	Urethral/vaginal discharge containing numerous WBCs No suprapubic pain/tenderness, urinary frequency/urgency and fever	Sexually transmitted infections (STIs): <i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> , <i>Trichomonas vaginalis</i> STIs
Cervicitis	Irritative voiding symptoms with mucopurulent vaginal or cervical discharge (containing numerous WBCs) and postcoital bleeding Cervical erythema and/or oedema with swabbing-induced bleeding	
Pelvic inflammatory disease	As for cervicitis with additional fever, cervical excitation tenderness ± evidence of tubo-ovarian mass	

Table II. **Differential diagnosis of uncomplicated cystitis in men**

Condition	Clinical findings in addition to dysuria and pyuria	Common aetiology
Urethritis	Urethral discharge present No suprapubic pain, urinary frequency/urgency or fever	STIs: <i>C. trachomatis</i> , <i>N. gonorrhoeae</i> <i>E. coli</i> , <i>Proteus</i> spp., <i>Klebsiella</i> spp.
Acute prostatitis	Back pain, fever, arthralgia/myalgia, rectal pain and obstructive voiding symptoms Tender, boggy prostate on examination	
Acute epididymitis	Fever and scrotal swelling + redness Epididymal tenderness	STIs or uropathogens (<i>E. coli</i> in patients with recent urinary tract instrumentation)

The reported incidence in women is 11% per year and approximately 50% of all women have at least one UTI in their lifetime.

Dipstick nitrite is used as a surrogate marker for bacteriuria. Infection due to uropathogens which do not reduce nitrate to nitrite (e.g. Gram-positive cocci) may be responsible for false-negative results.

The diagnosis can be presumed if pyuria is present on leukocyte esterase dipstick testing or microscopy. The finding of bacteriuria on microscopy is more specific but less sensitive.¹

In selecting an antibiotic for treatment^{7,9} several factors should be considered:

- Local microbial resistance patterns — resistance to β -lactam antibiotics (amoxicillin or ampicillin) and trimethoprim-sulfamethoxazole has become widespread. Using these drugs as first-line agents will give low cure rates and is not recommended.
- Duration of therapy with known efficacy for the clinical syndrome, versus cost and adverse effects — short courses of empirical antibiotic therapy are highly effective and cost-efficient in the treatment of uncomplicated cystitis in women. Most antimicrobials can be used for 3 days, with efficacy comparable with longer regimens and fewer side-effects and lower cost. Single-dose therapy can be used, but may result in lower cure rates and more frequent recurrences. Current guidelines for empiric treatment advocate a 3-day course of oral quinolone or amoxicillin-clavulanic acid/2nd generation cephalosporin. Alternatively, a single dose of either a quinolone or fosfomycin can be prescribed. Men who present with uncomplicated cystitis should be treated with a 7-day

course of antibiotics.

- Drug allergy and specific contraindications. Quinolone should not be used in pregnancy.

Uncomplicated (non-obstructive community-acquired) pyelonephritis

In women, this infection is similar to cystitis and is caused by similar bacteria. The clinical spectrum ranges from a cystitis-like illness with mild flank pain and fever or rigors, to a more severe syndrome of urosepsis or Gram-negative septicaemia.^{1,2,5}

Urine microscopy establishes the presumptive diagnosis. Pyuria is present and WBC casts may be seen. Pre-treatment urine culture and sensitivity tests should be obtained in all patients with suspected pyelonephritis, and blood culture should be taken in hospitalised patients (15 - 20% are positive).

Clinical severity will dictate treatment and further investigations:^{8,10}

- Patients with mild illness can safely receive oral treatment as outpatients with a quinolone or amoxicillin-clavulanic acid or 2nd generation cephalosporin for 10 - 14 days.
- Those with moderate-to-severe illness or patients with nausea or vomiting should be hospitalised for initial parenteral treatment with quinolone or ceftriaxone or aminoglycoside \pm ampicillin. With improvement or resolution of the clinical picture after 48 - 72 hours, the remaining treatment can be given orally. Fever and flank pain persisting beyond 72 hours of therapy warrant further investigation: urine cultures should be repeated and the urinary tract imaged (ultrasonography or computed tomography) to exclude abscess formation, obstruction or unrecognised urological abnormalities. Antibiotics should be changed according to susceptibility profiles of isolated bacteria.
- Post-treatment urine culture is preferable.

Recurrent cystitis in women

About 20% of young women with normal urinary tracts have recurrent UTI within 6 months of an initial episode of cystitis.² Over 90% of recurrences are due to reinfection — this occurs after 2 weeks of completing antibiotic treatment and may be caused by the same or a different organism. Occasionally the original uropathogen persists and causes recurrence within 2 weeks — this defines a relapse infection.

In addition to behaviour, host genetic factors and bacterial factors contribute to recurrence.

Prophylaxis^{1,2,7} is indicated for women who experience at least 2 symptomatic UTIs in less than 6 months. Eradication of active infection should be confirmed by negative culture at least 1 - 2 weeks after discontinuation of initial treatment. The choice of prophylactic regimen should be based on susceptibility of bacteria isolated from prior UTI, drug allergies and intolerance.

Effective measures decrease recurrences by up to 95% and may prevent pyelonephritis. These measures include:

- Continuous prophylaxis — an antibiotic is taken daily for at least 6 months. It has been safely and effectively continued for longer without emergence of microbial resistance.
 - Postcoital prophylaxis — in women who describe a clear relation between intercourse and UTI, a single dose of an antimicrobial is taken with each act of coitus.
- Another convenient, safe and inexpensive strategy is intermittent patient-initiated treatment.¹
- Women are instructed to start a 3-day course of an antibiotic agent at symptom onset. They are advised to seek medical attention if there is no resolution by 48 - 72 hours after completion of treatment.

Additional corrective measures:

- Atrophic vaginitis should be treated

with topical oestrogen cream in postmenopausal women.

- Women exposed to spermicides from diaphragms or condoms should consider alternative methods of contraception.
- There is no evidence that recurrent cystitis can be prevented by post-coital voiding. Poor urinary hygiene does not predispose to recurrent UTI and there is no rationale in giving specific instructions regarding voiding, wiping patterns, douching or wearing of pantyhose.¹

Cranberry juice⁷ has been long advocated as a measure to reduce the recurrence rate. Constituent glycoproteins and proanthocyanidins appear to inhibit bacterial adherence to uro-epithelium. Randomised trials suggested a daily dose of 200 - 750 ml juice to reduce recurrence by 12 - 20%. Variable therapeutic effect can be ascribed to variations in actual cranberry content of juice, capsules or tablets.

Probiotic formulations^{7,11} containing various lactobacilli and bifidobacteria can also be used as adjunctive treatment. The primary aim of vaginal application of probiotic-containing capsules is to restore the protective microflora. Various studies have shown that UTI recurrence can be significantly reduced by using probiotic capsules weekly for 1 year with similar efficacy to continuous antibiotic prophylaxis and without side-effects.

Complicated UTI

Where there are underlying medical conditions, pregnancy, hospitalisation or long-term urinary catheter use, UTI (whether cystitis or pyelonephritis) should be considered complicated. The frequency and impact of complicated UTI are determined by the underlying abnormalities and complicating factors may not be immediately obvious.^{2,5}

The clinical spectrum ranges from mild cystitis to life-threatening urosepsis. Prolonged periods of asymptomatic

bacteriuria often occur. A common feature is an inability to effectively clear organisms from the urinary tract (obstruction) or an increased frequency of introduction of bacteria into the urinary tract (instrumentation or reflux). A high frequency of recurrent infection is anticipated. If correction is possible, further infection may be prevented.

Complications of pyelonephritis^{2,12}

- Emphysematous pyelonephritis (EP) is an acute necrotising renal parenchymal infection with intrarenal \pm perinephric gas formation, primarily seen in diabetics. Delayed diagnosis adds to high morbidity and mortality.
- Intrarenal abscesses are most commonly due to *Staphylococcus aureus* infection with 30 - 50% of patients having concomitant diabetes mellitus.
- Acute papillary necrosis is presumed to be due to marginal blood supply which is further stressed by infection leading to infarction and papillary sloughing. Diagnosis is confirmed on retrograde urography.

Complicated UTI has a more diverse aetiology.^{5,6} Hosts with underlying disease are susceptible to infection with antimicrobial-resistant and/or unusual organisms and are at a higher risk for treatment failure.

E. coli remains the commonest infecting organism, but is isolated from only about 50% of patients. The remainder of isolates includes other enterobacteriaceae (*Klebsiella* spp., *Proteus* spp.), *Pseudomonas* spp. and Gram-positives (enterococci, coagulase-negative staphylococci and group B streptococci).

Pre-treatment culture (urine \pm blood) is mandatory in all patients. Urine culture should be repeated 1 - 2 weeks after completion of therapy, as the recurrence rate is high (especially if the underlying abnormality persists).

Treatment must be tailored to individual patient circumstances. Previous bacteriological test results, severity of illness and allergy history need to be considered.

- Oral fluoroquinolones provide a broad spectrum of antimicrobial activity and should be given for at least 7 days to patients with mild-to-moderate illness who can be treated as outpatients.
- More seriously ill patients should be hospitalised and empirical parenteral broad-spectrum antibiotics given. Preferred antimicrobials are quinolones or ceftriaxone or aminoglycoside \pm ampicillin or piperacillin-tazobactam (suspected enterococcal UTI). Therapy should be modified when the infecting organism has been identified and susceptibilities are known. Treatment duration is usually 10 - 14 days, but *Pseudomonas* and enterococcal infections may warrant more prolonged therapy.

UTI in patients with diabetes mellitus^{5,6,12-14}

In diabetic women there is a 2 - 4-fold higher incidence of bacteriuria. Contributing host factors include poor glycaemic control with impaired leukocyte function, recurrent vaginitis, anatomical and functional abnormalities and microangiopathy. Most cases (80%) are due to ascending infection with abovementioned uropathogens and non-albicans *Candida* spp. Haematogenous spread of infection (mostly *S. aureus*) accounts for the remainder of cases.

Upper tract involvement occurs in up to 80% of diabetics with UTI, and complications (emphysematous pyelonephritis, abscess formation or papillary necrosis) also occur more frequently. Clinical presentation is similar to that in non-diabetic patients except that bilateral infection is more common. Occasionally it may be asymptomatic, particularly in individuals with metabolic disturbance or reduced level of consciousness. Haematuria or flank pain may be

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Investigation of possible UTI in diabetic patients should include urinalysis and culture prior to initiation of therapy, together with assessment of renal function and glycaemic status. In patients with presumed pyelonephritis, a blood culture should be routine.

Imaging is essential owing to the high incidence of complications. All patients should have an abdominal X-ray to exclude renal emphysema. Severely ill patients should have screening ultrasound or computed tomography to exclude obstruction and identify calculi and inflamed oedematous parenchyma. Contrast enables a more accurate recognition of inflamed renal tissue, air or pus collection, but its use may be complicated by transient or permanent loss of renal function.

Treatment for bacterial UTI includes hydration, glycaemic control and non-nephrotoxic parenteral antibiotics. Fungal UTI should be treated with removal of catheters if present and

amphotericin B bladder irrigation. Alternatively a single intravenous dose of amphotericin B or oral fluconazole can be prescribed. A poor response to therapy suggests complications: emphysematous pyelonephritis often necessitates emergency nephrectomy and prompt surgical or percutaneous drainage is required for intrarenal or perinephric abscesses.

UTI in pregnancy^{5,7,15}

UTI is one of the most common infections of pregnancy. Bacteriuria occurs in 5 - 9% of women — a significant number of whom will develop symptomatic UTI during the course of the pregnancy. Most infections are caused by *E. coli* and causative host factors are physiological changes (smooth-muscle relaxation with stasis, less robust humoral immune response) and mechanical factors (pressure on bladder with reflux).

The clinical entities include asymptomatic bacteriuria (ASB), cystitis and pyelonephritis. Patients with untreated or inadequately treated ASB are at high risk of developing pyelonephritis which can lead to preterm labour, prematurity and low-birth-weight infants.

A urine culture should be obtained from all women in early pregnancy. Therapeutic options for treatment of UTI are guided by pathogen susceptibility and antibiotic safety profile in pregnancy (beta-lactams, nitrofurantoin).

- ASB should be treated with a 3-day course of antimicrobials.
- Symptomatic UTI should be treated for 7 days.
- Once UTI is documented, monthly screening urine cultures should be obtained for the duration of the pregnancy.
- Recurrent or persistent UTI may warrant daily antimicrobial prophylaxis and urological evaluation.

UTI in geriatric and institutionalised or catheterised patients²⁻⁶

Predisposing factors for development of UTI in the elderly patient include altered elimination (faecal impaction,

urinary retention, and anticholinergic drugs), anatomical variations (genital prolapse or prostate hypertrophy), hygiene issues (faecal soiling), neurological impairment affecting mobility, and voiding and hormonal changes.

The frail elderly with multiple health problems and complicated UTI often have an atypical or subtle presentation (delirium, agitation, incontinence or increased urine loss). Diagnosis is often delayed. Treatment should be according to principles as outlined for complicated UTI and complicating or contributing factors should be addressed. The best prophylaxis is to minimise catheter use and to improve general hygiene.

In hospital or long-term care, indwelling catheters are the major cause of UTIs. Additional risk factors include increasing duration of catheterisation, no administration of systemic antibiotics, female gender and older age, rapidly fatal underlying disease, diabetes mellitus and azotaemia as well as faulty aseptic management of catheter and/or collecting system.

Catheter-related bacteriuria is defined as the presence of $\geq 10^3$ CFU/ml of a predominant bacterial species and is usually asymptomatic, uncomplicated and resolves after catheter removal. It is however associated with increased morbidity and mortality.

The following should be kept in mind with regard to catheterisation:

- Avoid using catheters whenever possible.
- Appropriate indications for catheter use: bladder outlet obstruction, incontinence (with open sacral or perineal wounds; on request at end of life), output monitoring in critically ill patients, and during prolonged surgical procedures.
- A closed catheter drainage system should be used and proper aseptic techniques during insertion and maintenance must be adhered to.
- There is little evidence to suggest benefit with bladder irrigation,

antimicrobial drugs in drainage bags or rigorous meatal cleaning. Prophylactic systemic antibiotics are most useful in patients requiring catheterisation for 3 - 14 days and the benefit of systemic antibiotic prophylaxis is proven in patients undergoing surgery and requiring indwelling catheterisation (renal transplantation or transurethral resection of the prostate).

- More research is needed to evaluate the benefit of silver-coated catheters.

ASYMPTOMATIC BACTERIURIA

ASB^{2,5} is the presence of $\geq 10^5$ organisms/ml of urine on at least 2 successive cultures in patients without UTI symptoms. Incidence increases with age (Table III).

There appears to be a higher frequency of infection with coagulase-negative staphylococci and *Enterococcus* spp.

In healthy non-pregnant women, men and the well elderly ASB poses no threat, as symptomatic infection with complications rarely develops. Screening is useful only where treatment is mandatory, as in the following situations:^{2,5,9}

- individuals with ASB undergoing urological procedures are at risk of invasive infection (including bacteraemia and sepsis)
- patients with renal allografts in the early post-transplant period
- ASB in pregnant women, if left untreated, may progress to symptomatic infection (especially pyelonephritis) which is 4-fold higher than in non-pregnant women.

References available on request.

Table III. Incidence of asymptomatic bacteriuria in different patient groups

Patient group	Incidence
Non-pregnant and pregnant women	5 - 9%
Community-dwelling elders (≥ 65 years)	20 - 25%
• Women	5 - 10%
• Men	
Patients in long-term-care facilities	
• Without catheters	$\pm 40\%$
• With catheters	Nearly 100%

IN A NUTSHELL

UTI is a commonly encountered problem in clinical practice, particularly in women.

Symptomatic UTI includes lower or upper tract involvement (cystitis or pyelonephritis).

UTIs that occur in the setting of underlying medical conditions, pregnancy or long-term use of a catheter are considered to be complicated.

The incidence of asymptomatic bacteriuria increases with age. However, it poses no threat in healthy non-pregnant women, men and the well elderly. Screening should be limited to selected patient groups where treatment is mandatory (pregnancy, prior to urinary tract instrumentation, and renal transplantation).

UTI in the diabetic, elderly or debilitated patient may lack classic presentation.

Complications of upper tract infection are emphysematous pyelonephritis, abscess formation, papillary necrosis and bacteraemia. These are particularly prevalent in patients with diabetes mellitus.

Pregnant women with UTI are at risk of preterm labour, prematurity and low-birth-weight infants — they should undergo urine screening early

in pregnancy and asymptomatic bacteriuria should be treated aggressively.

Investigation and treatment of UTI should be individualised according to the clinical setting in which it occurs.

Dipstick tests are cheap, fast and convenient screening tools in patients with uncomplicated cystitis. Urine cultures should be performed in patients with complicating factors and blood cultures may be positive in up to 20% of patients with upper tract involvement.

Factors that should be taken into consideration in selecting an antibiotic for treatment are: local microbial susceptibility patterns, duration of therapy with known efficacy for the clinical syndrome versus cost and adverse effects and patient factors (allergy and specific contraindications) as well as clinical severity.

Antibiotic prophylaxis is indicated for women who experience at least 2 symptomatic UTIs in less than 6 months. Alternative strategies are intermittent patient-initiated treatment, correction of biological or behavioural factors and use of probiotics and cranberry extracts.