

Adult urinary tract infection

Bacterial infection of the urinary tract is one of the most common medical conditions resulting in significant morbidity and occasional mortality. Epidemiology, pathogenesis, investigation and management of adult urinary tract infection are reviewed.

Urinary tract infection is the second most common reason to prescribe antibiotics in the western world. Bacterial colonization of the urinary tract, almost exclusively by uropathogenic organisms arising from bowel or vaginal flora, and the subsequent host response results in the clinical spectrum of urinary tract infection. This may be split into upper and lower tract infection defined by the involvement (or lack of) of the upper tracts (pyelonephritis), and into complicated or uncomplicated infection. Complicated infection is defined as symptomatic urinary tract infection in a patient with functional, metabolic or structural genitourinary tract abnormalities.

Epidemiology

Uncomplicated lower tract infection (cystitis) accounts for the vast majority of urinary tract infections. By the age of 24 years a third of women will have experienced a urinary tract infection and 50% will have a urinary tract infection in their lifetime (Stamm, 2002). Young sexually active women have an incidence of urinary tract infection of 0.5–0.7 episodes per person year. Risk factors for cystitis in young healthy women are frequency of sexual intercourse, type of contraceptive used and a history of previous urinary tract infection (Hooton et al, 1996). Recent antimicrobial use, women who do not secrete ABH blood group antigens, patients with the P1 blood group phenotype and patients recently exposed to antimicrobial agents may also have a higher incidence of urinary tract infection.

Postmenopausal women have an incidence of symptomatic urinary tract infection of 0.07 per person year. Insulin-dependent diabetes mellitus and multiple previous urinary tract infections are the main risk factors in this group (Jackson et al, 2004). The incidence of urinary tract infection is much less in young males (5–8/10 000 person years). Uncomplicated pyelonephritis is much less common than cystitis (12–13/10 000 and 2–3/10 000 population in women and men respectively). Like cystitis, pyelonephritis is most frequent in young sexually active women, becoming more common in males as they age (Czaja et al, 2007).

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Pathogenesis

Urinary tract infections occur when uropathogens from faecal or vaginal flora colonize the periurethral area, enter the bladder via the urethra, overcome host defence mechanisms and stimulate a host response. Host defence mechanisms include the flushing effect of urine flow and the urothelial cell charge barrier. Secreted Tamm–Horsfall protein binds to bacterial fimbriae and prevents adherence. Bacterial invasion activates the host inflammatory system with subsequent clearance of the pathogen.

In the normal urinary tract the main determinant of bacterial colonization is the ability of uropathogenic microorganisms to adhere to the urothelial cell. Virtually all bacteria implicated in uncomplicated urinary tract infection have been demonstrated to have an adhesion molecule (lectins), which bind to specific binding sites (oligosaccharides) on the urothelial cell membrane. Multiple different adhesion molecules have been identified. Adhesion molecules are most commonly located on fimbriae (type 1, P), but may be on the bacterial cell surface. Once adherent the bacterial cell can invade the urothelial cell and stimulate a host response (Oelschlaeger et al, 2002; Mak and Kuo, 2006). The adhesion molecule is the main virulence factor determining the ability of uropathogenic bacteria to cause infection and the subsequent host response (Godaly et al, 2007).

Males have a lower incidence of urinary tract infection. This is probably because there is a greater distance between the anus and the urethral orifice and a drier periurethral environment (less bacterial growth). The longer male urethra and prostatic fluid (antimicrobial) may be additionally protective.

If there is an underlying abnormality that impairs host defence then non-uropathogenic bacteria (without adhesion molecules) may colonize the urinary tract and cause complicated urinary tract infection.

Uncommonly infection may result from haematogenous spread.

Microbiology

Most uncomplicated infections are caused by a relatively small group of uropathogenic *Escherichia coli*. *Staphylococcus saprophyticus* commonly causes urinary tract infection in young women. Other Gram-positive and Gram-negative organisms rarely cause uncomplicated urinary tract infection, but are responsible for a greater proportion of complicated urinary tract infection, particularly enterococci (Table 1).

Diagnosis

Cystitis presents as dysuria, frequency, urgency, suprapubic pain and occasionally haematuria. There are usually no specific findings on clinical examination. Pyelonephritis presents with fever, nausea, vomiting and flank pain and is usually associated with lower tract symptoms, which may occur before, with or after the upper tract symptoms. The kidney may be exquisitely tender. The clinical spectrum of pyelonephritis varies from mild flank pain to severe sepsis with multiorgan dysfunction syndrome. Presentation of urinary tract infection in children and the elderly may be subtle.

The presence of bacteriuria with pyuria, in the setting of an appropriate clinical presentation, confirms the diagnosis of urinary tract infection. Urine collected by suprapubic bladder puncture is normally sterile with no leucocytes and remains the gold standard. Clean catch urine (mid-stream) is routinely exposed to urethral organisms and a degree of contamination must be accepted. Contamination may be minimized with careful collection. Urine should be examined promptly or refrigerated to reduce bacterial growth.

A positive culture is generally accepted as 10^5 colony forming units per millilitre of urine (10^5 CFU/ml) in association with pyuria (10^4 white blood cells/ml or 10×10^6 /litre). This criterion is very specific but insensitive in young women with typical symptoms. A bacterial count of 10^2 CFU/ml and pyuria has been demonstrated to be relatively sensitive and specific in this population (Stamm et al, 1982). Partially treated infections, infections in males and infection caused by less common organisms may also have lower levels of bacteriuria. Urine may be sterile in infections which do not communicate freely with excreted urine. Leucocytes should be formally counted and the absence of pyuria (10×10^6 /

litre) suggests contamination. Sterile pyuria is usually caused by contamination of the urine with leucocytes from another source. Other causes are tubulointerstitial nephritis, urothelial malignancy, stone disease, chlamydia and infection with fastidious organisms (ureaplasma or mycobacteria).

Urine dipsticks that detect the presence of nitrite and leucocyte esterase may be a useful screening tool for urinary tract infection. Enterobacteriaceae convert urinary nitrate to nitrite. Nitrite is not detectable in sterile urine, urine which has not been exposed to bacteria for sufficient time for nitrite to be formed or urine colonized with non-converting organisms. The presence of leucocyte esterase correlates with pyuria. The role of urine dipstick and urine culture in primary care remains controversial. Young women with a typical presentation of acute cystitis are usually treated empirically with or without urine testing. It is generally accepted that any patient with suspected pyelonephritis, complicated infection, recurrent or relapsing infection or an atypical presentation should have urine cultured.

Asymptomatic bacteriuria

Asymptomatic bacteriuria is the isolation of bacteria from the urine in an asymptomatic patient. This has been defined as a bacterial count of $\geq 10^5$ CFU/ml (once in men and twice consecutively in women). In catheterized specimens a definition of $\geq 10^2$ CFU/ml is used (Nicolle et al, 2005). Prevalence increases with age in both males and females, from $<1\%$ in healthy young men and women to 15–20% in those aged >75 –80 years of age. Risk factors are sexual activity, diabetes mellitus, impairment of urinary flow, indwelling catheters and nursing home residence. Similar organisms cause asymptomatic bacteriuria as cause symptomatic urinary tract

Table 1. Bacterial aetiology of urinary tract infections

Organism	Urinary tract infection (%)		
	Uncomplicated	Complicated	
Gram-negative organisms	<i>Escherichia coli</i>	70–95	21–54
	<i>Proteus mirabilis</i>	1–2	1–10
	<i>Klebsiella pneumonia</i>	1–2	2–17
	Citrobacter species	<1	5
	Enterobacter species	<1	2–10
	<i>Pseudomonas aeruginosa</i>	<1	2–19
	Other	<1	6–20
Gram-positive organisms	Coagulase-negative staphylococci (<i>Staphylococcus saprophyticus</i>)	5–20 or more	1–4
	Enterococci	1–2	1–23
	Group B streptococci	<1	1–4
	<i>Staphylococcus aureus</i>	<1	1–2
	Other	<1	2

From Johnson and Feehally (2003), Schollum (2009); data for complicated infections from Nicolle (1997)

infection. Asymptomatic bacteriuria is associated with an increased risk of symptomatic urinary tract infection but no other adverse outcomes and screening is not warranted. Exceptions to this are in pregnancy (increased pyelonephritis, premature delivery, low birth weight) and patients undergoing a traumatic urinary tract intervention (mucosal bleeding) who should be screened and treated (Nicolle et al, 2005).

Uncomplicated lower and upper urinary tract infection

Infection is considered complicated if there are features which suggest a higher risk of treatment failure (Table 2). Pragmatically infections in young healthy women can be considered uncomplicated and infection in others as complicated. Young males usually respond rapidly to antimicrobial therapy and may also be considered as uncomplicated infection.

The differential diagnosis of cystitis is acute urethritis, acute prostatitis (males) or vaginitis and for pyelonephritis any cause of back pain with fever (pulmonary infection, intra-abdominal sepsis, pelvic inflammatory disease, spinal infection, obstruction with secondary infection or other renal disease with renal swelling).

No further investigation apart from possible urine culture is required for uncomplicated cystitis. Urine should always be cultured in suspected pyelonephritis. Urine culture may be negative if there is an obstructing lesion or if there has been prior antimicrobial use. In pyelonephritis imaging is usually not necessary but demonstrates an enlarged kidney with decreased opacity of the affected parenchyma (computed tomography). Imaging should be undertaken (ultrasound or computed tomography) if there has been no clinical improvement after 72 hours of appropriate therapy or on the second recurrence of pyelonephritis (suggestive of complicated infection).

Untreated cystitis generally resolves but with a higher rate of pyelonephritis or complicated infection. Antimicrobial therapy hastens recovery (Little et al, 2010a) with a bacteriological cure rate of 85–95%. Appropriately treated cystitis or uncomplicated pyelo-

nephritis does not usually cause acute kidney injury or lead to chronic kidney disease.

The Infectious Disease Society of America and the European Society for Microbiology and Infectious Diseases have published treatment guidelines for uncomplicated cystitis and pyelonephritis (Gupta et al, 2011). A number of recommendations have been made based on clinical efficaciousness and the risk of promoting antimicrobial resistance. Suggested empiric treatment for uncomplicated cystitis is:

- Trimethoprim-sulfamethoxazole 160/800 mg twice daily for 3 days or trimethoprim 100 mg twice daily for 3 days
- Nitrofurantoin 100 mg twice daily for 5 days (requires preserved renal function)
- Fosfomycin 3 g single dose (where available)
- Pivmecillinam 400 mg twice daily for 3–7 days (where available)
- Fluoroquinolones are highly efficacious but are associated with increasing resistance and should be reserved for other important uses
- β lactam agents are second line because they have less efficacy with increased toxicity
- Amoxicillin or ampicillin should not be used because they have poor efficacy and high prevalence of resistance.

Many young healthy women with acute pyelonephritis can be managed as outpatients. Indications for hospital admission are an inability to take medications or maintain hydration, compliance concerns, diagnostic uncertainty or if the patient is severely unwell. Suggested empiric therapy in these cases is:

- Oral fluoroquinolone (ciprofloxacin 500 mg twice daily 7 days, levofloxacin 750 mg daily 5 days) with or without an initial intravenous dose of ciprofloxacin (resistance <10%), an extended spectrum cephalosporin or an aminoglycoside. Cephalosporin or aminoglycoside must be given if there is >10% fluoroquinolone resistance
- Trimethoprim-sulfamethoxazole 160/800 mg twice daily for 14 days following an initial intravenous dose of an extended spectrum cephalosporin or aminoglycoside

Uncomplicated	Young healthy non-pregnant females
Infections considered complicated	Other conditions with an increased incidence of complicated infection (male sex, pregnancy, elderly, following recent urinary tract instrumentation, children, recent antimicrobials, diabetes mellitus, immunosuppression)
	Obstruction or other structural abnormalities of the urinary tract (nephrolithiasis, malignancies, strictures, bladder diverticula, cysts, fistulae, ileal conduits and other urinary diversions)
	Functionally abnormal urinary tract (neurogenic bladder, vesicoureteric reflux)
	Foreign bodies (urinary catheters, ureteric stents, nephrostomy tubes)
	Multi-resistant organisms
	Other

From Hooton (2003), Schollum (2009)

- Oral β lactams are less effective and if used should have an initial intravenous dose of an extended spectrum cephalosporin or aminoglycoside
- Patients who require hospitalization should be treated with an intravenous regimen of a fluoroquinolone, aminoglycoside (with or without ampicillin), extended spectrum cephalosporin or penicillin (with or without aminoglycoside) or a carbapenem, followed by a directed oral regimen.

Resistance patterns should guide empiric therapy. It is not clear at what point resistance prevalence correlates with an unacceptable rate of treatment failure. Trimethoprim-sulfamethoxazole treatment of resistant strains is associated with a 50% cure rate (90% susceptible strains) (Raz et al, 2002). The above guidelines suggest a resistance rate of 20% as a cut off for the empirical use of trimethoprim-sulfamethoxazole. The main predictors of empiric antibiotic failure are prevalent resistant strains, recent exposure to the chosen antimicrobial or travel to an area with high resistance rates (Gupta, 2003).

Most women with cystitis will improve without antimicrobial therapy (Foxman, 2010). Symptom duration does not seem to be altered if antimicrobials are delayed (Little et al, 2010b). While empiric therapy is most commonly used it may be reasonable to control symptoms with analgesics, reserving antimicrobials for those who do not improve (Foxman, 2010). There is little evidence supporting the use of urinary alkalization, cranberry products or high fluid intake for symptom control. Repeat culture of urine following treatment is not warranted unless symptoms have not resolved (Foxman et al, 2000).

Complicated urinary tract infection

Urinary tract infections are considered complicated if they occur in the setting of a structurally, functionally or metabolically abnormal urinary tract or in association with a condition which is associated with risk of treatment failure (Table 2). At initial presentation it may be difficult to identify a complicated infection. Longer lasting symptoms, more prominent systemic features and known abnormalities of the urinary tract suggest complicated infection. Complicated infections are associated with a wider range of causative organisms, with a higher rate of antimicrobial resistance. Urine should be cultured in all suspected complicated infections. Imaging is often indicated.

Complicated infections require a longer course of therapy (5–10 days lower tract, 10–14 days upper tract), based on microbial culture and sensitivities. Initial empiric therapy should be broad spectrum tailored to the likely causative organisms. Nitrofurantoin, trimethoprim-sulfamethoxazole, β lactams, fosfomycin and pivmecillinam should not be used for complicated infection (resistance, poor tissue penetration). Intravenous *vs* oral therapy is guided by the severity of presentation. Follow-up urine culture should be reserved for those who

do not clinically improve or have early recurrence (Hsueh et al, 2011). Infections related to conditions such as an obstructing stone are unlikely to improve without correction of the underlying pathology. Similarly, if the underlying structural or functional abnormality is not corrected, there is a high chance of recurrent infection (50% at 6 weeks).

Males

Young healthy men with cystitis may be considered uncomplicated and treated with a short course of therapy. In others treatment should be as for a complicated infection. Recurrent disease suggests prostatitis or structural abnormality and should be investigated with imaging of the renal tract. Follow-up urine culture is generally recommended in males because of the higher likelihood of underlying abnormalities. Prostatitis is probably the result of the reflux of infected urine into the prostatic ducts. The prostate is usually tender and swollen in association with lower tract symptoms. A long course of antimicrobial therapy (at least 1 month) is required (fluoroquinolone).

Pregnant women

About 1% of pregnant women will have cystitis. Asymptomatic bacteriuria and urinary tract infection are associated with an increased risk of pyelonephritis, premature delivery and low birth weight and should be treated with a 3–7-day course of an antimicrobial safe in pregnancy. Pyelonephritis in this setting has a higher complication rate and is usually managed as an inpatient. Pyelonephritis has a recurrence rate of 6–8% and antimicrobial prophylaxis for the rest of the pregnancy should be considered.

Diabetes mellitus

Urinary tract infection is more common in diabetics and should be considered complicated. Emphysematous pyelonephritis is an uncommon condition caused by gas-producing enterobacteriaceae occurring predominantly in diabetic patients (90%). It presents as fulminant pyelonephritis and gas is seen on plain X-ray and computed tomography (Figure 1). Treatment is with emergency nephrectomy and broad spectrum antimicrobials (mortality 60% without and 20% with nephrectomy). In diabetics a combination of infection and ischaemia may cause papillary necrosis. It presents as pyelonephritis with possible obstruction as a result of papillary sloughing.

Indwelling urinary catheter

Urinary catheter-associated infection is the most common nosocomial infection with bacteriuria present at a rate of 3–7% per day and symptomatic urinary tract infection 1.5/100 catheter days. Presentation may be subtle. Pyuria is often present and is not a reliable marker of infection. A urine sample is best taken follow-

ing catheter exchange and taken directly from the catheter. Asymptomatic patients should be neither screened nor treated. Empiric therapy should be broad spectrum and then tailored to cultures. Optimum duration is unknown but should be at least 7 days. The catheter should always be changed (biofilm is a reservoir of infection). The best prevention is to avoid catheterization or remove promptly. A sterile insertion technique, good catheter care and a closed circuit reduce the rate of infection. If a long-term catheter is required, intermittent self-catheterization may reduce the incidence of symptomatic infection (Hooton et al, 2010; Nicolle, 2012).

Renal abscess, perinephric abscess and lobar nephronia

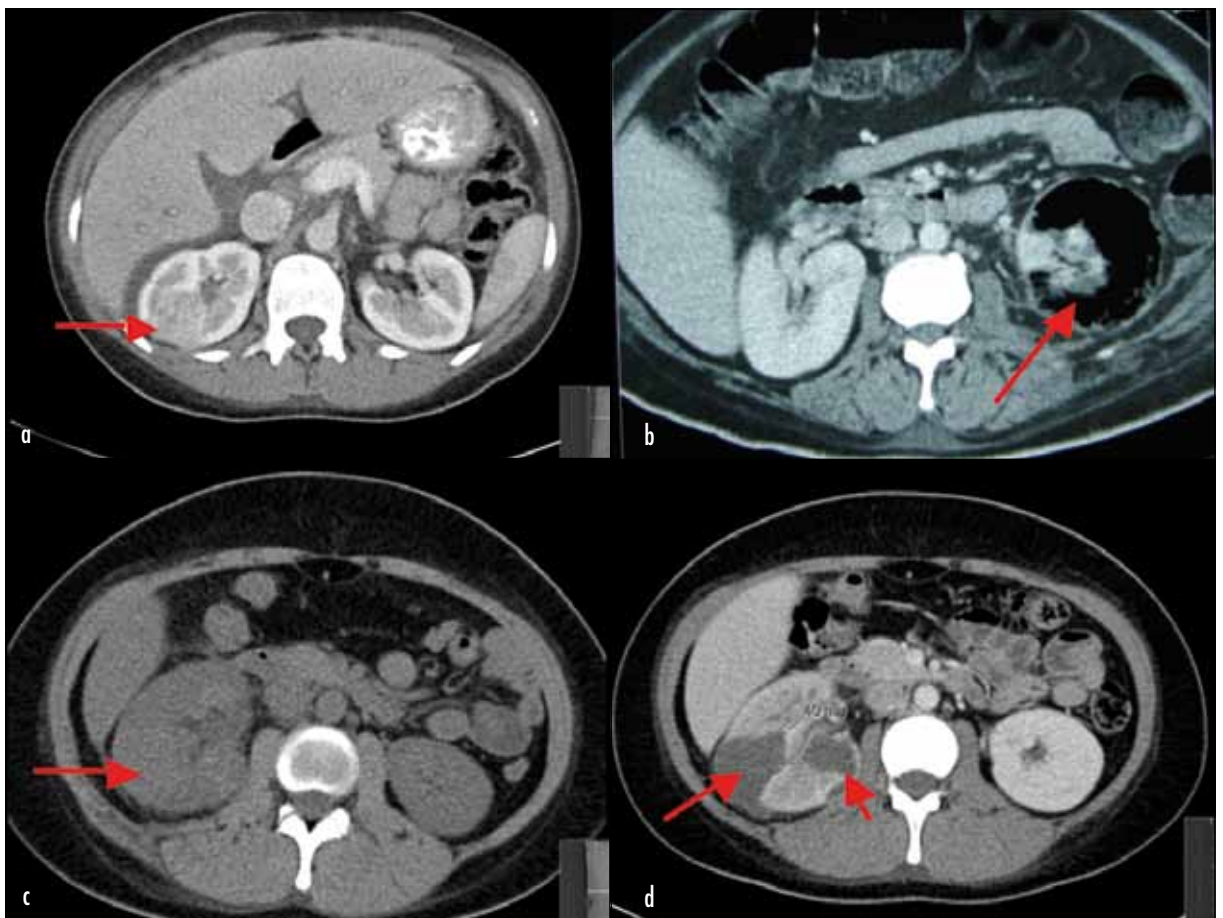
This is usually caused by pyelonephritis with liquefaction and walling off (*Figure 1*). Causative organisms are typically Gram-negative enterobacteriaceae. Lobar nephronia (focal pyelonephritis) represents a midway point between pyelonephritis and frank abscess formation (*Figure 1*). Abscess typically presents as severe non-responding pyelonephritis. Small cortical collections usually respond to prolonged (1–2 months) courses of

antimicrobials. Larger or non-responding collections typically require aspiration. Perinephric collections usually occur in association with obstruction or other complicating factors and typically will require drainage. Infected cysts usually occur with adult polycystic kidney disease and may be difficult to distinguish from a ruptured or haemorrhagic cyst. A prolonged (1 month) course of antimicrobials is usually required and occasionally cysts need to be drained.

Recurrent uncomplicated urinary tract infection

Around a quarter of healthy women with cystitis will have a second episode within 6 months. Fewer than 5% will have a third episode. This is usually reinfection with the same organism which has persisted in the gastrointestinal tract. Risk factors are the same as for initial urinary tract infection. Recurrence needs to be confirmed on urine culture. Prophylactic antimicrobials, either continuous or post-coital, reduce recurrence (Albert et al, 2004). Prophylaxis is generally considered in women with two or more infections in a 6-month period. Intermittent self-treatment with pre-prescribed antimicrobials rapidly improves symptoms. Prevention strat-

Figure 1. a. Acute focal pyelonephritis (lobar nephronia). b. Emphysematous pyelonephritis of the left kidney. c. Non-contrast computed tomography scan with acutely swollen right kidney with perinephric stranding consistent with acute pyelonephritis. d. Same patient 1 week later with renal abscess formation.



egies are not well validated and include avoidance of spermicidal agents, post-coital voiding and liberal fluid intake to encourage high urine flow. Topical vaginal oestrogen may reduce the frequency of urinary tract infection in postmenopausal women (Perotta et al, 2008). A Cochrane review on cranberry juice suggested this may be beneficial in preventing recurrence (Jepson and Craig, 2008), but trials have suggested little benefit (Barbosa-Cesnik et al, 2011).

Conclusions

Urinary tract infection remains a very common infection particularly in primary care. The differentiation between complicated and uncomplicated infection has important consequences with regard to investigation and treatment. Empiric therapy without confirmatory culture is appropriate in young healthy women with cystitis. All others should have a urine culture and broad spectrum empiric therapy, followed by directed therapy based on culture and sensitivity results. The optimum duration of antibiotics remains unclear in most complicated infections, but longer courses are clearly required in this setting. Anecdotally the most common error in treating urinary tract infection is inappropriate short courses of antibiotics for complicated infection. **BJHM**

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KEY POINTS

- Urinary tract infection remains one of the most common bacterial infections.
- Young healthy women with uncomplicated cystitis can be treated safely and effectively with short courses of empiric antimicrobials, without urine culture.
- All other presentations should have urine sent for culture.
- Bacterial adhesion molecules are the main virulence factors of uropathogenic bacteria.
- Recurrence is common and can usually be managed with antimicrobial prophylaxis.
- Complicated infection implies an increased risk of treatment failure and requires a longer period of antimicrobial therapy.
- Radiological investigation should be reserved for those not responding to appropriate therapy or in those with a suggestion of an underlying structural abnormality of the urinary tract.