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Current Management Strategies for Uncomplicated and Complicated Cystitis

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1. Introduction

Acute cystitis is defined as a superficial infection of the bladder mucosa. Approximately 10% of females are diagnosed with cystitis on an annual basis and over 50% of females will have at least one episode of cystitis during their lifetime (Foxman 2002, Foxman et al. 2000). Typically, uncomplicated cystitis occurs in late adolescence and during the second and fourth decades in females with up to 30% of females 20 to 40 years of age having a history of cystitis (Hooton et al. 1996). Symptoms such as fever, chills and flank pain are absent as acute cystitis is not associated with involvement of the upper urinary tracts. Risk factors for acute cystitis include sexual intercourse, the use of spermicides and ascending bowel flora. Males with underlying structural and functional deficiencies of the genitourinary tract may also develop acute cystitis (Krieger et al. 1993). After the initial infection many patients tend to have recurrence with 25% to 50% of patients having another infection within 1 year. Recurrent episodes of cystitis are defined as symptomatic infections that follow the clinical resolution of a previous episode after treatment and their incidence is 3% to 5%.

Although the vast majority of patients presenting with cystitis respond promptly to appropriate therapy, early identification and treatment of patients with complicated cystitis remains a significant clinical challenge to physicians and urologists. Herein, we discuss appropriate management strategies for patients presenting with symptoms consistent with both uncomplicated and complicated cystitis. We also place particular emphasis on appropriate antimicrobial treatment regimens for cystitis and discuss emerging patterns of resistance among different uropathogens.

2. Acute uncomplicated cystitis

2.1 Clinical presentation

Typically, cystitis presents with symptoms that include dysuria, frequency, urgency and suprapubic pain. Occasionally, foul smelling urine and haematuria may develop (Fig. 1). The likelihood of cystitis in female patients presenting with these symptoms ranges from 50% to 90% (Bent et al. 2002, Wong et al. 1985). The likelihood cystitis is up to 90% in a female patient who has had cystitis and presents with symptoms suggestive of recurrence (Gupta et al. 2001a, Gupta et al. 2001b). As cystitis only affects the mucosal layers of the bladder fever and rigors do not develop. Differential diagnosis for females presenting with these symptoms should include vaginitis, sexually transmitted infections (STIs) and urethral pathology.

It is important to differentiate cystitis from other conditions where dysuria may also be present. Specific features within the history, physical examination and voided urine may differentiate between vaginitis, urethral infections caused by STIs and other miscellaneous conditions associated with dysuria. Characteristic features of vaginitis include irritative voiding with vaginal irritation and an insidious onset. Urinary symptoms such as frequency, suprapubic pain and haematuria are usually absent. The patient may also give a history of vaginal discharge and multiple sexual partners. Common causes of STIs are herpes simplex virus (HSV), gonorrhoea and chlamydia. Urethritis also causes subacute dysuria and is associated with a history of urethral discharge and multiple sexual partners. In male patients urethral discharge with inflammatory cells or pyuria is characteristic and common causes of urethritis in males include gonorrhoea, chlamydia, HSV and trichomoniasis. Culture and immunological analysis are indicated for diagnostic purposes

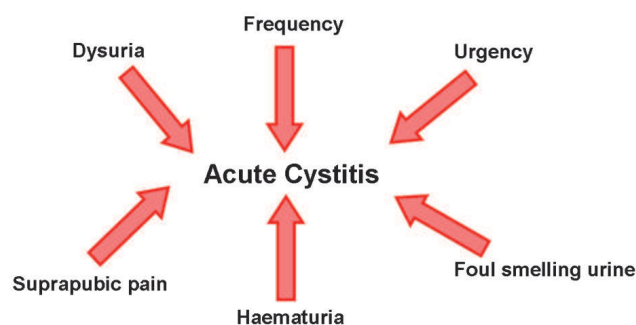


Fig. 1. Common presenting symptoms associated with acute cystitis. Typically, patients present with dysuria, frequency, urgency and suprapubic pain.

2.2 Risk factors

The most important risk factors for acute cystitis in female patients are previous episodes of cystitis and frequent or recent sexual activity as celibate females rarely present with cystitis (Scholes et al. 2000). The relative odds of acute cystitis during the first 48 hours after sexual intercourse are increased by 60 fold and spermicidal agents increase the risk of infection from *E. coli* or *S. saprophyticus* by 2 - 3 fold (Fihn et al. 1998, Nicolle et al. 1982, Strom et al. 1987). Females that frequently develop recurrent episodes of cystitis are more likely to have a maternal history of the condition and to have developed their first episode at an early age (Fihn 2003, Scholes et al. 2000). In healthy postmenopausal females sexual activity is a less important predictor of cystitis in comparison to younger females and oestrogen deficiency is believed to play a greater role (Boyko et al. 2002). Recurrent cystitis in postmenopausal females is more likely in patients with cystoceles, urinary incontinence and a previous history of genitourinary surgery (Raz et al. 2000). Female patients with diabetes mellitus are twice as likely to develop cystitis compared to non-diabetic females. The risk of acute cystitis also increases in elderly females residing in institutionalised settings with the risk of infection showing a direct correlation with increasing age and physical disability (Nicolle et al. 2005).

2.3 Laboratory diagnosis

A laboratory diagnosis of suspected acute cystitis is based on microscopic urinalysis that indicates the presence of pyuria, bacteriuria and haematuria. Pyuria on microscopy has a

sensitivity of 95% and a specificity of 70% (Fihn 2003). The presence of bacteriuria has a sensitivity of 40% to 70% and a specificity of 85% to 90% depending on the number of bacteria identified (Hurlbut and Littenberg 1991). Dipstick analysis for bacteria (nitrite) or pyuria (leukocyte esterase) are convenient but remain less sensitive than microscopic assessment of the urine. The accuracy of the findings on a culture of midstream urine (MSU) depends on how a positive urine culture is defined. Traditionally, 10^5 cfu/ml is applied to a voided urine sample. Although the specificity is high it is important to note that the sensitivity is only in the region of 50%. Lowering the threshold to 10^2 cfu/mL in cases of young females with suspected cystitis raises the sensitivity without affecting the specificity (Nicolle et al. 2005, Stamm 1982). Therefore, urine culture remains the definitive diagnostic investigation for acute cystitis and the presence of 10^2 cfu/mL or more of urine indicates active infection.

Admittedly, routine urine culture is not always necessary for diagnostic purposes (McIsaac et al. 2002). It is considered more cost-effective to manage and treat patients symptomatic of uncomplicated cystitis without an initial urine culture because antimicrobial therapy is often completed before culture results are made available. This theory was validated in one study that demonstrated pre-therapeutic urine cultures for UTIs increases cost by up to 40% but only decreases the duration of symptoms by 10% (Carlson and Mulley 1985). Therefore, in females with recent onset of symptoms suggestive of cystitis, without the features of a complicated UTI, a urinalysis that is positive for bacteriuria, pyuria, haematuria or a combination should provide sufficient evidence of a UTI and a urine culture may be omitted. Importantly, a urine culture should be obtained when symptoms and urine examination findings leave a diagnosis of cystitis in doubt. In addition, pretherapeutic urine cultures are also necessary for managing patients with a recent history of antimicrobial therapy. It has also been demonstrated that treating acute uncomplicated cystitis by telephone consultation is safe and effective in primary care settings (Barry et al. 2001, Fenwick et al. 2000, Saint et al. 1999). Importantly, inclusion criteria for these studies are females at low risk (i.e. without a prior history of UTI, without symptoms suggestive of vaginitis or cervicitis and less than 55 years of age). Females that do not meet these criteria should be seen in person and examined (Fenwick et al. 2000).

2.4 Causative microorganisms

E. coli is the responsible uropathogen in 75% to 90% of female patients diagnosed with acute cystitis and *Staphylococcus saprophiticus* accounts for 10% to 20% of cases (Jordan et al. 1980, Latham et al. 1983, Ronald 2002). Less common organisms include *Klebsiella*, *Proteus* and *Enterococci*. *E. coli* and other *Enterobacteriaceae* are the most commonly diagnosed organisms in male patients.

2.5 Management

A 3 day course of oral trimethoprim- sulfamethoxazole (TMP-SMX) results in eradication of pathogens within 7 days after commencing treatment in approximately 94% of females (Warren et al. 1999). Single-dose treatment is less efficacious than the 3 day course with eradication rates approaching 87%; however single-dose treatment is associated with fewer side-effects (11% versus 18%) (Warren et al. 1999). TMP-SMX is effective and inexpensive for empirical therapy. Therefore, TMP-SMX is recommended in areas where the prevalence of resistance to these drugs among *E. coli* strains causing cystitis is less than 20% (Warren et al.

1999). When used alone, TMP is as efficacious as TMP-SMX and is associated with fewer side effects, probably because of the absence of the sulfa component. It can be prescribed to patients who are allergic to sulfa.

Interestingly, a number of more recent studies have demonstrated that resistance to TMP-SMX is increasing in many different countries (Bean et al. 2008, Daza et al. 2001, De Francesco et al. 2007, Ling et al. 2006, Sader et al. 2005) (Fig. 2). One study from Israel demonstrated that 29% of cultures grew TMP-SMX resistant organisms in patients with uncomplicated cystitis. In this study microbiological cure was achieved in 86% of patients with TMP-SMX susceptible microorganisms but in only 42% of those with TMP-SMX resistant organisms (Raz et al. 2002). Another prospective study from the United Kingdom (UK) demonstrated resistance to TMP in 13.9% of isolates and patients with resistant isolates had a longer median time to symptom resolution (7 versus 4 days; $p=0.0002$), more frequent revisits to their attending physician (39% versus 6% in the first week, $p<0.0001$), more subsequent antibiotics (36% versus 4% in the first week, $p<0.0001$) and higher rates of subsequent bacteria at 1 month (42% versus 20% with susceptible isolates) (McNulty et al. 2006). Recent studies from the United States have demonstrated TMP-SMX resistance rates of 15% to 23% in isolates from patients with acute uncomplicated cystitis (Colgan et al. 2008, Hames and Rice 2007). In a study from Japan 17% of isolates from patients with cystitis showed resistance to TMP-SMX and abandonment of TMP-SMX as first line therapy for acute uncomplicated cystitis is currently under consideration in this region (Yamamoto et al. 2009).

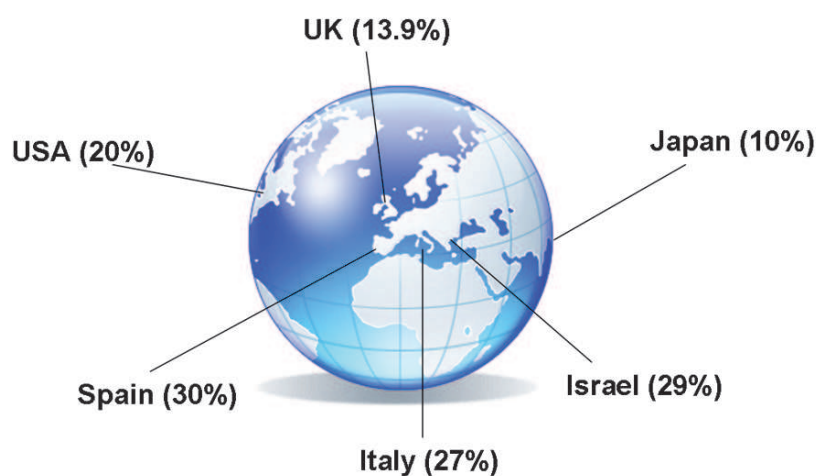


Fig. 2. Increasing rates of resistance for TMP-SMX treatment regimen for acute uncomplicated cystitis.

Resistant strains can be partially predicted from a history of recent antimicrobial usage. It has also been demonstrated that females who have been treated with TMP-SMX are 16 times less likely to be re-infected with an isolate resistant to this agent compared with females who have not take recent antimicrobial therapy (Brown et al. 2002). Furthermore, females that have taken other antimicrobial agents are two-fold more likely to be infected with a resistant isolate. Although the resistance rate to TMP-SMX is as high as 20% in some regions the bacteriologic eradication rate is approximately 80% and the clinical cure rate is approximately 85% (Manges et al. 2001, Wright et al. 1999). On account of these increasing

resistance rates some authorities advocate the following criteria for prescribing TMP-SMX (Gupta et al. 2001b, Steinke et al. 1999):

- No known drug allergy
- No recent history of antibiotic usage
- Local prevalence to resistance is less than 15 – 20%

Although less than 5% of urine isolates are resistant to nitrofurantoin, it is considerably less active than TMP-SMX against aerobic Gram-negative rods other than *E. coli*. Furthermore, nitrofurantoin is more expensive than TMP-SMX. It is usually well tolerated, however it is frequently prescribed for 7 days and this may cause significant gastrointestinal upset. The macrocrystalline formulation is taken every 6 hours and the monohydrate macrocrystal is taken twice daily. The monohydrate formulation is associated with fewer side-effects. Nitrofurantoin is not associated with plasmid-mediated resistance and is a suitable choice for patients with recent exposure to other antimicrobial agents (Fihn 2003).

Fluoroquinolones offer excellent activity and are usually well tolerated (Henry et al. 2002). Their resistance is less than 5% in most regions (Hooton et al. 2004, Warren et al. 1999); however resistance rates are beginning to increase worldwide (although not as high as that of TMP-SMX) (Yamamoto et al. 2010) (Muratani and Matsumoto 2006). In the Mediterranean region up to one-third of strains that demonstrate reduced susceptibility to fluoroquinolones and cause uncomplicated cystitis belong to two clonal groups: O15:H1 and O25:H4 (Cagnacci et al. 2008). This implies that strains belonging to these two clonal groups play a major role in determining the increasing rate of fluoroquinolone resistant *E. coli* strains in the community. One study from Japan reported fluoroquinolone resistance in 8% of isolates from patients with acute uncomplicated cystitis (Yamamoto et al. 2009). Worryingly, resistance rates for *E. coli* isolated from acute uncomplicated cystitis to ciprofloxacin increased from 15.2% in 2002 to 23.4% in 2006 in South Korea (Yamamoto et al. 2010) (Fig. 3).

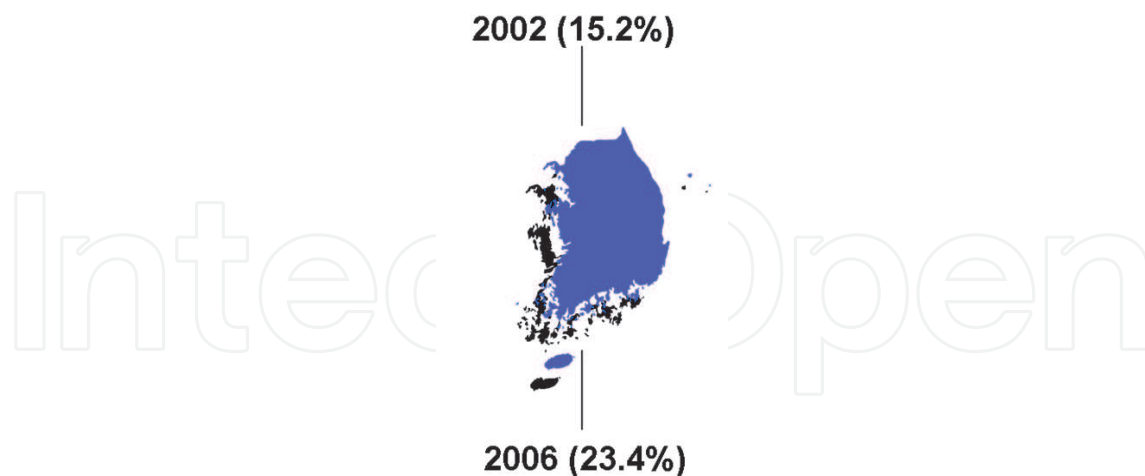


Fig. 3. Increasing rates of resistance for *E. coli* against ciprofloxacin in South Korea from 2002 to 2006.

The efficacy of ofloxacin is greater than TMP-SMX with recurrence rates of 8% to 9% 6 weeks after therapy has been completed (Hooton et al. 1991). Other fluoroquinolones have similar efficacy however they should be regarded as a second line treatment option due to their high cost and to preserve their sensitivity against uropathogens. Their use for

uncomplicated cystitis should be limited to patients that are allergic to less expensive drugs, to patients with previous exposure to antimicrobial agents causing bacterial resistance and to regions where resistance to TMP-SMX is greater than 20%. When TMP-SMX is contraindicated a 3 day course of ciprofloxacin, levofloxacin, norfloxacin, lomefloxacin or gatifloxacin is an appropriate alternative. Importantly, fluoroquinolones are less active against *S. saprophyticus* and many Gram-negative uropathogens (Fihn 2003).

Fosfomycin tromethamine is taken as a single dose of powder from a sachet and is another option for treating uncomplicated cystitis. It is less effective than TMP-SMX and fluoroquinolones and should only be considered when more effective agents cannot be prescribed (Warren et al. 1999). Further limitations of fosfomycin tromethamine are its poor efficacy against *S. saprophyticus* and its expensive nature. The high *in vitro* resistance to ampicillin and sulfonamide and the high cost of amoxicillin/clavulanate and the cephalocrySTALLINE sporins limit their usefulness in the setting of acute uncomplicated cystitis. More than 90% of females report the absence of acute urinary symptoms within 72 hours after commencement of antimicrobial therapy (Fihn et al. 1988). Phenazopyridine or Uristat can be prescribed in females with severe persistent dysuria. Although this compound is available over the counter there is concern that females with severe dysuria are not seeking medical care and are also at risk of side effects such as headache, gastrointestinal upset, rash and nephrotoxicity (Fihn 2003). Resistance rates of *E. coli* to antibiotic regimes are illustrated in Table 1.

Antimicrobial Agent	Italy	Spain	USA	UK	China	Japan
Ampicillin	49	65	-	54	-	-
Amoxicillin/clavulanate	8	37	12	12	29	2
Piperacillin	30	-	-	-	-	-
Piperacillin/ tazobactam	1	68	-	-	7	-
Nitrofurantoin	9	7	3	5	-	1
TMP	-	-	-	39	-	-
TMP-SMX	27	37	20	-	-	10
Ciprofloxacin	19	22	5	9	51	8
Gentamicin	6	10	-	5	39	2
Cefalexin	-	-	-	8	-	-
Cephazolin	7	-	-	-	-	-
Cefpodoxime	-	-	2	6	-	5
Cefuroxime	-	13	24	-	-	-
Cefprozil	-	-	3	-	-	-
Cefotaxime	-	4	-	-	14	-
Ceftazidime	-	-	-	-	3	-
Ceftriaxone	2	-	-	-	-	-
Cefdinir	-	-	2	-	-	5
Cefoperazone	-	-	-	-	17	-
Cefoperazone/sulbactam	-	-	-	-	5	-
Cefipime	-	3	-	-	8	-

Table 1. Resistance rate of *E. coli* isolated from patients with community acquired infections (depicted as percentage) (Bean et al. 2008, Daza et al. 2001, De Francesco et al. 2007, Ling et al. 2006, Sader et al. 2005, Yamamoto et al.).

2.5.1 Cranberry juice

Proanthocyanidins found in cranberry juice have been long advocated to play a preventative role against cystitis. It appears that proanthocyanidins inhibit the attachment of uropathogens to the surface of the uroepithelium. Randomised trials suggest that 200-750 ml of cranberry juice or cranberry-concentrate tablets reduce the risk of symptomatic recurrent infection by 12-20% (Avorn et al. 1994, Kontiokari et al. 2001, Stothers 2002). Interestingly, the amount of cranberry juice found within products marketed as cranberry juice is highly variable and ranges from 5-100%.

2.6 Duration of therapy

In female patients with uncomplicated cystitis 3 days of therapy is the preferred treatment regimen. One study that reviewed over 300 clinical trials of single-dose, 3-day or 7-day treatment with TMP-SMX, fluoroquinolones and β -lactam antimicrobial agents found that 3-day therapy is more effective than single-dose therapy (Table 2). In addition, 3-day therapy with TMP-SMX, amoxicillin or cloxacillin is associated with cure rates that are comparable with longer courses of therapy and an incidence of adverse effects that are as low as single-dose therapy (Warren et al. 1999). Seven-day therapy is associated with a higher incidence of adverse effects and is only recommended in females with symptoms longer than 1 week, in male patients and in individual patients that have complicating risk factors

Circumstance	Drug	Dosage	Frequency	Duration (Days)
Female				
Healthy	Ciprofloxacin	500mg	BD	3
	Levofloxacin	500mg	QDS	3
	TMP-SMX	1 double strength tablet (160 - 800mg)	BD	3
	Trimethoprim	100mg	BD	3
	Nitrofurantoin	100mg	BD	3
	Norfloxacin	400mg	BD	3
Symptoms >7 days, recent UTI, Age >65 years, Diabetes, Diaphragm use	TMP-SMX	As Above	As Above	7
	Fluoroquinolone			7
Pregnancy	Amoxicillin	250mg	TDS	7
	Cephalexin	500mg	QDS	7
	Nitrofurantoin	As Above	As Above	7
Males				
	Fluoroquinolone	As Above	As Above	7
	TMP-SMX	As Above	As Above	7

Table 2. Current treatment regimens for acute uncomplicated cystitis.

2.7 Cost of therapy

The cost of treating acute uncomplicated cystitis involves the initial evaluation, the cost of the drug administered and the subsequent follow-up (Table 3). Good cost effectiveness is achieved with adequate efficacy against the most common uropathogen, *E. coli*. Intuitively, the lower the effectiveness against *E. coli*, the greater number of revisits, cases of progression to pyelonephritis and the higher the follow-up cost. Notably, antimicrobial cost is a poor predictor of cost-effectiveness as demonstrated in one study that compared the most expensive and least expensive drugs (fluroquinolones and TMP-SMX respectively). Results showed that both regimens are equally cost effective and that both of these drugs are also more cost effective against nitrofurantoin (Rosenberg 1999).

Antimicrobial Agent	Approximate Retail Cost (\$)	Side effects
Trimethoprim-sulfamethoxazole (TMP-SMX)	1.83	Anorexia. Nausea, vomiting, rash, urticaria, blood dyscrasias, hypersensitivity, hepatic necrosis
Trimethoprim	4.33	Diarrhoea, rash, glossitis, taste changes, blood dyscrasias, hypersensitivity
Norfloxacin	25.21	Dizziness, restlessness, headache, diarrhoea, nausea, rash, vaginitis, convulsions, psychosis, hypersensitivity, tendon rupture
Ciprofloxacin	53.56	Similar to norfloxacin
Levofloxacin	43.92	Similar to norfloxacin
Gatifloxacin	21.61	Similar to norfloxacin
Lomefloxacin	35.96	Similar to norfloxacin
Nitrofurantoin macrocrystals	35.29	Anorexia, nausea, vomiting, headache, pulmonary hypersensitivity, hepatotoxicity, haemolytic anaemia, peripheral neuropathy
Nitrofurantoin monohydrate macrocrystals	29.96	Similar to nitrofurantoin macrocrystals (gastrointestinal effects less common)
Fosfomycin tromethamine	33.97	Nausea, vomiting, vaginitis, rash, hypersensitivity

Table 3. Cost of treatment regimens for acute uncomplicated cystitis (Rosenberg 1999).

2.8 Follow-up

In general, young female patients that are asymptomatic after antimicrobial therapies do not require a follow-up visit or repeat MSU. A follow up visit is recommended with MSU in older females and in all male patients with cystitis. Urological evaluation with ultrasound, computed tomography (CT) or cystoscopy is unnecessary in females and is also usually unnecessary in male patients that respond appropriately to antimicrobial therapy (Abarbanel et al. 2003, Lipsky 1989). However, one study demonstrated that up to 50% of males with UTIs have a significant urological abnormality. Finally, patients that do not respond to antimicrobial therapy should undergo appropriate microbiological evaluations (Andrews et al. 2002).

3. Asymptomatic bacteriuria

Asymptomatic bacteriuria can be defined as a microbiological diagnosis based on the isolation of a specified quantitative count of bacteria in a properly collected specimen of urine from a patient who is without symptoms or signs consistent with cystitis. Absence of symptoms is usually obvious in healthy patients, however asymptomatic UTIs may be more difficult to diagnose in catheterised or neurologically compromised patients. A single catheterised urine specimen with a solitary isolate of 10^2 cfu/mL is diagnostic of bacteriuria in catheterised male and female patients (Nicolle et al. 2005). Concomitant pyuria ranges from 30% in young females to 100% in catheterised patients (Hooton et al. 2000). Importantly, other co-factors like bladder calculi can induce mucosal inflammation in this patient cohort. Therefore, the presence of pyuria alone is insufficient for a diagnosis of bacteriuria.

The prevalence of asymptomatic bacteriuria among the general population varies with age, gender and the presence of abnormalities in the genitourinary tract (Nicolle et al. 2005) (Table 4). *E. coli* is the most common uropathogen isolated in patients with asymptomatic bacteriuria and it is usually a less virulent strain than in isolates from symptomatic patients (Svanborg and Godaly 1997). Enterobacteriaceae and Gram-positive uropathogens are more commonly isolated in patients with abnormalities of the genitourinary tract. *Pseudomonas aeruginosa* and *Proteus* are more prevalent among patients living in residential care.

Patient Population	Prevalence (%)
Premenopausal females	1.0 - 5.0
Pregnant females	1.9 - 9.5
Postmenopausal females (age: 50-70)	2.8 - 8.6
Diabetic patients	
Males	0.7 - 11
Females	9.0 - 27
Elderly patients in the community	
Males	3.6 - 19
Females	10.8 - 16
Elderly patients in nursing homes	
Males	14 - 50
Females	25 - 50
Patients with spinal cord injuries	
Self-intermittent catheterisation (SIC)	23 - 89
Sphincterotomy and condom catheter <i>in situ</i>	57
Patients undergoing haemodialysis	28
Indwelling catheter	
Short-term	9 - 23
Long-term	100

Table 4. Prevalence of asymptomatic bacteria among different patient populations (Nicolle et al. 2005).

3.1 Management of asymptomatic bacteriuria

In general, management of asymptomatic bacteriuria is governed by the patient cohort and their risk factors for adverse outcomes that may be prevented with appropriate antimicrobial treatment. In adult populations it has been shown that asymptomatic bacteriuria is not harmful and treatment of asymptomatic bacteriuria does not decrease the frequency of symptomatic UTIs or improve patient outcomes. Therefore, screening and treating asymptomatic bacteriuria is discouraged in populations other than in pregnant females and in patients undergoing urological procedures (Nicolle et al. 2005) (Table 5).

Patient Cohort	Recommended	Not recommended
Premenopausal non pregnant females		X
Pregnant females	X	
Diabetic females		X
Elderly patients residing in the community		X
Elderly patients residing in nursing homes		X
Patients with spinal cord injuries		X
Patient with indwelling catheters*		X
Urological interventions	X	
Immunocompromised patients		X

*Antimicrobial treatment of asymptomatic female patients with catheter-associated bacteriuria persisting >48 hours should be considered.

Table 5. Algorithm for screening and treating asymptomatic bacteriuria (Nicolle et al. 2005).

4. Complicated cystitis

Complicated cystitis may occur in patients with a compromised urinary tract or by a very resistant uropathogen. The clinical spectrum of complicated cystitis can range from mild cystitis to life-threatening infections of the kidney and urospeis (Table 6). Urine cultures are mandatory to identify the invading uropathogen and its antimicrobial susceptibility in this group of patients. The following are common host-factors that predispose to complicated cystitis:

- Functional and/or structural abnormalities of the urinary tract
- Recent instrumentation of the urinary tract
- Recent usage of antimicrobial therapy
- Diabetes mellitus
- Immunosuppression
- Pregnancy
- Hospital-acquired infections

Due to the wide range of host conditions and uropthogens that are associated with complicated cystitis appropriate guidelines for empirical therapy remain limited. Patients with mild to moderate illness can be treated on an outpatient basis with oral fluroquinolones. If the susceptibility pattern of the pathogen is known TMP-SMX may also be effective (Stamm and Hooton 1993).

Pathogens	Mitigating Circumstances	Recommended Empirical Treatment
<i>E. coli</i> , <i>Proteus</i> species, <i>Klebsiella</i> species, <i>Pseudomonas</i> species	Mild-to-moderate illness, no nausea or vomiting-outpatient therapy	Oral* norfloxacin, ciprofloxacin or ofloxacin for 10-14 days
<i>Serratia</i> species, enterococci, staphylococci	Severe illness or uropoiesis-hospitalisation required	Parenteral** ampicillin and gentamicin, ciprofloxacin, levofloxacin, ceftriaxone, aztreonam, ticarcillin-clavulanate or imipenem-cilastin until fever has subsided; then oral trimethoprim-sulfamethoxazole, norfloxacin, ciprofloxacin or levofloxacin for 14-21 days

* Oral regimens for pyelonephritis and complicated UTI are as follows: trimethoprim-sulfamethoxazole, 160 to 800 mg, BD; norfloxacin, 400mg, BD; ciprofloxacin, 500 mg, BD; levofloxacin, 500 mg, 500 mg/day.

** Parenteral regimens are as follows: ciprofloxacin, 400mg, BD; levofloxacin, 500mg/ day; gentamicin 1mg/kg TDS; ceftriaxone, 1-2 g/ day; ampicillin, 1 g QDS; imipenem-cilastin, 250-500 mg QDS; ticarcillin-clavulanate, 3.1 g QDS; and aztreonam 1 g TDS.

Table 6. Treatment strategies for complicated cystitis (Stamm and Hooton 1993).

For hospitalised patients intravenous ampicillin and gentamicin provides adequate coverage against most pathogens. Antimicrobial therapy can also be modified when sensitivity data are available. Therapy is usually continued for 10 to 14 days and switched from parenteral to oral whenever possible. Repeat urine culture should be performed 7 and 14 days after therapy to ensure adequate efficacy has been achieved (Fihn 2003).

4.1 Unresolving cystitis

Persistent infection suggests that initial antimicrobial therapy has been inadequate at eliminating bacterial growth and concomitant symptoms from the genitourinary tract. Repeat urinalysis and MSU are indicated if the symptoms of UTI do not resolve by the end of treatment or if symptoms begin to recur shortly after therapy. If the patient's symptoms are severe it is prudent to commence empirical therapy with a fluoroquinolone until the MSU results have been obtained.

Resistance to the antimicrobial agent selected to treat the infection is the most common cause for patients with persistent unresolving UTIs. The patient may have a recent history of antimicrobial therapy and colonisation of the bowel with resistant bacteria has subsequently developed. In addition, tetracycline, sulfonamides and β -lactams cause plasmid-mediated R factors that simultaneously carry resistance to multiple antimicrobial agents. The development of resistance in a previously susceptible population of bacteria is the second most common cause of resistant UTIs and this issue may arise in up to 5% of patients that are receiving antimicrobial therapy. Resistance to antimicrobial therapy is easily diagnosed as the culture taken on therapy shows that the previously susceptible population has been replaced by resistant bacteria of the same species. More resistant strains of bacteria usually

emerge when the concentration of antimicrobial therapy in the urine is insufficient to eradicate all bacteria present. This phenomenon usually occurs in patients who are underdosed and in patients who are poorly compliant with their prescribed regimen. Rapid reintroduction of a new resistant species while the patient is undergoing antimicrobial therapy may also cause resistant UTI. Reinfection mimicking unresolved bacteriuria should increase the index of suspicion for an enterovesical fistula. The following list represents the more common causes of persistent unresolving cystitis

- Bacterial resistance to the antimicrobial agent selected for treatment.
- Development of resistance from previously susceptible bacteria
- Bacteriuria resulting from 2 different bacterial species with different susceptibilities
- Reinfection with a new, resistant species during initial therapy for the original susceptible organism
- Azotemia
- Analgesia abuse leading to papillary necrosis
- Staghorn calculi providing a nidus for resistant bacteria to attach

If the repeat urine culture (obtained from when the patient was on therapy) demonstrates that the initial bacterial species is still present and susceptible to the antimicrobial agent selected to treat the infection, it is likely that the unresolved infection is caused by an inability to deliver sufficient concentrations of antimicrobial agents into the urinary tracts or an excessive number of bacteria may be over-riding the activity of the antimicrobial agent.

In addition, antimicrobial levels are usually lower than the minimal inhibitory concentration required for eradicating the infecting organism in patients with uraemia. Severe defects in the medullary collecting system impair the kidney's concentrating ability and can dilute the antimicrobial agent, particularly in patients with papillary necrosis. Large masses of bacteria within the genitourinary tract are frequently seen with a large staghorn calculus. In this situation the urinary concentration of antimicrobial agent may be large, however it may be inadequate to sterilise the large volume of infected urine. This phenomenon may occur because susceptible bacteria cannot be inhibited once a specific critical density is reached. Rarely, patients with a variant of Munchausen's syndrome may present with unresolving cystitis. These patients tend to inoculate their bladders with uropathogens or wilfully avoid antimicrobial agents. Careful bacteriologic observations usually indicate the implausibility of the clinical picture.

4.2 Laboratory diagnosis

In cases of unresolving cystitis urinalysis and urine culture are required to investigate the uropathogen responsible for the persistent infective process. Renal function and imaging of the genitourinary tract should be performed if repeat culture demonstrates sensitivity of the uropathogen to the antimicrobial agent prescribed. This investigative regimen is employed to identify any abnormalities within the urinary tract. Empirical treatment of unresolving cystitis is based on the assumption that the infecting uropathogen is resistant. Fluoroquinolones provide sufficient antimicrobial coverage in most situations and should be prescribed for 7 days. Adjustments to this regime can be performed when bacterial susceptibilities have been made available. Finally, urine cultures should be repeated during and 7 days after therapy to ensure adequate eradication has been achieved.

4.3 Recurrent cystitis

Recurrent episodes are caused by re-emergence of bacteria from a site within the urinary tract (persistence) or from new infective uropathogens outside the urinary tract (reinfection) (Fig. 4). Bacterial persistence must be caused by the same uropathogen on each occasion and reinfections typically occur at varying intervals and are usually caused by different species of bacteria. It is important to differentiate between persistence and reinfections as management protocols differ. Patients with bacterial persistence can be cured of recurrent cystitis by identifying and surgically removing/ correcting the focus of infection. Patients complaining of recurrent reinfection usually require long-term medical management as a structural defect is not usually present. Reinfections in males occasionally occur and are usually as a result of an underlying abnormality such as urethral stricture. In these situations surgical evaluation is warranted.



Fig. 4. Re-emergence of bacteria from within the urinary tract (persistence) or invasion of new bacteria (reinfection) is the most common causes of recurrent cystitis.

4.3.1 Bacterial persistence

After the initial episode has resolved recurrence with the same organism arises from a site within the genitourinary tract. The site of bacterial persistence is usually excluded from high concentrations of the antimicrobial agent. It is generally accepted that there are 12 correctable urological abnormalities that may cause bacteria to persist within the genitourinary tract. These abnormalities are illustrated in Table 7 and may be difficult to diagnose. Some causes may require cystoscopic localisation of the infection (with ureteral catheters) to accurately define the focus of bacterial persistence.

- Infected stones
- Chronic bacterial prostatitis
- Unilateral infected atrophic kidneys
- Ectopic ureters and ureteral duplication
- Foreign bodies
- Urethral diverticula and infected periurethral glands
- Unilateral medullary sponge kidneys
- Non-refluxing, normal appearing, infected ureteral stumps after nephrectomy
- Infected urachal cyst
- Infected communicating cysts of the renal calyces
- Papillary necrosis
- Perivesical abscess with fistula to bladder

Table 7. Urological abnormalities causing bacterial persistence that may be amenable to surgical correction.

It is important to identify patients with bacterial persistence as they represent the only patient cohort with a surgically curable cause of recurrent UTIs. Radiological and endoscopic evaluation of the urinary tract is necessary with excreting urography/ CT and cystoscopic assessment providing the initial screening investigations. Diverticulum and nonrefluxing ureteral stumps can be diagnosed with retrograde urography. In patients in

whom the focus of infection cannot be eradicated, long-term, low-dose antimicrobial suppression is necessary to prevent symptoms of infection. The antimicrobial drugs used for low-dose prophylaxis will also be effective for bacterial suppression if the persistent strain is susceptible. These include nitrofurantoin, TMP-SMX, cephalexin, and the fluoroquinolones

4.3.2 Recurrent infections

Females with recurrent infections and who are exposed to vaginal spermicides from either condoms or diaphragms should consider alternative methods of contraception or protection from sexually transmitted infections (STIs). Continuous and postcoital prophylaxis with low-dose antimicrobial agents is effective in treating recurrent cystitis and prophylactic treatment should not be commenced until active infection has been eradicated (Hooton 2001). Absence of infection can be confirmed by a negative urine culture 1-2 weeks after treatment has been discontinued.

Continuous prophylaxis is a potential option for females who have had 2 or more symptomatic infections over a 6 month period. Randomised, placebo-controlled trials have demonstrated that continuous prophylaxis with nitrofurantoin, trimethoprim (\pm sulfamethoxazole), ciprofloxacin or norfloxacin decreases recurrent episodes by 95% (i.e. from 2 to 3 episodes per patient/ year to 0.1 to 0.2 episodes per patient/ year) and may also prevent episodes of pyelonephritis (Hooton 2001). Notably, one agent is not recommended over another because studies to date have lacked sufficient statistical power. In general, antimicrobial prophylaxis is initiated on a trial basis for a 6 month period. If good outcomes are reported the agent may be continued for 2 to 5 years without the emergence of a resistant organism (Stamm et al. 1991). The rate of chronic adverse effects associated with antimicrobial agents ranges from 7% to 40% for trimethoprim containing regimens, from 0% to 40% for nitrofurantoin, from 7 to 21% for norfloxacin and up to 13% for ciprofloxacin (Chew and Fihn 1999). Gastrointestinal disturbances, rash and yeast vaginitis are the most common adverse effects encountered (Fig. 5).

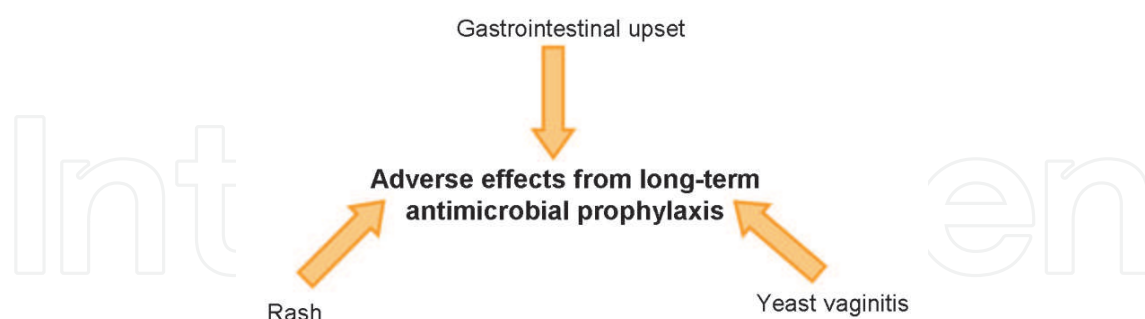


Fig. 5. Common adverse effects associated with long-term antimicrobial prophylaxis against recurrent episodes of cystitis.

Post-coital prophylaxis is an attractive option for female patients that describe a direct association between sexual intercourse and subsequent cystitis. A reduction in the frequency of recurrences has been demonstrated when nitrofurantoin, TMP-SMX or fluoroquinolones have been administered post-coitus (Stapleton et al. 1990) (Table 8). Intermittent self-treatment as opposed to continuous treatment has also been recommended in some scenarios. Many females can accurately self-diagnose acute cystitis and may be instructed to

commence a 3-day course of an antimicrobial agent at the onset of symptoms (Gupta et al. 2001a). However, females are advised to seek medical attention if symptoms persist 48-72 hours after completing the appropriate antimicrobial course. Interestingly, several studies have also demonstrated that postcoital voiding does not play a preventative role for recurrent cystitis. In addition, it appears that poor urinary hygiene does not predispose to recurrent cystitis (Scholes et al. 2000, Strom et al. 1987).

Regimen	Infections per patient per year	Reference
Nitrofurantoin, 50 or 100 mg daily	0.09	(Bailey et al. 1971)
Nitrofurantoin, 50mg daily	0.19	
Placebo	2.1	
Sulfamethoxazole, 500mg daily	2.5	(Harding et al. 1982)
TMP-SMX, 40 and 200mg daily	0.1	
Methenamine mandelate, 2g daily + ascorbic acid 2g	1.6	
Nitrofurantoin, 50mg daily	0.32	(Kasanen et al. 1978)
Methenamine hippurate, 1g daily	0.39	
Trimethoprim, 100mg daily	0.13	
TMP-SMX, 80 and 400 mg daily	0.19	
Cephalexin, 125 mg daily	0.10	(Gower 1975)
TMP-SMX, 40 and 200 mg daily	0.00	(Stamey et al. 1977)
Nitrofurantoin macrocrystals, 100mg daily	0.74	
TMP-SMX, 40 and 200 mg 3-times weekly	0.1	(Harding et al. 1979)
TMP-SMX, 40 and 200 mg daily	0.15	(Stamm et al. 1980)
Trimethoprim, 100 mg daily	0.00	
Nitrofurantoin macrocrystals, 100mg daily	0.14	
Placebo	2.8	
Nitrofurantoin, 50 mg twice daily	0.19	(Brumfitt et al. 1981)
Methenamine hippurate, 1g twice daily	0.57	
TMP-SMX, 40 and 200 mg 3-times weekly	0.14	(Harding et al. 1982)
Trimethoprim, 100 mg daily	1.53	(Brumfitt et al. 1983)
Methenamine hippurate, 1g daily	1.38	
Povidone-iodine wash, twice daily	1.79	
TMP-SMX, 40 and 200 mg daily	0.2	(Wong et al. 1985)
Self-administered cotrimoxazole, 4 x 80 and 400mg	2.2	
Cephalexin, 250 mg daily	0.18	(Martinez et al. 1985)
Trimethoprim, 100 mg daily	1.0	(Brumfitt et al. 1985)
Nitrofurantoin macrocrystals, 100 mg daily	0.16	
Nitrofurantoin, 200 mg daily	0.00	(Nicolle et al. 1989)
Norfloxacin, 200 mg daily	0.00	
Norfloxacin, 200 mg daily	0.04	(Raz and Boger 1991)

Table 8. Low-dose prophylactic regimes for recurrent cystitis in females.

5. Conclusions

It is important for urologists to be familiar with appropriate management strategies for cystitis because of its highly prevalent nature in the community. Currently, recommended treatment regimens for uncomplicated cystitis include 3-day therapy with fluoroquinolones or nitrofurantoin as resistance rates appear to be increasing when TMP-SMX is administered. Worryingly, recent studies have demonstrated an increasing number of isolates of fluoroquinolone-resistant pathogens and this merits concern for the future. Female patients that complain of frequent recurrences should be advised to avoid exposure to vaginal spermicides and prophylaxis or methods of self-administration may be considered. Imaging studies should be reserved for patients presenting with complicated episodes of cystitis. The increasing incidence of antimicrobial resistance in conjunction with the highly prevalent nature of cystitis suggests that prudent and appropriate use of antimicrobial agents is becoming increasingly important.

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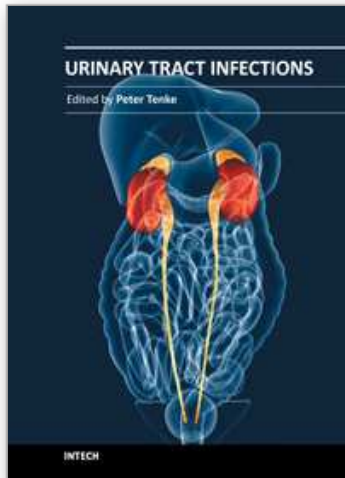
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Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, and they are also the leading cause of hospital-acquired infections. Therefore, the appropriate management of UTIs is a major medical and financial issue. This book covers different clinical manifestations of UTI, with special emphasis on some hard-to-treat diseases, and special conditions in respect of treatment; antibiotic resistance and the available alternative strategies for the prevention and treatment of UTIs and it deals with urinary tract infections in children. The aim of this book is to give a summary about the different aspects of the diagnosis, management and prevention of urinary tract infections for all medical disciplines.

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