Bacterial cystitis in women

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Background
A woman presenting with symptoms suggestive of bacterial cystitis is a frequent occurrence in the general practice setting. One in three women develop a urinary tract infection (UTI) during their lifetime (compared to 1 in 20 men).

Objective
In this article we provide an outline of the aetiology, pathogenesis and treatment of bacterial cystitis in the primary care setting. We suggest measures that may assist before urological referral and work through a common clinical scenario.

Discussion
Bacterial cystitis in unlikely if the urine is both nitrite and leuco-esterase negative. Empirical antibiotics are justified if symptoms are present with positive urinary dipstick, but microscopy, culture and sensitivity of urine is warranted to ensure appropriate empirical therapy and identification of the causative organism. Risk factors for UTI in women include sexual intercourse, use of contraceptive diaphragms and, in postmenopausal women, mechanical and/or physiologic factors that affect bladder emptying such as cystocoele or atrophic vaginitis. Discussion regarding risk factors and UTI prevention is important. Women with recurrent UTIs (defined as three or more episodes in 12 months or two or more episodes in 6 months) should be screened for an underlying urinary tract abnormality (ultrasound) and may benefit from prophylactic therapy. Patients with complex or recurrent UTIs, persistent haematuria, persistent asymptomatic bacteriuria, or urinary tract abnormalities on imaging may benefit from referral to a urologist.

Keywords: urological diseases; general practice; women's health; cystitis

Cystitis is a clinical syndrome characterised by dysuria, frequency and urgency, with or without suprapubic pain. Causes of cystitis can be infective (bacterial, viral, other) or noninfective. The commonest clinical entity is bacterial cystitis due to common urinary tract pathogens.

Bacterial cystitis is usually associated with bacteriuria (bacteria in the urine) and pyuria (presence of white cells in the urine), but both can occur without infection. Bacteriuria may be due to either colonisation or infection of the urinary tract, or contamination of the collected urine specimen. Pyuria indicates inflammation, which is usually due to bacteria but can be due to other causes. Sterile pyuria requires further investigation for tuberculosis, bladder stones, or cancer.

Noninfective cystitis may be caused by urothelial carcinoma, bladder calculi, chemicals (ifosphamide, cyclophosphamide) or interstitial cystitis. Inflammation of the bladder, from either infective or noninfective causes, produces the characteristic cystoscopic finding of squamous metaplasia (*Figure 1*) and may also lead to cystitis cystica (*Figure 2*).

About 250 000 Australians develop a UTI each year.[1] Women are more commonly affected than men; with 1 in 3 women and 1 in 20 men developing a UTI at some point during their lifetime.[2] Urinary tract infections occur more commonly in older men, especially in the presence of lower urinary tract dysfunction. Nearly 1 in 3 women develop a UTI requiring treatment before the age of 24 years.[2]

Classification

Urinary tract infections may be classified as:

- simple (occur in a structurally and functionally normal urinary tract), or
- complex (occur in an abnormal urinary tract or in the presence of other factors listed in *Table 1*).

In Australia, *Escherichia coli* is the most common uropathogen causing up to 95% of simple UTIs.[3] In addition to *E. coli*, complex UTIs may also be caused by *Proteus* and *Klebsiella* species, *Enterococci*, Group B *Streptococci* and *Pseudomonas aeruginosa*.[3] Complex UTIs tend to be associated with increased severity and complications. The resultant treatment may be multimodal.

Pathogenesis

Most UTIs are caused by normal bacterial flora entering the urinary tract via ascent through the urethra from the bowel, vagina, or perineum. It is not the presence, but rather the expression of the organism's virulence factors which allow their adherence to the perineum and urethra. This is followed by migration into the bladder with invasion of the urothelium leading to symptoms secondary to the inflammatory response.

Protective factors

There is innate immunity in the lower urinary tract via the flushing out of organisms by urine as well as entrapment of bacteria by the urethral lining. These cells are shed in the urine leading to removal of bacteria from the lower urinary tract. In addition, the normal flora of healthy vaginal mucosa and perineal area contains micro-organisms such as lactobacilli, and an acidic pH environment, which prevent the adherence of uropathogens. Factors that cause urinary stasis and alter the vaginal and perineal environment (spermicides or vaginal atrophy) may alter these protective mechanisms.

Risk factors

The increased incidence of UTIs in women may be attributed to urethral length, which provides an effective barrier to bacterial ascent. The female urethra is generally less than 5 cm compared to the male, which is more than 15 cm.

Risk factors for UTIs in younger women include:

- sexual intercourse
- contraceptive diaphragms (especially with spermicides), and
- past history of childhood UTIs.[4,5]

Prior antibiotic use may also increase the risk of UTI by altering the normal perineal flora.

In postmenopausal women, mechanical and/or physiologic factors that affect bladder emptying are strong risk factors for UTI. Factors associated with UTI in this age group include:

- urinary incontinence
- cystocoele and large postvoid residual volumes
- atrophic vaginitis, and
- a history of UTIs before menopause.[6]

While rare, diverticular disease of the urethra may also present with symptoms of recurrent UTI. Complex UTIs with risk factors listed in *Table 1* require aggressive investigation and intervention with urological input if surgical causes are found.

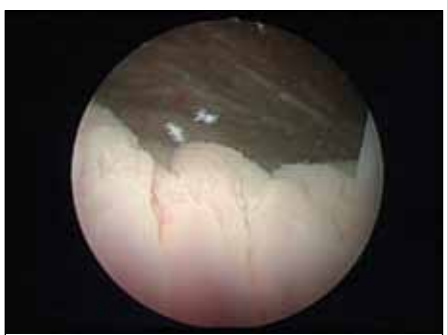

Figure 1. Squamous metaplasia of the trigone occurs in response to inflammation of the bladder and causes the trigone to have a white furry appearance. The condition is benign and is associated with UTI

Asymptomatic bacteruiria

Asymptomatic bacteriuria (ASB) is the presence of a positive urine culture in the absence of symptoms and is more common in the elderly. Recurrent ASB warrants further investigation to exclude urinary tract abnormalities, such as bladder stones, diverticulae, foreign bodies, chronic retention, malignancy and upper tract abnormalities.

Treatment and investigation of ASB is particularly critical in:

- pregnancy
- urolithiasis
- vesicoureteric reflux
- renal transplant recipients
- the immunocompromised, and
- before instrumentation of the urinary tract.

Some authors[7] believe that ASB does not require treatment in other patient groups, however, the alternate view remains that ASB should be treated and investigated to ensure there is no other coexisting pathology.

While counterintuitive, treatment of ASB has not been shown to improve the outcome in patients with indwelling catheters[7] or in those who self catheterise. These patients should only be treated if symptomatic with suprapubic pain or signs of sepsis.

Investigation of cystitis

History and symptoms are usually adequate to make a diagnosis of cystitis and to exclude complex

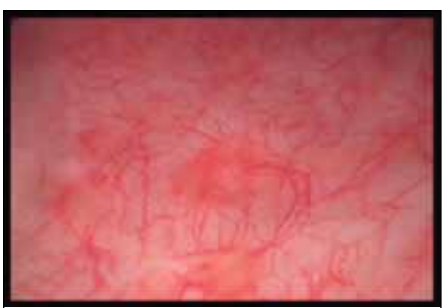

Figure 2. Cystitis cystica may also occur with inflammation. It consists of small fluid filled 'blisters' sitting beneath the urothelium. The cysts are formed by the liquefaction of small islands of normal urothelium sitting within the lamina propria. This is a benign condition

Table 1. Risk factors for complex UTI

Patient factors	Male child <12 years Pregnancy Male >50 Immunosuppressed (diabetes, renal failure)
Structural/ functional factors	Presence of indwelling catheter Chronic retention Bladder outflow obstruction Polycystic kidneys Upper tract calculi Bladder stones
Bacterial factors	Nosocomial/ multiresistant organisms

a UTI. Although it may seem cost effective to treat on history alone,[8] urine culture is useful to confirm infection and identify the causative organism. This limits unnecessary use of antibiotics and identifies patients who would benefit from further evaluation. Urine dipstick analysis can be used as a fast method of examining fresh urine[9] and if nitrite (with or without leuco-esterase) positive, the patient is likely to have a UTI.

Antibiotic treatment is justified in this setting but a midstream urine (MSU) specimen should preferably be sent for microscopy, culture and sensitivity (MCS) to ensure appropriate empirical therapy and identification of the causative organism. If leuco-esterase alone is positive, a UTI will be present in 50% of patients and, depending upon symptoms, treatment may be delayed until MCS is performed.[8] The likelihood of a UTI is low if the urine is both nitrite and leuco-esterase negative.

Microscopy, culture and sensitivity of a MSU is the gold standard diagnostic test for UTIs, and should be performed for most patients. Quantitative bacteriuria of 10^5 colony forming units (CFU) per mL is sufficient for a diagnosis of UTI. Growth of a single organism at lower CFUs is also diagnostic.

Follow up

After clinically successful treatment of UTI, repeat urine examination for bacteriuria is only required in pregnant women to ensure bacterial clearance. Asymptomatic bacteriuria in this population is associated with pyelonephritis and low birth weight.[10]

Further investigations are not required in premenopausal women with one or two recurrent uncomplicated UTIs, as anatomical or functional

urologic abnormalities are uncommon. However, urinary tract ultrasound is indicated if seemingly uncomplicated cystitis recurs frequently (two episodes in 6 months or three or more episodes in 12 months) or shows a pattern of bacterial persistence. Urinary tract ultrasound also confirms the degree of bladder emptying by measurement of postvoiding residual. Abnormalities on ultrasound may require specialist evaluation and further investigation with contrast enhanced computerised tomography (CT).

Postmenopausal women with recurrent cystitis should be evaluated by vaginal examination for pelvic organ prolapse and vaginal atrophy as these conditions may mimic the symptoms of cystitis. Older patients with recurrent UTIs should also be screened for diabetes.

Microscopic haematuria often occurs with UTI and, if persistent 6 weeks following resolution of cystitis, requires further investigation. All patients with macroscopic haematuria require urological evaluation if they have risk factors for urothelial carcinoma (smokers, prior exposure to cyclophosphamide, chemicals or radiation). In the absence of risk factors these patients should be monitored to ensure the haematuria has resolved. All patients with persistent haematuria (macroscopic or microscopic) should be referred to a urologist with urine cytology (three specimens on three separate days) and upper tract imaging. A urinary tract ultrasound is an acceptable preliminary investigation and if needed, can be followed by contrast CT urogram or retrograde pyelography. Cystoscopy is also performed to evaluate the urothelium of the bladder.

Treatment

Women with a simple UTI should be treated with empirical first line antibiotic therapy such as trimethoprim 300 mg orally at night for 3 days or cephalexin 500 mg orally twice daily for 5 days.[3,11] Other first line choices include amoxycillin with clavulanate, or nitrofurantoin. Amoxycillin (without clavulanate) is only recommended if the organism has shown to be susceptible.

Quinolones may be required in complex UTI and should only be used as a second line agent when resistance has been documented or in the presence of *P. aeruginosa*.[3]

Trimethoprim is contraindicated in pregnancy and hence cephalexin (for 10 days) is recommended as first line therapy. Alternatives include nitrofurantoin and amoxycillin with clavulanate.

A 3 day course of antibiotics is similar to a prolonged course (5–10 days) in achieving symptomatic cure, but is not as effective in achieving complete bacterial eradication.[12] It is appropriate to prescribe a longer course of antibiotics for women in whom complete bacterial eradication is important (such as in pregnancy, urolithiasis and in the immunocompromised) even though prolonged treatment is associated with a higher rate of side effects.

Adjuvant therapy with urine alkalinisers can help alleviate the dysuric symptoms of cystitis.[3]

Sufficient fluid intake (at least 2 L/day) is thought to have a 'flushing' effect on the urinary tract, avoiding urinary stasis and bacterial proliferation. Other factors such as good hygiene, postcoital voiding, anterior to posterior wiping patterns and the wearing of cotton underwear may reduce the risk of UTIs. Alternatives to diaphragms and spermicides should be considered. Cranberry products may reduce bacterial adherence and may reduce the incidence of UTIs, however the optimum dosage and formulation (eg. juice, extract, tablets) is yet to be established.[13] Lactobacillus containing probiotic yoghurt (either vaginal or oral) to restore commensal vaginal flora has been proposed for prophylaxis of cystitis in postmenopausal women, but the data remains inconclusive and no recommendations can be made for its use.[14]

Treating recurrent UTIs

Women with recurrent UTIs being considered for prophylactic antibiotic therapy may benefit from a urological opinion to exclude altered anatomy or foreign bodies. Prophylactic antibiotic regimens for women with recurrent cystitis may reduce recurrence by up to 95%[14] (see *Case study*). Regimens include:

- long term prophylaxis
- self start therapy, or
- postintercourse prophylaxis (*Table 2*).

With self start therapy, a urine specimen should be collected for MCS before the taking first antibiotic tablet. The most practical method is to give the patient pathology request forms to obviate the need for an urgent appointment with a GP. The patient then presents for review once the MCS results are available. This ensures appropriate antibiotic use and provides a microbiologial 'history' to aid in further treatment. Continuous prophylaxis with bacteriostatic agents, such as hexamine (methanamine) hippurate 1 g orally twice daily, may also be helpful.[15] Urine alkalinsing agents can provide symptomatic relief and may also reduce the incidence of UTI.

In the presence of atrophic vaginitis, the risk of UTIs may be reduced by improving the vaginal tissues with oestrogen replacement.[16] However, hormone therapy is a complex and controversial issue and beyond the scope of this article.

Case study

A sexually active woman, 25 years of age, presents with recurrent bacterial cystitis. This is her third episode of cystitis in 12 months. She is otherwise fit and well. Urinary tract infection is confirmed initially on the basis of symptomatology and dipstick urinalysis followed by formal MCS. She has a history of *E. coli* UTI sensitive to standard antibiotics, and empirical treatment is initiated with trimethoprim 300 mg orally at night for 3 days.[3,11] A urinary tract ultrasound was normal.

Case study discussion

If UTIs occur postintercourse, then postintercourse prophylaxis may suffice. Spermicides and diaphragms should be replaced with other means of contraception.[4] If the episodes are unrelated to intercourse it would be reasonable to start treatment for recurrent UTIs. Evidence based prophylactic regimens may reduce recurrence of UTIs by up to 95% and are listed in *Table 2*.[17]

In this young woman, self start intermittent therapy would be a reasonable option to trial for 12 months, as she has only had three infections in 1 year. A woman with more frequent infections may only tolerate a 6 month trial. If this fails, then low dose continuous prophylaxis for 3 months would be appropriate. There should be a low threshold for evaluation with urinary tract ultrasound. Urological evaluation may be required if infections persist.

Conclusion

The incidence of UTIs is high. All the evaluation and treatment measures outlined above may be undertaken in the general practice setting. However, referral to a urologist is beneficial in the setting of recurrent UTIs, persistent

Table 2. Antibiotic recommendations for recurrent UTIs in nonpregnant adult females[3,11]

	Duration	Treatment options	Dose	Frequency
Continuous prophylaxis	3–6 months	Trimethoprim	150 mg	At night
		Cephalexin	250 mg	At night
		Nitrofurantoin*	50 mg	At night
		Trimethoprim + sulphamethoxazole	160/800 mg	At night
Self start therapy	3 days	Trimethoprim	300 mg	At night
	5 days	Cephalexin	500 mg	12 hourly
	3–5 days	Nitrofurantoin	50 mg	6 hourly
	5 days	Amoxycillin + clavulanate	500/125 mg	12 hourly
	3 days	Norfloxacin	400 mg	12 hourly
Post-intercourse	Single dose	Trimethoprim	150 mg	
	Single dose	Cephalexin	250 mg	
	Single dose	Nitrofurantoin	50 mg	
	Single dose	Trimethoprim + sulphamethoxazole	160/800 mg	

* Nitrofurantoin may have side effects that need to be considered with prolonged therapy, such as pulmonary toxicity (interstitial pulmonary fibrosis), peripheral neuropathy (usually beginning with lower limb parasthesiae), and hepatotoxicity (chronic active hepatitis)[11]

haematuria, persistent ASB or in the presence of urinary tract abnormalities on imaging. The presence of pelvic organ prolapse, intractable atrophic vaginitis, or severe lower urinary tract symptoms may also be indications for specialist referral.

Summary of important points

- If leuco-esterase alone is positive, bacteria will be present in 50% of patients. The likelihood of UTI is low if the urine is both nitrite and leuco-esterase negative.
- Empirical antibiotics are justified if symptoms are present with positive urinary dipstick. It is advisable that the MSU specimen be sent for MCS to ensure appropriate empirical therapy and identification of the causative organism.
- Patients with persistent haematuria postinfection must be investigated to exclude the presence of urothelial carcinoma.
- Women with recurrent UTIs should be screened for an underlying urinary tract abnormality.
- Patients with persistent ASB or complex UTIs require further evaluation to ensure there are no surgical causes.

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Conflict of interest: Prem Rashid has been a visitor to the American Medical Systems (AMS) USA manufacturing facility undertaking a cadaveric dissection clinic and observed operative procedures by implant urologists affiliated with AMS. He has also acted as a consultant for Coloplast, AstraZeneca, Hospira & Abbott Pharmaceuticals. No commercial organisation initiated or contributed to the writing of this article.

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