Urinary tract infection in gynaecology and obstetrics

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Abstract
Cystitis is a common problem in the general population affecting 50% of women in their lifetime. Pregnant women are prone to asymptomatic bacteriuria and screening and treatment is important, due to the risk of neonatal complications. Gynaecological patients are at greater risk of developing urinary tract infections, because of concomitant prolapse, vaginal atrophy, voiding dysfunction and incontinence. Recurrent UTI is a substantial problem in this group.

Dipstick testing is efficient and cost effective in the primary healthcare, but this is not recommended in obstetrics and gynaecology, where precise sensitivities must be used to ensure complete treatment. Nitrofurantoin is the antimicrobial agent of choice, because of minimal adverse effects and low resistance rates, in particular, now that antibiotic resistance is an increasing concern. Recent studies have demonstrated that refractory overactive bladder is associated with low count bacteriuria (<10⁵ CFU/ml); antibiotic randomised trials are in progress.

Keywords antibiotic resistance; asymptomatic bacteriuria; nitrofurantoin; overactive bladder; prophylactic antibiotics; recurrent UTI; urinary tract infection

Introduction
Traditionally, acute urinary tract infection (UTI) is treated by the general practitioner, but the Obstetrician/Gynaecologist often encounters such patients, thus knowledge of this subject is important. Gynaecological problems, such as cystocele and postoperative voiding difficulties, may also lead to recurrent UTI, which can be difficult to treat. In the last decade, antibiotic resistance is an increasing concern. Thus, a review of this important subject is timely.

Classification
UTIs are classified according to their location, clinical symptoms and microbiological findings. Infection of the upper tract (pyelonephritis) comprises infection of the renal parenchyma and may be associated with systemic sepsis, in contrast to infection of the lower tract (cystitis) that is located in the bladder alone.

Complicated UTIs are related to underlying anatomical or functional abnormality (e.g. renal calculi, fistula, renal transplants) and need referral to the Urologist. They usually take longer to respond to treatment and if the underlying cause is not removed they are likely to re-occur. This may be within days, weeks or months from the original infection.

Uncomplicated UTI occur in women with a normal urinary tract and react quickly to therapy.

The problem of acute UTI in gynaecology and obstetrics
Cystitis describes inflammation of the bladder, usually in response to bacterial infection. Classically, the patient presents with typical symptoms of urgency, frequency, dysuria, suprapubic discomfort, and discoloured foul smelling urine caused by inflammation of the bladder in response to bacterial invasion. Cystitis is a common clinical diagnosis. Approximately 50% of all women experience a UTI at some time in their life. They account for 1–3% of general practitioner consultations in the UK and approximately 150 million cases per year worldwide. Risk factors for UTI are summarised in Box 1.

In the majority of cases, gram negative coliform bacilli (Enterobacteriaceae) account for the infection and Escherichia Coli remains the most prevalent uropathogen (77%). Infection is commonly preceded by colonisation of the perineum and periurethral area by rectal flora.

Diagnosis using urine dipsticks assessing nitrite, leucocyte esterase and erythrocytes are frequently used in the primary care setting. The presence of leucocytes implies inflammation of the urothelium. Nitrites are strongly suggestive of significant bacte- riuria and empirical antimicrobial treatment should be commenced. Urine dipstick testing is convenient and has proven to be cost-effective in general practice. In most patients UTI is a single event and no further investigation is needed.

The natural history of cystitis is resolution of the symptoms within 4–7 days. In the GP setting, in fit healthy young women, delaying antibiotics by 48 hours to allow for resolution of symptoms reduces the use of antibiotics without significantly prolonging symptoms. There are several “self-help” measures patients can initiate themselves. Increasing fluid intake shortens the intervals between voids and achieves a high flow rate, therefore diluting and flushing out the microorganism. Urine alkalising preparations, e.g. a teaspoon of bicarbonate of soda dissolved in water taken every few hours, provide symptomatic relief by reducing the acidity of the urine, thus reducing the stimuli to bladder afferent nerves.

However, in obstetrics and gynaecology we are looking at a different population. In this group, a reduction of symptoms to an average of 3 days with antibiotic treatment is to be predicted. A short course has been proven to be as effective as a long course in uncomplicated cystitis.

Microbiological culture remains the gold standard and is to be recommended in gynaecology patients. The type of bacteria isolated and their count are noted, as well as the antibiotic sensitivities and the red and white cell count. Bacteriuria without white cells and with large numbers of squamous epithelial cells is highly suggestive of contamination. Antimicrobial treatment will often be initiated prior to the urine culture and the empirical treatment subsequently altered according to the sensitivity results. Therefore, one should choose the drug that is most likely to eliminate the most common microorganism, which is E. coli.
Although trimethoprim is commonly prescribed as a first line drug for UTI, its increasing resistance makes it less suitable. Nitrofurantoin has the lowest likelihood of organism resistance (0–4%) and there has been no rise in resistance despite its extensive use for more than 5 decades. Due to its bladder-specificity, nitrofurantoin attains high urine levels making it an efficacious treatment for cystitis. The serum concentrations are low, therefore it cannot be used to treat pyelonephritis or UTI induced sepsis. Nitrofurantoin is effective against most common uropathogens, i.e. *E. coli*, enterococci, Klebsiella, and Enterobacter, but does not treat *Pseudomonas* or Proteus. It does not alter intestinal or introital flora, generally avoiding vaginal monilia. Therapeutic urinary concentrations are higher when nitrofurantoin is taken on a full stomach. It should not be taken with urine alkalising preparations, as the absorption of nitrofurantoin is better in an acidic environment.

The macrocrystalline formation (Macrodantin) has additional benefits as it slows absorption prolonging urinary excretion, and it has less side effects such as nausea and vomiting, making it more tolerable for the patient. It is also one of the few oral drugs that is effective against uropathogens that produce extended spectrum beta-lactamase (ESBL). In the last 2 decades, gram negative bacteria that possess plasmid-mediated ESBL genes (which confer resistance to penicillin with clavulanate or sulbactam and 3rd generation cephalosporins) are becoming an increasingly worrisome problem. The altered genetic factors can be spread between species making antibiotic treatment more difficult.

**Asymptomatic and symptomatic bacteriuria in pregnancy**

Bacteriuria is defined as the presence of bacteria in urine and may be either symptomatic or asymptomatic. Physical and physiological changes in pregnancy, including decreased urine osmolality, glycosuria and the progesterone dilation effects upon the ureteric smooth muscle, favour bacterial colonisation, making asymptomatic bacteriuria (ABU) a common finding. In “healthy” women the prevalence varies between 1 and 9%, but in pregnancy this doubles to 2–15%. Asymptomatic bacteriuria in the non-pregnant female does not usually require treatment. However, in obstetric patients treatment is important, due to the risk of neonatal complications.

The risk of ABU progressing to pyelonephritis in pregnancy is also increased due to compression of the ureters at the pelvic rim, causing upwards reflux of urine. Screening, by routine urine culture in early pregnancy, is recommended by the RCOG. *E. coli* is the most frequently found microorganism (up to 86%), although *Klebsiella pneumoniae*, *Proteus mirabilis* and Staphylococcus may also be cultured. *Gardnerella vaginalis* and *Ureaplasma urealyticum* may be found, in contrast to the non-pregnant population. *Streptococcus agalactiae* (Group B streptococcus (GBS)) is clinically important due to its association with obstetric complications such as chorioamnionitis, intrapartum fever and early-onset neonatal GBS disease. Patients with diabetes gravidarum are also more likely to suffer from GBS asymptomatic bacteriuria. Growth greater than 10⁵ CFU/ml requires treatment in pregnancy and intrapartum antibiotics according to the RCOG guidelines (www.rcog.org.uk Green-Top No. 36). Screening and targeted treatment significantly reduces the risk of pyelonephritis, premature delivery and low birth weight and has been proven cost-effective.

Additionally, 20–40% of ABU progress to symptomatic UTI, of which 20–50% are complicated by premature delivery. Cystitis itself is the most frequent medical diagnosis in pregnancy, affecting 1% of women. Dipstick urinalysis is frequently used to allow prompt commencement of empirical antibiotics, but should be combined with MSU culture and sensitivity.

Nitrofurantoin is safe to use in pregnancy, except at term as it can cause neonatal haemolysis.

A 7–10 day course of antibiotics is required so as to eradicate the infection, as persistent infection may cause (premature) labour or progress to pyelonephritis. Patients known with recurrent UTI’s are at increased risk and may use antibiotic prophylaxis during pregnancy, such as nitrofurantoin 50 mg up to 36 weeks or cephalaxin 250 mg once daily.

Early onset-sepsis in the neonate caused by antibiotic-resistant microorganisms has been associated with maternal use of antibiotics during pregnancy and labour (of which 6% were prescribed for UTIs). Further studies have shown negative effects of antibiotics in pregnancy, such as cerebral palsy, sepsis, epilepsy and jaundice in the neonate. However, most of these studies have featured antibiotics that were prescribed for PROM and chorioamnionitis. More research is needed to confirm these findings.

**Pyelonephritis in gynaecology and obstetrics**

Patients with pyelonephritis may attend the emergency department and patients with abdominal or suprapubic pain are often triaged to gynaecology. Such women often complain of loin tenderness, suprapubic tenderness from the cystitis, fever, and are often generally unwell.

In pregnancy, patients presenting with symptoms and signs of pyelonephritis usually require admission for parenteral antibiotics as well as analgesia. These patients can rapidly become quite ill. A renal tract ultrasound should be performed to check for hydronephrosis. Generally, broad-spectrum antibiotics are commenced prior to the culture results and are subsequently narrowed when the culture results are available. If there is no clinical improvement within 24–48 hours, re-assessment of the woman and discussion with the microbiologist is needed. Antimicrobial treatment is continued for at least 10–14 days in pregnancy to reduce the risk of relapse. Caution is warranted when prescribing analgesia, due to the risks to the foetus; NSAIDs should be avoided in pregnancy. The risk of premature labour is substantial, particularly if tachycardia and pyrexia are
present, thus tocolysis should be considered (see www.rcog.org.uk Greentop guideline 1B for guidance). Milder forms of pyelonephritis may be managed with oral antibiotics.

**UTI in the urogynaecology setting**

The patients seen in the urogynaecology department with concomitant issues such as prolapse, voiding dysfunction and incontinence are a more complex group of patients. Women with high post void residuals, due to voiding dysfunction or women with cystocele harbouring stagnant urine, are at increased risk of developing UTIs. Additionally, faecal incontinence and the use of pads for urinary incontinence predispose patients to UTI. Therefore, recurrent UTI in this population is a common problem.

**Defining bacteriuria**

Until recently, bacterial concentrations of $10^5$ colony-forming units (CFU)/ml were considered the diagnostic threshold for infection. This criterion was established in the 1950s by Kass, who had studied the relationship between bacteriuria and pyelonephritis in outpatient women, but not in patients with frequency/urgency symptoms. A later study by Stamm revealed that this cut off actually missed 50% of cystitis in symptomatic patients, who did respond to antimicrobial treatment. Experts now believe bacteriuria $>10^2$ CFU/ml to be a more superior threshold with an improved balance between sensitivity and specificity. If a higher threshold of $10^3$ CFU/ml is used, the specificity improves further (90%) with little loss of sensitivity (80%). The European Association of Urology (EUA) has recently changed their criteria accordingly (Box 2). Mild pyuria with less than 10 leucocytes/mm$^3$, is considered normal. The pyuria count rises as the infection becomes more pronounced, thus in early stages of cystitis the pyuria count may be quite low. Pyuria $>10$ leucocytes/mm$^3$ in the absence of bacteria implies other pathology, ie. carcinoma, calculi, TB infection. This is known as sterile pyuria and should be investigated.

**Pathogenesis**

The interaction between the host and microorganism before infection takes place is complex. *E. coli* has been studied extensively, it being the most common uropathogen.

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**Criteria for diagnosing UTI modified from EUA guidelines**

- **Classical bacterial cystitis**
  - $>10^5$ CFU/ml and pyuria with symptoms of dysuria, urgency, frequency, foul smelling urine and nocturia

- **Low-count bacterial cystitis**
  - $>10^3$ CFU/ml and pyuria

- **Asymptomatic bacteriuria**
  - $>10^5$ CFU/ml without pyuria or symptoms

- **Pyelonephritis**
  - $>10^4$ CFU/ml with additional febrile symptoms and loin pain

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There are several host defence mechanisms in place to help prevent infection. First, the washout effect of the flow of urine is the most important. Secondly, uroplakin membrane proteins and a proteoglycan mucin layer covering the urothelium limit permeability to bacterial invasion, and bacterial adherence. Thirdly, immunoglobulin (IgA) and soluble proteins (Tamm–Horsfall) protect the bladder by binding and trapping *E. coli*. If the microorganism does actually attach to the epithelium, then Toll-like receptors are activated, to initiate pathways so that infected cells are exfoliated. Finally, lactobacilli colonisation of the vagina, particularly in premenopausal women, produces lactic acid, which maintains a low pH, thus inhibiting the growth of bacteria.

Bacterial pathogens have numerous characteristics enabling survival and colonisation of the bladder. Adherence to the urothelium by *E. coli* (Figure 1) is aided by Pili or fimbiae. This is a vital step in the colonisation process, which avoids the washout effect. Recent studies have shown that *E. coli* can even reside inside the urothelial cells, making them difficult to eradicate by antimicrobial treatment.

**Resistance to antibiotics**

The World Health Organisation has reported a worrying increase in resistance to antimicrobials among uropathogens. The rates of resistance vary greatly between different countries, depending on the use of particular antimicrobials. A large European study (ECOSENS) looked at the change in *E. coli* resistance to 14 antimicrobials across Europe between 2000 and 2008. They chose five countries expected to either have high (Portugal and Greece) or low (UK, Austria, Sweden) resistance rates. This large publication confirmed the continuing high resistance in community uropathogenic *E. coli* to ampicillin, sulfamethoxazole, trimethoprim and trimethoprim/sulfamethoxazole throughout Europe (Table 1). Resistance to four or more antimicrobials was low in the UK (10.9%). There were no isolates with extended-spectrum beta-lactamase found at the start of the study, compared to eleven that were identified 8 years later.

**Recurrent UTI**

Recurrent UTI is defined by the EUA as at least three episodes of UTI confirmed by culture in the preceding 12 months. Recurrent
UTI is a problem, because approximately a third of women with acute cystitis have a recurrence within 6 months of the primary infection. Almost half of the patients with more than one UTI will suffer recurrence. Reinfection with the same or different organism occurs in 80–90% and a third of these arise from the original bacteria. Bearing in mind the risk factors for recurrent UTI (Box 3), it is important to check for atrophy, increased post void residuals (ie. >100 ml), cystoceles and urethral diverticulae when examining the patient.

As mentioned, dipstick testing may be used in primary care. However, dipstick is not appropriate in the urogynaecology patient with pelvic organ prolapse and incontinence. The sensitivity is generally poor, allowing approximately a quarter of the patients with a UTI to be missed. Uropathogens should be identified on culture and microscopy and sensitivity testing are warranted.

In recurrent UTIs, the MSU sample must also be assessed for fastidious microorganisms, ie. *U. urealyticum*, *Chlamydia trachomatis* and *Mycoplasma hominis* (which requires a separate request). It is useful to give patients three sterile urine jars to go home with, so that they can give a specimen when they first develop symptoms and all microbiological information can be captured. A renal scan should be performed to exclude upper urinary tract problems such as hydronephrosis, calculi, complex renal cysts and dilated ureters (indicating vesicoureteric reflux). Further assessment with X-ray or CT may be indicated depending on the findings. Women with frank haematuria or persistent microscopic haematuria should be referred to the urologist for further assessment.

Patients with a large cystocele and post void residual may benefit from a vaginal ring pessary to reduce the prolapse. If this is effective, pelvic floor repair should be discussed. In the absence of prolapse, patients should be taught to double empty. First, the patient is told to void as usual. After finishing, she must stand up and rotate the pelvis a few times, stimulating the afferent nerves. Then, she should try to empty the bladder further by sitting leaning forward and relaxing the pelvic floor for 1–2 minutes.

Vaginal atrophy is associated with a decrease in lactic acid bacilli, leading to a rise in vaginal pH. This in turn promotes the growth of uropathogenic bacteria and increases the risk of UTI. Accordingly, two RCTs have shown that oestriol cream and oestradiol pessaries significantly reduce the risk of recurrent UTIs.

### Resistance to antimicrobials over the last decade.

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<tbody>
<tr>
<td>Ampicillin</td>
<td>26.1</td>
<td>28.0</td>
<td>31.8</td>
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<td>Mecillinam</td>
<td>1.6</td>
<td>0.9</td>
<td>1.0</td>
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<tr>
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<td>16.1</td>
<td>14.4</td>
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<td>Ciprofloxacin</td>
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<td>3.9</td>
<td>0.5</td>
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<tr>
<td>Nitrofurantoin</td>
<td>1.4</td>
<td>0.3</td>
<td>0.0</td>
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<td>Gentamycin (IM or IV)</td>
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<td>1.3</td>
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<td>Fosfomycin</td>
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<td>1.2</td>
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<td>Cefadroxil</td>
<td>2.8</td>
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**Table 1**

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<table>
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<th>Risk factors for recurrent UTI</th>
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<tr>
<td>Urinary tract obstruction</td>
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<tr>
<td>Calculi or foreign bodies</td>
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<td>Vesicofistula</td>
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<td>Diverticulae</td>
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<td>Cystocele</td>
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<td>Urinary tract anomalies</td>
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<tr>
<td>Vesicoureteric reflux</td>
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<tr>
<td>Trauma</td>
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**Box 3**

**Figure 2** (a) and (b). Follicular cystitis noted during cystoscopy performed for recurrent UTIs.
Cranberry products were found to have limited benefit for UTI prevention by the Cochrane review. However, recent evidence suggests that products containing at least 36 mg of the active component (PACS) are the most effective. Furthermore, a pocketbook by Kilmartin (www.angelakilmartin.com) describes many self-help tips that are helpful to patients suffering from recurrent cystitis. General hygiene is most important, including bathing the perineum regularly with salt water to remove E. coli and cotton underwear is recommended to promote ventilation of the perineum. If UTI’s occur after sexual intercourse, voiding within 15 minutes of ending decreases the risk of UTI. Post coital single dose antibiotic therapy has been proven to be as effective as continuous daily treatment and has the benefits of less antibiotic use (reducing the risk of resistance). Some women find “self-start therapy” a useful option, whereby they commence antibiotics themselves at the first signs of a UTI in cases of episodic recurrence.

In recurrent UTI not responding to these measures, a prophylactic antibiotic may be chosen, depending on previous culture/sensitivity patterns as well as the patient’s allergy history. Nitrofurantoin 50–100 mg nocte is generally the first choice (as described above) and the second choice is usually Trimethoprim 100 mg. Both drugs do not cause vaginal monilia. The third line choice is Cephalexin 125–250 mg, which may promote monilia as it is broad spectrum. If further UTIs are proven, 6 months of antibiotics are prescribed, nitrofurantoin being the preferred treatment. Consistent nitrofurantoin for longer than 12 months is associated with a small risk of pulmonary fibrosis (usually in patients with renal insufficiency) and is not advised.

Patients with recurrent UTI not responding to these measures should undergo cystoscopy. Follicular cystitis (Figure 2a and b), characterised by yellow raised areas of the urothelium on cystoscopy, suggest intracellular bacterial communities and may be eradicated with diathermy.

UTI in refractory overactive bladder patients

The overactive bladder (OAB) is a debilitating condition associated with symptoms of urgency, frequency, urge incontinence and nocturia. It is more prevalent in the elderly, but affects younger women with a bedwetting history in childhood. Since Urogynaecologists have moved away from the term “urodynamically proven detrusor overactivity” towards the term “overactive bladder syndrome”, (which by definition excludes bacterial cystitis) the awareness of “non classical UTI” in OAB patients is increasing. The concept that at least one third of refractory OAB patients have some degree of bacterial cystitis (ie. low-count bacteriuria with or without pyuria) has been reported by four research groups in the last four years, although these patients do not generally complain of dysuria or foul-smelling urine. Further research comparing the “classical” to the “low count” cystitis definition in OAB patients revealed a significant increase in the diagnosis of bacteriuria when the low-count threshold for diagnosing bacteriuria was used (>10^2 CFU/ml rather than >10^3 CFU/ml). Using this cut off, the likelihood of bacteriuria in OAB patients is as high as 40–50%. Two non-randomised studies have shown benefit for antibiotics; a randomised controlled trial is currently in progress.

FURTHER READING


Practice points

- Diagnosis and treatment of suspected UTI on the basis of dipstick urinalysis alone is reasonable/cost effective in general practice, but it is not appropriate in obstetrics and gynaecology patients, in whom precise sensitivity testing must always be performed.

- Treatment of both asymptomatic and symptomatic bacteriuria in pregnancy is important due to the risks of obstetric complications.

- Antimicrobial therapy must be chosen with care, due to increasing multi-resistant among uropathogens.

- Nitrofurantoin is the 1st drug of choice, due to its low resistance pattern and few side effects.

- Using the classical criteria for cystitis (10^5 CFU/ml) as opposed to the low-count threshold (10^3 CFU/ml) leads to significant under diagnosis of UTI, particularly in fit, healthy women with OAB.