In Clinical Practice

Bob Yang · Steve Foley
Editors

Female Urinary Tract Infections in Clinical Practice

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Introduction

Urinary tract infections (UTIs) are one of the most common infections worldwide, estimated to affect around 150 million people each year. The "burning issue" of UTIs has been reported as early as 1550 BC by the ancient Egyptians.

UTIs disproportionally affect more women than men. Over 50% of all women will have one infection in their lifetime, of which 20% develop recurrent infections.

Recurrent urinary tract infections (rUTIs), which can be relapses or reinfections, are defined as ≥2 UTIs in a 6-month period or ≥3 infections in a 12-month period.

Fifteen percent of all antibiotics used in humans are to treat or prevent UTIs. The overuse of antibiotics has given rise to the rapid emergence of bacterial resistance. So great is the issue that the World Health Organization has triggered a global action plan, declaring antibiotic resistance as one of the biggest threats to global health in our lifetime.

As a result, there is a pressing need to find alternative antibiotic-free methods in preventing UTIs. This is currently a hot topic in the specialist field of Urology with more and more exciting products becoming available, either targeting the bacteria or enhancing the body's own natural defences.

This pocket handbook we hope will provide an overview for healthcare professionals, students and the scientifically minded members of the public on UTIs in women, from underlying cause to diagnosis, management and prevention.

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Chapter 1
Pathophysiology of UTIs

Emma Duffield and Bob Yang

- **Infection can ascend from external gut/vaginal bacteria or arise from haematogenous spread (latter more rare)**
- **The body has natural chemical, mucosal and physical defence mechanisms to protect from UTIs**
- **Gender, genetics, anatomy, function and comorbidities can all influence an individual's susceptibility to UTIs**
- **Asymptomatic bacteriuria in most cases needs no treatment**
- **Asymptomatic bacteriuria should be treated prior to urological procedures, in immunosuppressed patients or in pregnant women**

1.1 Six Categories of UTIs

Urinary tract infections can be largely categorised into six distinct groups depending on the patient's urinary tract anatomy and previous incidence of infection. These are listed and explained further below:

1. Uncomplicated infection
   A UTI that occurs in an individual with:

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- An anatomically and functionally normal urinary tract.
- Intact host defence mechanisms (i.e. no associated conditions that would hinder the body's natural defences).

2. Complicated infection
   When a UTI occurs in someone with an anatomically abnormal urinary tract or with an external, often obstructive, structure in the tract.

   - Examples of this include calculi, obstruction from an external mass or vesicoureteric reflux (all of which predispose to UTIs).

3. Isolated infection
   This is defined as either the first incident of infection or when infections are separated by a minimum of 6 months (i.e. classified as distinct and unrelated episodes).

   - This type of UTI affects a considerable proportion of young females (25–40%).

4. Unresolved infection
   When a UTI has not responded to antibiotic therapy.

   - This can be due to infection with multiple pathogens (with difficult resistance profiles) or because of single highly resistant UTI-causing bacteria.

5. Reinfection
   Reinfection UTI refers to bacterial persistence despite antibiotic therapy.

   - Unlike unresolved infections, this is due to bacteria residing in places where antibiotics cannot reach or places where the bacteria persist within the urinary tract, rather than because of resistance.
   - Examples of these dwelling places for bacteria include infected stones and urethral/bladder diverticula.
   - There are two ways in which a UTI can be defined as a 'Reinfection'.
     – The first is when a UTI has been treated and, when cultured, the individual's urine initially shows no

growth. However, a few weeks down the line their urine grows the same bacteria that caused the original UTI. This is sometimes called a "persistent infection".

– The second is when the original UTI is treated, but a new organism grows from urine cultures taken post-treatment. The majority of rUTIs in women (95%) occur this way [1, 2].

6. Relapse
   A relapse UTI is when the individual is re-infected with the same organism within 2 weeks of completing treatment of a urinary tract infection.

   • Clinically, it is very difficult to differentiate between a relapse and a persistent infection [3].

1.2 How Do UTIs Occur?

The first step of uncomplicated UTI development is the colonisation of the periurethral region with uropathogens. These could have migrated from the anus (gut bacteria), from the vagina, or have been introduced externally (e.g. during sexual intercourse). These microbes inhabit the distal urethra and ascend towards the bladder [4]. Once in the bladder, the uropathogen uses specialised bacterial appendages (flagella and pili) and expresses adhesins in order to attach to and invade the most superficial cells of the bladder wall, the urothelium [5–7]. At this point the body's immune system kicks in; neutrophils infiltrate the bladder and start clearing the bacteria.

Either through invasion into host cells or resistance, some bacteria are able to evade the immune response and proliferate in the bladder wall, forming biofilms. They use the nutrients within invaded host cells to survive and multiply [8]. All the while, the proteases and toxins they produce cause damage to urothelial cells [4]. At this point the symptoms of a UTI become apparent—i.e. the burning/stinging

on micturition, even haematuria (blood in urine) in some cases.

The substances released by these damaged cells may promote further ascension to the kidneys. Bacterial toxins may also play a role by inhibiting ureteric peristalsis and thereby reducing the risk of being washed away by urine flow [5–7].

When uropathogens reach the kidney, they continue to produce toxins and cause cell damage [4]. The consequent inflammatory response by the body is called pyelonephritis. Pyelonephritis mostly occurs due to ascension from the bladder, but can be caused by haematogenous spread. If the inflammatory response is on-going it can cause tubular obstruction leading to interstitial oedema. This has the potential to progress to interstitial nephritis and acute kidney injury [5–7].

If untreated or improperly managed, UTIs can spread across the tubular epithelial barrier into the bloodstream causing urosepsis [4].

1.3 Natural Defences

The vast majority of UTIs are caused by bacteria [9, 10]. Even a healthy individual will exhibit some colonisation of the periurethral region. However, not all of this colonisation will lead to a urinary tract infection. The body has developed mechanisms of defence against microbial invasion.

Healthy urine has a high osmolality and an acidic pH [9, 11] making it a less hospitable environment for pathogens. UTI-causing micro-organisms prefer a more neutral pH and, when they proliferate, will change their environment so it is more suitable for further growth of their population—a urine pH of greater than or equal to 7.5 generally indicates UTI [12].

In a similar vein, the acidic environment of the vagina protects against colonisation and consequent urogenital infections. *Lactobacillus* is a naturally occurring coloniser of the vagina and keeps the average pH below 5; a low enough level

to prevent rapid bacteria proliferation and cause disruption to the adhesion of *E. coli* [12]. *Lactobacillus* thrives in high-oestrogen environments (i.e. younger women rather than post-menopausal). This will be discussed further in the risk factors section of this chapter.

There is also the aspect of mechanical defence against UTIs. The flow of urine produced during micturition can physically flush out any harmful microbes present in the tract [11]; this is why those with UTIs are advised to drink plenty of water. Another physical barrier is the vesicoureteric valve that acts as a blockade to ascending infection [9].

In terms of mucosal immunity, a number of defensive mechanisms exist. The urothelium itself secretes chemokines, cytokines and mucosal IgA to fight off invading pathogens. A mucus-like protective glycosaminoglycan (GAG) layer lines the inner wall of the bladder and prevents toxins from reaching epithelial cells, thereby preventing cell damage and bacterial invasion [11].

1.4 What Are the Risk Factors and Why?

Despite sophisticated defence mechanisms, infections can still occur. Certain individuals are more likely to develop UTIs than others. This can be due to a range of risk factors.

1.5 Gender-Related

Females have a shorter urethra than males. This means there is a shorter urethral distance for pathogens to travel to reach the bladder and so predisposes women to UTIs [6]. On top of this, high exposure to anal pathogens can increase risks of UTIs. This could be due to faecal incontinence or sexual practices. Twenty-five percent of women who present with cystitis will have a recurrent episode in the next 6 months [8].

Use of antibiotics in women can alter the vaginal flora and allow the overgrowth of bacteria, increasing risk of infection [9]. Frequent or recent sexual intercourse is also a risk factor (in women) through the introduction of external bacteria [8]. Spermicide-coated diaphragms and condoms can cause mucosal irritation and provide potential attachment sites for uropathogens, aiding in their invasion [5, 6].

In young women, high levels of oestrogen encourage the formation of non-pathogenic *lactobacilli* colonies. *Lactobacillus*, the commensal vaginal bacterium thrives on oestrogen stimulation to proliferate and keeps the vaginal pH microenvironment acidic via the synthesis of lactic acid. This inhibits pathogenic growth. Post-menopause, the lower levels of circulating oestrogen leads to an increase in vaginal pH due to both a lack of *Lactobacilli* and a general loss of vaginal architecture and moisture. Consequently, the environment becomes more hospitable for harmful UTI-causing bacteria such as *E. coli*. This means post-menopausal women are more susceptible to these infections [13].

1.6 Functional

Once in the bladder, microbes reside in the urine until they attach themselves to the urothelium. When the bladder voids completely, it flushes out the pathogens in the urine. An inability to fully empty the bladder puts an individual at increased risk of suffering from a UTI. Incomplete voiding can be due to developmental abnormalities in the urinary tract (e.g. VUJ reflux allows pooling of urine and can facilitate ascension to the kidney [5, 6]), age-associated anatomical changes (e.g. strictures and pelvic organ prolapse) or functional loss (e.g. nerve damage, stone obstruction). Pregnancy can also cause impaired bladder emptying [9] through progesterone-mediated relaxation of smooth muscle in the bladder and ureters, and through physical compression by the enlarged uterus [5, 6].

1.7 Disease-Related/Iatrogenic

Diabetes increases the sugar levels in the urine making it a good environment for bacterial proliferation (plenty of sugar to use as a bacterial energy source). Immunosuppressive conditions such as HIV/AIDS, or drugs that decrease the body's immunity also increase the risks of UTI as neutrophil infiltration at the attachment stage is reduced [8].

Those who have had recent instrumentation (cystoscopy, catheter, stent placement) or surgery to the urinary tract are at increased risk of UTIs via introduction of external pathogens into the system [9, 10].

1.8 Genetic

A strong family history (particularly in first-degree relatives) of recurrent UTIs suggests genetic factors can influence an individual's susceptibility [5, 6]. Theories include decreased physiological IgA secretion by uroepithelial cells and specific vaginal mucus properties that are less inhibitory to binding of uropathogens [5, 6].

Studies have looked into genetic polymorphisms and their impact on defence mechanisms against UTIs, in particular receptors involved in the inflammatory response to infection [14]. Toll-like receptors and their signalling pathways play a big part in detecting infection and coordinating the subsequent pro-inflammatory response. This process occurs when these receptors are activated through their binding to virulence factors from uropathogens (e.g. Type 1 and P fimbriae) [15]. This sets off a cascade of signals that results in the inflammatory immune response, release of cytokines and activation of neutrophils.

In a study looking at 1261 women (aged 18–49) with asymptomatic bacteriuria, it was found that certain polymorphisms relating to the receptors driving this inflammatory response were associated with higher levels of asymptomatic

bacterial colonisation, which in itself is a risk factor for UTI development [16]. Other studies have had similar results [17]. This supports the theory that a genetic component to UTI susceptibility exists.

1.9 Asymptomatic Bacteriuria

The diagnosis of UTIs is through clinical assessment and analysis of midstream urine microscopy, culture and sensitivities (MC&S)—urine dipsticks are unreliable and are not gold standard for diagnosis. However, bacteria may be present in the urine in the absence of symptoms; it is thought that around 10% of men and 20% of women aged over 65 have asymptomatic bacteriuria [18]. NICE defines asymptomatic bacteriuria as '*Bacteria in a urine sample taken from a person who does not have any of the typical symptoms of lower or upper urinary tract infection*' and specify that this should be confirmed by two consecutive urine samples [18].

As discussed earlier, peri-urethral colonisation is common and, provided the individual has functioning host defences, most cases of asymptomatic bacterial colonisation in the urine self-resolve without the need for treatment. However, in those with decreased defences and at high risk for UTIs (pregnant women, instrumentation, immune-suppression etc.) asymptomatic bacteriuria is a risk factor for development of a UTI.

For those with bacteriuria and clinical features of a UTI, the aim and outcome of treatment is for bacterial eradication and symptomatic relief. Asymptomatic bacteriuria can also be treated to prevent future infections, but it must be stressed that the vast majority of cases do not require antibiotic therapy. According to NICE guidelines, asymptomatic bacteriuria should not be treated in non-pregnant women or in those who have a catheter [18].

However, in the presence of risk factors (e.g. pregnancy, immunosuppression, planned surgical instrumentation) asymptomatic bacteriuria should be treated in order to minimise the risk of it developing into symptomatic infection or even urosepsis.

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Chapter 2
Presentation and Diagnosis

Bob Yang and Steve Foley

- **Classical symptoms: dysuria, frequency, urgency, lower abdominal pain**
- **Assessment of a patient with recurrent UTIs includes taking a history, examination (including pelvic examination for prolapse and vaginal health assessment), urine dipstick, urine MC&S**
- **Mid-stream urine is the gold standard for urine MC&S—minimises skin/vaginal contamination**
- **In patients with recurrent UTIs, cystoscopy usually shows no pathology and its' use should be in targeted patient, for example if there is a suspicion for cancer**
- **Urine dipstick can provide a result within 2 min. The presence of leucocytes has a sensitivity of 50–95% in detecting infections. The presence of nitrites almost certainly means the presence of infection, but has a sensitivity of only 35–85% as not all bacteria's form nitrites in urine**.

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2.1 Clinical Symptoms

The classical symptom of a UTI is cystitis—a group of symptoms including dysuria (pain on passing urine), frequency (urinating often), and urgency (strong sudden desires to urinate, sometimes with difficulty in reaching the toilet) with lower abdominal pain. In general systemic symptoms are mild or absent in cystitis. The urine itself may appear odorous or cloudy.

Diagnosis often is made on symptoms alone, with more symptoms associated with a higher chance of confirming an underlying infection [1, 2].

2.2 History

It is important when taking the patient history to determine the frequency of infections. Three or more infections in 12 months would warrant a diagnosis of recurrent UTI. Voiding patterns and behaviour (e.g. volume of urination, how much fluid intake, does it occur more commonly in the day or night, after certain activities or is associated with any incontinence) is key in assessing for evidence of voiding dysfunction.

A good past medical history is key in determining risk factors such as menopause, diabetes or stone disease. In particular, check the patient has not had previous pelvic surgery that may predispose them to infections.

Sexual history is important, vaginal itching or discharge is a positive predictor for Sexually Transmitted Infections (STIs) and actually has been shown to be a negative predictor for UTIs.

2.3 Examination

As these examinations involve intimate parts of the patient, it is good practice to offer a chaperone to your patient.

Abdominal examination is important to assess for suprapubic or flank tenderness. At the same time, it is important in the abdominal examination to feel for and exclude a palpable kidney (caused by hydronephrosis, cysts, tumours, etc.) or a full bladder.

Vaginal examination is to assess for generalised vaginal health—in particular fluid, moisture, discharge, pain and elasticity to assess for evidence of atrophy, menopause or STIs.

Pelvic organ prolapse can also be assessed at this stage, which may cause patients difficulty in fully emptying their bladder and pre-dispose them to infections.

2.4 Urine Analysis

Patients should be advised to perform a mid-stream urine "clean" catch. This involves good hand hygiene, cleaning the genitalia with water, holding open the labia (skin around the urethra which is the exit to the bladder and vagina) and catching the mid-portion of the urine having discarded the initial flow. This technique will minimise the chance of urine contamination from the skin or vagina.

Urine dipstick: A urinary dipstick analysis is a quick way to assess for the presence of urinary blood, leucocytes, nitrites and detect the pH of the urine. After dipping the dipstick in the urine, results are available within 2 min and can help the clinician determine if there is an underlying UTI.

- Blood: Haemoglobin from the red blood cells can occur in the urine during UTIs from the inflammation of the bladder lining. In severe infections with extensive inflammation, there can even be bleeding heavy enough to turn the urine visibly red (visible haematuria). Haemoglobin reacts when it comes into contact with the indicator on the dipstick.
  - However the presence of menstruation, intrinsic renal disease, urinary malignancy, stones, severe exercise and dehydration can give a false positive reading when no infection is actually present.

- Leucocytes: The present of white blood cells in the urine is defined as **pyuria**. Neutrophils are present in infected urine and produce an enzyme (leucocyte esterase), which reacts with the dipstick to change colour. **This takes reaction can take up to 2 min,** thus it is important appropriate time is given to allow for this reaction to fully occur when dipping the urine.
  - The presence of urinary white blood cells in the absence of bacteriuria (bacteria in the urine) is termed **sterile pyuria**. This can be seen in bladder cancer (in particular carcinoma *in situ*), urinary tract stones and interstitial cystitis but also in partially treated UTIs and atypical organisms including tuberculosis and shistosomiasis.
  - The sensitivity of leucocytes in detecting infection is 50–70%.
- Nitrites: Gram-negative bacteria's are the most common type of UTI causing bacteria, in particular *E. coli*. They can convert urinary nitrates into nitrites. These are detected on dipstick (via a reaction to form a red azo dye).
  - If this test is positive, it is very specific for infection (specificity 92–100%). Therefore if a patients' urine is nitrite positive, it is almost certain that bacteria is present.
  - However the sensitivity is only 35–85% as many UTI causing bacteria's are not able to convert nitrates into nitrites.
- pH: Normal urine ranges between 5.5 and 6.5. Alkaline urine (higher pH levels then normal) suggests the presence of ammonia creating bacteria (*Proteus*, *Klebsiella*, *Pseudomonas*).
  - The urease enzyme produced by these bacteria splits the urea in urine into carbon dioxide and ammonia, which then raises the urinary pH.
  - This also increases the risk of urinary tract stone formation, which can become a nidus for persisting infections.

Microscopy, Culture and Sensitivity: The standard diagnostic investigation for detecting the causative organism is urine microscopy, culture and sensitivity (MC&S). As mentioned above, the detection of bacteria in the urine is defined as **bacteriuria**. This test will also provide answers to which antibiotic the bacteria are sensitive to, thus allowing for an appropriately targeted antibiotic to be prescribed.

A urine culture containing a bacterial count $>10^5$/ml is deemed diagnostic for a UTI. However levels between 10^2 and 10^4 have now been shown to be associated with active infection. One reason for the lower levels is due to increased voiding of urine during infections due to the bladder irritation washes out bacteria within the bladder, thus can produce a deceptively lower level.

Urine MC&S is recommended in cases of recurrent UTIs and complicated infections.

2.5 Further Investigations

Urological imaging will be discussed in the next chapter.

Urine flow studies: Flow rate (how fast urine can leave the patient's body) and post void residuals (how much urine is left in the bladder after voiding) are essential measurements. A strict fluid diary (where a patient charts their fluid intake and urine volume over 3 days) is an invaluable tool to assess the patient. The patients can often surprise themselves with how little fluid they actually drink per day.

- Urodynamic studies are more invasive and involve a small catheter sitting in both the bladder and rectum of the patient during the study. The bladder is then slowly filled and when appropriate, the patient is asked to pass urine. This test provides vastly more information than normal flow studies, but in cases of recurrent UTIs, will often be normal if performed on every patient and therefore is a waste of resource but also put the patient through an unnecessary invasive test. Instead, this test should only be ordered by urological specialists and used in targeted patients, especially in cases where a neuropathic bladder is suspected.

Cystoscopy: A small flexible camera can be inserted into the bladder to see the inner lining of the bladder directly under local anesthetic. Whilst easy to perform with minimal complications, it is nevertheless an invasive investigation with a risk of infection. Its use should again be utilised in a targeted manner, especially in cases of unexplained persistent visible or non-visible haematuria where a bladder lesion needs to be excluded. Furthermore, evidence of urinary obstruction or a fistula (an abnormal connection between the bladder and bowel or bladder and vagina) would also warrant a flexible cystoscopy to aid in confirming the diagnosis.

- Studies have reported the chance of finding any significant pathology on cystoscopies range between 0% and 8% in cases of recurrent UTIs. Where an abnormality was found, the patients were generally over 50 years old [3, 4].

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Chapter 3
Role of Imaging in UTIs

Safia Rehman and Archie Speirs

Abbreviations

CT	Computed tomography
CTU	CT urography
IVU	Intravenous urography
MRI	Magnetic resonance imaging
RCS	Renal cortical scintigraphy
US	Ultrasound

- UTI is mainly diagnosed by a typical history with positive urinalysis result.
- Routine imaging is not required for the diagnosis of uncomplicated UTI in adult patients.
- The role of imaging is mainly in complicated UTI where it aids in identifying the extent of disease as well as any associated complications.

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- Ultrasound is usually the first line imaging modality for investigation of complicated, recurrent and atypical UTIs. It is readily available, cheap, easy to perform and does not involve ionising radiation or use of contrast medium.
- CT Urography (CTU) has become an important imaging modality for complicated UTIs.

3.1 Introduction

The diagnosis of urinary tract infection (UTI) in adults is primarily based on a typical presentation with urinalysis findings suggestive of UTI. In general, routine radiologic imaging is not required for diagnosis and treatment of uncomplicated cases in adult patients. Appropriate imaging not only defines the extent of disease but also identifies significant complications. This may help in treatment adjustment. It can also guide the interventional radiologist in planning the management of pyonephrosis and abscess [1].

3.2 Diagnostic Indications

Radiological evaluation is required in cases where there is [2]:

- Failure of response to conventional therapy.
- Recurrent or unusual presentation.
- Diagnostic uncertainty in critically ill patients.
- Suspicion of complications.
- Possible previously occult structural or functional abnormalities that may require intervention.
- Increased susceptibility for more severe life-threatening complications e.g. diabetics, elderly or immunocompromised patients.
- Need to characterize the severity of the infection to direct future therapy or intervention.
- Need to evaluate the extent of organ damage following an episode of a resolved acute UTI.

3.3 Imaging Modalities

In the past, ultrasound (US) and plain radiographs have been used with intravenous urography (IVU) in the evaluation of patients suspected of having complicated UTI. They allowed detection of calculi, obstruction and incomplete bladder emptying. Their role however was limited in the evaluation of renal inflammation and infection.

Ultrasound may detect congenital anomalies, hydronephrosis, parenchymal abnormalities such as scarring or cysts, perinephric collections, ureteral dilatation, bladder wall thickening, ureteroceles and calculi [1].

- The urinary bladder should always be imaged with measurement of post-void residual urinary volume and bladder wall thickness to estimate outflow obstruction.

Computed Tomography (CT) has now become the main modality for the diagnosis and follow-up of complicated UTI.

- CTU is performed in different phases of excretion after intravenous contrast medium administration. It not only defines the extent of disease but also identifies significant complications.
- The disadvantage of CT is that it exposes the patient to radiation and involves the administration of iodinated contrast medium with its possible side effects [1].

Magnetic resonance imaging (MRI) is becoming more common especially in patients with iodinated contrast allergy. It also enables multiplanar acquisition like CT but avoids ionising radiation exposure.

- There are, however, potential pitfalls related to MRI. Gas-forming infections and calculi can cause signal voids which are difficult to interpret. While these are rare in children, they are common in adults and can limit the value of MRI. It is also expensive and requires IV contrast administration. Because of cost restraints, availability limitations and length of scanning; MRI is not routinely used.

- It is mainly used as problem solving tool or where other imaging modalities are unsuccessful or unsuitable [1].

Radionuclide imaging can be used in adults to assess renal function with renography (e.g. using 99mTc-DTPA or MAG3).

- Renal cortical scintigraphy (RCS) using 99mTc-DMSA is limited to use in scar and acute pyelonephritis detection.
- Conventional (VCUG) or radionuclide (RNC) voiding cystourethrography can detect vesico-ureteric reflux (VUR) and aids in differentiation of outlet obstruction [1].

Guidelines have varied over the years due to the changes in accessibility of different modalities and attitudes towards ionizing radiation exposure. Imaging modality choice is dictated by a number of factors e.g. local availability and expertise, renal function, patient's age and local expertise, and patient factors [1, 3, 4]. Repeated follow up in such cases is usually not required unless there is a new indication.

3.4 Uncomplicated UTI

These patients are usually managed with a course of antibiotics or their symptoms self-resolve and thus imaging for an uncomplicated UTI is unnecessary. Current guidelines state that females should be imaged if they suffer three or more UTIs in a 12 months' period [4]. Imaging has an important role in diagnosis, especially in atypical presentations.

3.5 Complicated UTI

Imaging is indicated when patients respond poorly to appropriate antibiotic therapy after 3 days. Women aged 60 or above with recurrent or persistent unexplained UTI should be considered for bladder cancer workup.

Women with recurrent UTI who have risk factor for an abnormality of the urinary tract should also be referred for specialist review [4]. These risk factors include:

- Prior history of urinary tract surgery or trauma.
- Bladder or renal calculi.
- Obstructive symptoms such as straining, hesitancy, poor stream.
- Urine culture positive for urea splitting organisms with increased predisposition for urinary calculi.
- Persistent bacteriuria despite appropriate antibiotic treatment.
- History of abdomino-pelvic malignancy with symptoms suggestive of urinary fistula.

Surgical candidates with a known abnormality of their renal tract e.g. cystocele, vesicoureteric reflux, or bladder outlet obstruction [5] should also be imaged appropriately.

3.6 Imaging Findings in Acute UTI

3.6.1 Cystitis

The differentiation of cystitis from pyelonephritis is mainly clinical with patients having upper tract infection being more severely ill. Imaging may occasionally be required to differentiate upper and lower tract infection if it will affect management. Poor bladder emptying can usually be diagnosed with US and flow rates. US also assesses wall thickness and post-void residue. Floating debris or sediment may be seen on US. In cystitis, a trabeculated wall may be seen at IVU and post-void residue in cystitis [1]. CT will not only the wall thickness, adjacent inflammatory changes as well as presence of calculi and wall calcifications can be assessed on CT.

Emphysematous cystitis is a rare and potentially fatal condition occurring invariably in the diabetic patients. The gas produced by the microorganisms dissects within the bladder wall and can be identified on plain radiographs, US and CT. The various types of cystitis (cystitis cystica, cystitis glandularis, and eosinophilic cystitis) require pathologic diagnosis. Tuberculous and schistosomal bladder infection in acute phase produces nonspecific bladder wall thickening and

ulceration. The history of immunosuppression and origin from endemic areas is important considerations [2].

3.6.2 Pyelonephritis

Majority of the cases of pyelonephritis in young and healthy women are uncomplicated and thus do not need imaging [3]. Imaging seldom leads to changes in management and is thus not routinely used. The role of imaging is in the detection of complications where early intervention is of crucial importance. Helical CT, MRI and RCS appear to be equally sensitive for detecting acute pyelonephritis with US being significantly less accurate. Contrast enhanced CT is superior to IVU and US in detecting parenchymal abnormalities, delineating disease and detecting complications [1]. US however still remains the primary choice of imaging in most cases of suspected upper UTI due to its lack of harmful radiation, easy accessibility, and low cost. CT scan should be considered as second-line imaging modality [2]. Pregnant women with possible acute pyelonephritis. However, differentiating physiological from significant pelvicaliectasis can be difficult. US may fail to show any abnormalities, despite abnormalities documented at CT.

Unenhanced CT can detect calculi, gas formation, haemorrhage, parenchymal calcifications, obstruction, renal enlargement and inflammatory masses; although the kidneys themselves often appear normal. Low attenuation ill-defined wedge-shaped area radiating from papilla to the cortical surface, with or without swelling and with poor corticomedullary differentiation is typical. US may also show focal, poorly marginated hypo- or occasionally hyperechoic areas, caused by interstitial oedema and/or haemorrhage. However, the sensitivity is poor when compared with contrast enhanced CT. In adult patients, renal scarring and functional impairment following acute pyelonephritis are rare and CT is almost as sensitive as scintigraphy in detecting abnormalities of acute pyelonephritis [1]. RCS is limited in the assessment of anatomy and complications.

There is limited experience of MRI in acute pyelonephritis, however it can be invaluable tool where there is contraindication to use of iodinated contrast. MRI is superior in delineation of anatomic details and assessment of signal changes due to presence and distribution of oedema. There is usually low signal intensity on T1-weighted images and increased signal intensity on T2-weighted images in the affected area, with loss of corticomedullary differentiation. MRI can also provide immediate information about the presence of chronic scars versus acute infection, an advantage when compared with RCS where one has to wait for months. Renal MRI potentially offers a cost-effective and radiation-free alternative in the radiological evaluation of pyelonephritis. Combination of different sequences allow comprehensive assessment of renal infection and its complications [1].

3.6.3 Hydronephrosis and Pyonephrosis

In the past, IVU was used for assessment of obstructive uropathy. US is a sensitive detector of pelvicalyceal dilatation. It can also detect calculi at the vesicoureteric and pelviureteric junction but not elsewhere and is unable to assess normal ureters. When pyonephrosis is present, US may show echoes secondary to gas-forming organisms or echogenic material in the collecting system. There can be a urine debris level, but usually the features are those of simple hydronephrosis. In acute obstruction calyceal dilatation may be minimal and US can be misleading. Both air and calculi appear echogenic on sonography, therefore radiographs may be required to differentiate between the two [1].

CT is the investigation of choice in adult hydronephrosis as it depicts hydronephrosis and often the underlying cause; however, pyonephrosis is difficult to distinguish from uninfected hydronephrosis. Unenhanced CT has an accuracy of 97% in the detection of ureteral calculi and can also diagnose obstruction. However Contrast-enhanced imaging is more desirable as it allows the assessment of parenchyma and function can be performed with contrast enhanced excretory phase study [6].

When hydronephrosis becomes infected, it is a urological emergency and urgent intervention is needed in order to prevent permanent loss of function and life-threatening bacteraemia [1]. It can be treated with retrograde stent insertion which requires theatre and often general anaesthesia. Although some experts can perform it under local anaesthesia in women. Imaging guided (CT, US or fluoroscopy) aspiration or percutaneous nephrostomy (PCN) placement is an alternative option [7]. These aspirates also need to be sent for culture and sensitivity analysis since there may be discrepancy between the aspirate and urine result. Decompression of the system not only drains the infected urine but also helps in increasing the renal plasma flow and delivery of antibiotics locally. This is also a useful measure for stabilisation of the patient so that elective definitive surgery can be performed, if needed. Following antibiotics and drainage, recovery of renal function following antibiotics and drainage [1].

3.6.4 Pyonephrosis

Early diagnosis of pyonephrosis is important for a timely intervention. On US, one can look for pelvicalyceal dilatation, echogenic debris or fluid-fluid levels within the collecting system and occasionally the incomplete (dirty) echoes of collecting system gas. Echogenic debris (i.e., the lack of a completely anechoic collecting system) is the most reliable sign of pyonephrosis [2]. Pelvic and ureteral wall thickness, renal enlargement, parenchymal or perinephric inflammatory fat stranding and a striated nephrogram can occur in both pyonephrosis and obstructive uropathy, although in pyonephrosis changes should be more severe. Renal pelvic wall thickening (2 mm) has a sensitivity of 76% for pyonephrosis. Thickening of the fascia and bridging septa are also nonspecific. Fluid–fluid levels and gas within the collecting system may occasionally be seen. As in the case of sonography, presence of gas within the collection system in the absence of instrumentation, is the most accurate indicator of presence of infected fluid [1]. The collecting system fluid may be of higher

than usual attenuation values and the contrast material may layer above and anterior to the purulent fluid on excretory studies. However, again the fluid attenuation measurements are not helpful in differentiation from hydronephrosis. MRI offers little over CT. It also demonstrates findings similar to those seen at CT. Dilated pelvicalyceal system, debris within the system, and fluid-fluid levels are often present [2].

3.6.5 Renal Abscess

On US, abscesses appear as hypoechoic or anechoic complex masses. Loculations and septations may also be present. The differentials include hemorrhagic cysts, multilocular cysts, cystic neoplasms or infected cysts on US. CT is the most accurate modality for the diagnosis and follow-up of abscesses. Early abscesses appear as peripheral cortical lesions and are small wedge-shaped or rounded areas of hypoattenuation on CT. They are irregular, poorly marginated and hypoenhancing. A mature abscess is sharply marginated with peripheral enhancement [1]. Presence of gas within an inflammatory abscess is an uncommon finding but is strongly suggestive of an abscess. Subcapsular or perinephric extension can be clearly delineated on CT. On MRI, they are of heterogeneous low signal intensity on T1-weighted imaging and increased inhomogeneous signal on T2-weighted imaging. Extension beyond the renal capsule can be accurately assessed with MRI [1].

Small abscesses may respond to conservative treatment with antibiotics and resolve. Those failing to respond require percutaneous drainage under US or CT guidance, which may be curative in up to two-thirds of patients (even with perinephric extension). Multiple drains can be placed, if necessary. Even if they are not curative, they allow stabilisation of the patients for surgical planning. After acute pyelonephritis, small cystic fluid collections without wall thickening or rim enhancement may be seen. These may require CT-guided aspiration in order to differentiate them

from true abscesses [7]. In the past, renal abscesses were treated with surgical debridement, drainage, and nephrectomy. With the advent of effective antibiotics and percutaneous techniques, these are now reserved for occasional complicated and unresponsive cases [8].

3.7 Imaging in Recurrent UTIs

3.7.1 Chronic Pyelonephritis

The imaging findings are characterised by renal scarring, atrophy and cortical thinning. The residual normal tissue may hypertrophy forming a pseudomass, the papillae may retract from overlying scar leading to clubbed calyces and the calyceal system may dilate and thicken. All these changes lead to overall renal asymmetry. As with scars elsewhere, there may be dystrophic calcification. Once the radiologic changes of chronic pyelonephritis have been established, repeat imaging is not needed unless there is a new indication [2].

3.7.2 Urinary Tract Tuberculosis

Urinary tract is the most common extrapulmonary site of tuberculosis, most commonly via hematogenous seeding. Progressive infection with granuloma formation, caseous necrosis, and cavitation can ultimately lead to the destruction of the whole kidney [8]. The imaging features include pelvi-infundibular strictures, papillary necrosis, cortical low-attenuation masses, scarring and calcification [2]. These changes are not specific but a combination of three or more of these findings is highly suggestive of tuberculosis, even if there is no documented pulmonary disease [10]. Both kidneys are usually involved, although asymmetrically. The calcifications are highly variable e.g. amorphous, speckled or curvilinear patterns; calcium in a parenchymal mass; lobar calcification; or "putty kidney" (calcified thick material filling a dilated collecting system). Some of these could be demonstrated on IVU in the past [1, 8–10].

US has limited use in the evaluation of genitourinary TB. An infiltrating pattern is seen as increased echogenicity due to calcifications, infected debris and/or abscesses. There may be hydronephrosis or pyonephrosis with dilated calyces and a small renal pelvis. CT can not only assess calcifications but also the perinephric extension. This includes extension to peri- and pararenal spaces and/or formation of a psoas abscess [1]. The granulomas can coalesce to form a tuberculoma which may mimic a mass. As the disease progresses, cavities may form which communicate with the collecting system. There may be large caseating granulomas, focal or diffuse cortical scarring, non-function and dystrophic amorphous calcifications. In end-stage disease, a non-functioning small calcified renal remnant is left and autonephrectomy is seen [1].

Collecting system involvement manifests as ulceration, wall thickening and fibrosis with stricturing involving the collecting system. Various patterns of hydronephrosis can be seen e.g. hydrocalyx. Bladder involvement is seen in one-third of genitourinary TB. This is seen as a shrunken bladder with wall thickening. Granulomas can present as filling defects mimicking carcinoma. Calcification, however, is rare and alternate diagnoses like schistosomiasis should be considered in appropriate clinical setting. During therapy, imaging follow up is needed since strictures may develop or worsen on therapy. These may require interventions like antegrade balloon dilatation and stenting.

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Chapter 4
Antibiotics

Yih Chyn Phan and Bob Yang

The common classes of antibiotics used to treat UTIs that clinicians should be familiar with include penicillin, cephalosporin, carbapenems, fluoroquinolones, aminoglycosides, and fosfomycin. These are explored further below and summarised in Table 4.1.

4.1 Trimethoprim

Trimethoprim is a bacteriostatic antibiotic which binds to dihydrofolate reductase and inhibits the reduction of dihydrofolic acid to tetrahydrofolic acid which is an essential precursor in the thymidine synthesis pathway in bacterial DNA synthesis.

- The dosage of trimethoprim to treat UTI is usually 200 mg BD.

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Table 4.1 Summary of antibiotics used in urinary tract infections

Class of antibiotics	Type of antibiotics	Mechanism of action	Commonly used names of antibiotics	Comments
Trimethoprim	Bacteriostatic	Inhibits bacterial thymidine synthesis	N/A	Being a folate antagonist, trimethoprim should not be prescribed for pregnant ladies who are in their first trimester
Nitrofurantoin	Bacteriostatic	Believed to be inhibition of several bacterial enzymes involved in the synthesis of DNA, RNA and other bacterial metabolic enzymes	N/A	Not to be used in pregnant ladies who are in their third trimester as it may induce neonatal haemolysis. Risk of lung fibrosis and hepatotoxicity
Penicillin	Bactericidal	Interferes with bacterial cell wall synthesis	Ampicillin Amoxicillin Flucloxacillin Penicillin V Benzylpenicillin Piperacillin	Contraindicated in patients who have hypersensitivity to penicillin. Encephalopathy is also another rare but serious side of penicillin
Fluoroquinolones	Bactericidal	Inhibits DNA gyrase	Ciprofloxacin Levofloxacin Ofloxacin Moxifloxacin Norfloxacin	Contraindicated if patients have a history of tendon rupture or tendonitis

Aminoglycoside	Bactericidal	Inhibits bacterial protein synthesis	Gentamicin Neomycin Amikacin Tobramycin Streptomycin	Well known side effects of this class of medication are ototoxicity and nephrotoxicity
Fosfomycin	Bactericidal	Inhibits enzyme-catalyzed reaction in bacterial cell wall synthesis	N/A	
Cephalosporin	Bactericidal	Disrupts bacterial cell wall synthesis	First generation: cefazolin, cephalexin Second generation: cefoxitin, cefaclor, cefuroxime Third generation: ceftriaxone, cefotaxime, ceftazidime Fourth generation: cefepime	About 0.5–6.5% of penicillin-sensitive/allergic patients will also be sensitive to cephalosporins
Carbapenem	Bactericidal	Disrupts bacterial cell wall synthesis	Meropenem Ertapenem Imipenem Doripenem	

4.2 Nitrofurantoin

Nitrofurantoin is another bacteriostatic antibiotic. It has several mechanisms of antimicrobial action but none of which is properly and fully understood [1]. However, it is well established that intracellular nitroreductases produce the active form of the drug via reduction of the nitro group; and the resultant active intermediate metabolites bind to bacterial ribosomes and causes inhibition of several bacterial enzymes involved in the synthesis of DNA, RNA and other metabolic enzymes in the bacteria. Patients prescribed nitrofurantoin (especially if for a prolonged course) must be warned of the risk of lung fibrosis and hepatotoxicity. Some guidelines recommend regular liver function screening and chest X-Rays, though discussions at international meetings often feel such surveillance is excessive unless in the presence of new symptoms.

- The dosage of nitrofurantoin to treat UTI is usually 50 mg QDS or 100 mg BD.

4.3 Penicillin

First discovered incidentally in 1928, penicillin works by interfering with bacterial cell wall synthesis through inhibiting the formation of peptidoglycan cross-links in the bacterial cell wall. Without a cell wall which is essential to the survival of some bacteria, bacteria die.

- Typically penicillin based agents used in UTIs are Amoxicillin 500 mg TDS.

However, bacteria have evolved to secrete β-lactamase, an enzyme which inactivates penicillin based agents by using hydrolysis to break the β-lactam antibiotic ring, thus deactivating its bactericidal properties.

The rising incidence of amoxicillin resistance (quoted as high as 50% in certain areas of the UK) has led to the development of co-amoxiclav. This contains a β-lactam drug

called clavulanic acid which is a beta-lactamase inhibitor, thus mitigating the bacteria's ability to inactivate amoxicillin.

- The dosage of co-amoxiclav to treat UTI is usually 625 mg TDS.

4.4 Fluoroquinolones

Fluoroquinolone is a bactericidal antibiotic which works by inhibiting DNA gyrase, therefore, blocking DNA replication [2]. Commonly used fluoroquinolones include ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, and norfloxacin. Patients, in particular athletes, should be warned of the risk of tendinopathy with fluoroquinolones which can occur within hours of initiating treatment and last months after cessation. Tendon rupture is the end result, and principally the Achilles tendon is most affected.

- Commonly Ciprofloxacin 500 mg BD is utilised in the treatment of UTIs.

4.5 Aminoglycosides

Aminoglycosides are natural or semisynthetic antibiotics derived from actinomycetes [3]. It is a bactericidal agent which inhibits bacterial protein synthesis by binding to the 30s ribosome subunit in the bacteria, leading to the misreading of mRNA. This misreading results in the synthesis of abnormal peptides which accumulate intracellularly and eventually lead to bacteria cell death. This class of antibiotics includes gentamicin, neomycin, amikacin, tobramycin, and streptomycin. This class of medications is well known to be associated with ototoxicity and nephrotoxicity. Clinicians need to exercise caution in prescribing this class of drug to elderly patients or patients with renal failure due to nephrotoxicity and when accumulated, the risk of ototoxicity.

- Commonly gentamicin is used as first line and is given according to lean body mass. The dosage varies from 3, 5 to 7 mg/kg depending on indication, disease severity, underlying renal disease and local policies.

4.6 Fosfomycin

Fosfomycin is an old antibiotic agent which was discovered in 1969 and it is a bactericidal antibiotic agent [4–6]. It works by inhibiting an important enzyme-catalyzed reaction in the first and crucial cytoplasmic step of the synthesis of the bacterial cell wall. Due to this unique mechanism of action, cross-resistance is unlikely; and, therefore, it allows fosfomycin to retain significant in vitro activity against many Gram-positive and Gram-negative pathogens.

- The usual dosage of Fosfomycin is 3 g stat.

4.7 Cephalosporin

Cephalosporin has a similar mode of action on bacteria as penicillin, but it is less susceptible to β-lactamases which are produced by bacteria [7]. Commonly, cephalosporins are grouped into "generations" by their antimicrobial properties. Essentially, each newer generation of cephalosporin has significantly greater Gram-negative antimicrobial properties than the preceding generation. The first cephalosporins were designated as first-generation cephalosporins, i.e. cefazolin and cephalexin. The second-generation cephalosporins, i.e. cefoxitin, cefaclor and cefuroxime have more extended-spectrum activity than the first-generation cephalosporins. Third-generation cephalosporins include ceftriaxone, cefotaxime and ceftazidime; while cefepime is a fourth-generation cephalosporin which has a very broad-spectrum activity.

4.8 Carbapenems

Carbapenems is another member of β-lactam antibiotics. Similar to other antibiotics in this class of antibiotics, carbapenems work by disrupting the bacterial cell wall synthesis. Of all the different β-lactams, carbapenems possess the broadest spectrum of activity and greatest potency against Gram-positive and Gram-negative bacteria [8]. Therefore, it is often used as the last line of antibiotics regime. Commonly used carbapenems include meropenem, ertapenem, imipenem and doripenem.

4.9 Multidrug-Resistance Bacteria

Unsurprisingly, in recent years, we have witnessed the rise and spread of multidrug-resistance bacteria such as extended-spectrum beta-lactamases (ESBL), vancomycin-resistant enterococci (VRE) and carbapenem-resistant enterobacteriaceae (CRE) globally [9]. Without any doubt, it is a very serious concern. Therefore, knowledge of the local epidemiology of multidrug-resistant bacteria is key in determining empirical antimicrobial therapy. Furthermore, in order to combat these multidrug-resistance bacteria, clinicians and scientists worldwide are racing against time to find new antibiotics. Several new drugs or drug combinations are being studied or currently in the market include new or old cephalosporins or carbapenems combined with new or old β-lactamase inhibitors, i.e. ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam; new aminoglycosides, i.e. plazomicin; and new fluoroquinolones, i.e. finafloxacin [10, 11]. Cefiderocol, which is a siderophore cephalosporin, is currently being studied to treat complicated urinary tract infections [12, 13]. The preliminary result of this trial is promising. We anticipate the results of this promising trial with much eagerness.

4.10 Antibiotics Prophylaxis

Recurrent UTI is defined as more than two infections in 6 months or three within 12 months. Clinical guidelines from European Association of Urology (EAU) [14] and the National Institute for Health and Care Excellence (NICE) [15] recommend several methods for preventing recurrent UTIs including avoidance of risk factors, vaginal oestrogens, immunoprophylaxis or long-term low-dose antibiotic prophylaxis.

Common long-term low-dose antibiotic prophylaxis regime include **nitrofurantoin 50 or 100 mg once daily, trimethoprim 100 mg once a day,** and **fosfomycin treatment 3 g every 10 days**.

Interestingly, although meta-analyses advocate the use of continuous antimicrobial prophylaxis for 6–12 months for the treatment of recurrent UTIs [16, 17], clinical guidelines usually only recommend a treatment period of 3–6 months. Studies by Price et al. [18] and Ahmed et al. [19] show that nitrofurantoin is superior to other antibiotics; however, it carries a higher risk of adverse events. For example, long-term use of nitrofurantoin could cause lung fibrosis. Therefore, clinicians should always exercise caution and counsel patients appropriately prior to starting them on long-term prophylactic nitrofurantoin.

Alternatively, in patients who have recurrent UTIs and perceived to have good compliance, clinicians could consider this group of patients to self-diagnose and self-treat with a short course of an antimicrobial agent.

Current 2019 EAU guidelines recommend the use of continuous or post-coital antibiotic prophylaxis to prevent recurrent UTIs when non-antimicrobial interventions have failed

- In these cases, it is essential to warn patients of long term side effects.

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Chapter 5
Lifestyle Modifications

Bob Yang and Steve Foley

- **Increase fluid intake—advise to drink 2–3 L/day overall. In patients who drink less than 1.5 L/day, advise an additional 1.5 L to their usual fluid intake per day**
- **Sexual hygiene—increased coital frequency, sexual partners, use of diaphragms and spermicide increase risk of UTI. Advise pre coital genital washing, post coital micturition, wiping front to back**
- **Personal hygiene—advise care when shaving or using products around the genital-urinary region, regular underwear changes and avoid tight fitting undergarments**
- **Voiding—advise techniques to reduce amount of residual urine in bladder post void, including double voiding, pelvic floor exercises and pelvic tilting**
- **Weight loss—higher risk of UTI and pyelonephritis if BMI over 30**

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5.1 Introduction

As with all treatments in medicine, lifestyle modifications is a vital part in preventing recurrent UTIs, yet this is the part often skimmed or skipped over in consultations.

There are many (comparatively simple) measures that can decrease the risk of UTI recurrence. However actual clinical studies on how effective these interventions are is limited in quality due to how heterogonous and multi-factorial the data is.

In real life clinical practice, the lack of side effects means there is little reason not to recommend these behavioural changes and anecdotally, a big difference can be made to rates of recurrence and healthcare utilisation when patients are appropriately counselled on these conservative measures alone.

The current 2019 EAU guidelines recommend the use of behavioural modifications to reduce the risk of recurrent UTIs.

5.2 Oral Hydration

Increasing fluid intake is one of the most common pieces of advice given to patients. The idea behind this is to increase the unidirectional flow of urine through the urinary tract, thus reducing the chance of bacterial migration backwards up into the bladder as well as "flushing away" any bacterial already present. The current British Association of Urological Surgeons (BAUS) patient advice sheet for recurrent cystitis advises 2 L of fluid a day.

A recent study in 2018 showed in 140 premenopausal women with recurrent UTIs who reportedly drank less than 1.5 L/day, increasing their fluid intake significantly improved their recurrent UTIs over the 12 months study period. The authors reported that patients who had an extra 1.5 L added to their usual fluid intake increased the number of times they voided and the volume of urine with each void, and

subsequently reported almost halving the number of UTI episodes, with a longer period of time between each UTI episode [1].

A caveat to this is the risk of over-hydration in the more zealous patients, patients with predominately overactive lower urinary tract symptoms (increasing fluid intake in overactive bladder patients will actually worsen symptoms) or in patients requiring fluid restriction due to other underlying disease, especially renal or heart failure—whereupon advising a significant increase in fluid intake should be done with caution with specialist input.

5.3 Sexual Hygiene

Sexual intercourse and recurrent UTIs have been linked in many studies in the past, with some even suggesting which sexual positions cause the least number of UTIs! However the vast majority of these studies were done in small groups of patients and were further limited by not having a control group and the inability to control environmental/behavioural/other risk factors.

Studies show that the majority of UTIs occur within 24 hours of intercourse, with increased coital frequency (and new sexual partners) increasing the risk of UTIs. In fact a study found that university students had a 2.4 times higher risk of UTIs if they had intercourse 3 days a week compared to students who has been abstinent in the week. For those who had intercourse every day, the risk was reported to be nine times higher than the abstinent group! [2].

Pre and post sex voiding of urine is often advised as a way to prevent UTIs. Though the evidence for this is light, the simplicity of this suggestion and the theoretical benefits it should derive by flushing away any pathogenic contaminant from the bladder means clinicians often advise it. Furthermore before and after coitus, women should be encouraged to clean their genital areas (wiping from front to back) in order to minimise spread of uropathogens from the perianal/vaginal region to

the urethra. If the male partner is uncircumcised, they should also clean under the foreskin to lower the bacterial load present, which may decrease the risk of post-coital UTI.

Finally, the use of diaphragms and spermicides has also been shown to be an independent risk factor for UTIs. The likely cause of this is either due to the diaphragm changing the bladders ability to void; therefore preventing complete bladder emptying or the insertion of the device facilitates the entry and colonisation of bacteria within the urinary tract. Furthermore the diaphragm and spermicide may alter the vaginal flora and microenvironment, weakening the commensal acidic defence against uropathogens [2–4].

5.4 Personal Hygiene

The current BAUS patient advice leaflet suggests avoiding the use of bubble baths, talcum powder or deodorants in the genital area as well as avoiding shaving and waxing close to the vaginal/urethral opening. Other studies advise avoiding douching. Similar to above, the theory is to avoid changing the protective acidic microenvironment of the vagina as well as avoid the direct introduction of uropathogens.

Needless to say, it is important to maintain good personal hygiene and change underwear daily, avoiding tight fitting garments including pantyhose and tights.

Once again, though theoretically these interventions makes sense, the actual evidence for these interventions are lacking but the lack of harm in their suggestion means they are often quoted by clinicians.

5.5 Voiding

Any significant amount of urine left in the bladder after voiding is a risk for infection, and thus conservative measures have often been recommended to reduce this amount. These are:

- Double voiding: encouraging the patient to pass urine multiple times per trip to the toilet to fully empty bladder.
- Pelvic floor exercises: Strengthening the musculature of the pelvic floor will aid in voiding. Pelvic floor exercises (either via the local continence service or physiotherapy service) may help patients void to completion. They are also especially important in patients with dysfunctional voiding such as incontinence. Furthermore, they can help patients who also have an overactive bladder, which can mimic UTI symptoms.
- Pelvis tilting forwards: When sitting on the toilet, tilting the pelvis forwards can help with bladder emptying by straightening the urethra. This involves:
  - Ensuring knees are higher than hips when sat on toilet (a stool underfoot may help)
  - Leaning forwards with elbows on knees
  - Straighten back and bulge out abdomen

5.6 Weight Loss

It is worth briefly noting that clinically obese patients (BMI over 30) appear to be at higher risk of UTIs (and pyelonephritis) than non-obese patients in one study in over 95,000 patients in 2012. However it is difficult to ascertain the cause and effect relationship between the two. Nevertheless, the well-established benefits of weight loss in obese patients means this is a lifestyle modification clinicians should already been actively encouraging [5].

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Chapter 6
Cranberry

Bob Yang and Steve Foley

- **Oral preparations available in various forms—juice, capsules, tablets, powder**
- **Utilises proanthocyanidins within cranberry to prevent bacteria sticking to the bladder lining**
- **Various trials on the effectiveness of cranberry do not uniformly support which type of cranberry product to use**
- **Cochrane review 2012 showed no significant benefit in preventing recurrent UTIs, which superseded the 2008 Cochrane review which did show significant benefit**
- **Huge variability within studies cast doubt on the reliability of the conflicting Cochrane reviews—Therefore Cranberry may still be helpful in preventing uncomplicated UTIs in women**

6.1 Introduction and Mechanism of Action

Cranberry is grown from the shrub Vaccinium Macrocarpon and throughout history, its various forms has been investigated for its' potential to prevent UTIs. Formulations are varied, from juice to tablets, capsules and powder.

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Within cranberry contains proanthocyanidins. Pathogens that cause UTIs often contain P-fimbriae on their surface to help them stick to the lining of the bladder and invade. Proanthocyanidins in theory bind to the P-fimbriae on the surface of uropathogens, in particular *E. coli*, thus inhibiting the bacteria's ability to stick to the inner epithelial cell lining of the bladder wall.

Studies in both *in vitro* [1, 2] laboratory tests and in *in vivo* [3, 4] animals studies have shown a dramatic decrease in bacterial loads when treated with cranberry or a proanthocyanidin derivative and thus opened the door to the introduction of this treatment into clinical practice.

6.2 Clinical Evidence

There have been two Cochrane reviews on Cranberry use in preventing UTIs. Twenty-four trials with 4473 patients overall were investigated in the 2012 review which concluded that there were no significant benefit between cranberry product use and placebo. [Relative risk reduction of 0.86 (95% CI 0.71–1.04).] This was the case in elderly, pregnant women, cancer patients and patients with spinal cord injuries or neuropathic bladders [5].

However the 2008 Cochrane review superseded by the 2012 review actually found a benefit with cranberry products in preventing UTI recurrence. This study included ten trials and found a relative risk reduction of 0.65 (95% CI 0.46–0.90) [6].

However it is worthwhile noting that within each cranberry trial analysed for the Cochrane review showed a lack of standardisation in the type of cranberry product used. High dropout rates were also seen, especially in studies investigating cranberry juice where patients found consuming large volumes of cranberry juice difficult and therefore could not complete the study.

Finally the population of patients on which the conclusions were based were hugely varied. These studies included complex patients with underlying conditions including neuropathic

bladders, spinal cord injury and previous radiotherapy as well as elderly patients and children. On the other hand, the early studies on Cranberry were in uncomplicated UTI groups, in particular women who were otherwise healthy.

Later studies started then to investigate the effect of cranberry in preventing UTIs in increasingly heterogeneous groups of patients.

In the 2012 Cochrane review, 30.3% of the total weight to the calculation of overall risk reduction was from patients with neuropathic bladders or spinal injuries and radiotherapy patients. Only 24.5% were contributed by results from healthy women with recurrent UTIs [7]. This might explain the discrepancy between the earlier and later Cochrane reviews.

Overall, because of the 2012 Cochrane review, the current guidelines from National Institute of Clinical Excellence UK (NICE) do not list Cranberry products as a treatment or prevention for UTIs and the current European Association of Urology (EAU) guidelines states "no recommendation for use can be made".

However the huge variability within all the studies mentioned above means further assessment into the discrepancy between the two high profile meta-analyses is required. The confusion on whether Cranberry (proanthocyanidins) treatment is or is not effective has meant medical professionals still often suggest cranberry as a prophylaxis, especially in uncomplicated cases of recurrent UTIs in women.

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Chapter 7
D-Mannose

Bob Yang and Steve Foley

- **A naturally occurring sugar in human metabolism but is not absorbed into the body**
- **Prevents bacterial sticking to the bladder lining—in particular inhibiting *E. coli* adhesion**
- **2 g d-Mannose dissolved in 200 ml water taken daily for 6 months utilised for prophylaxis**
- **1.5 g Mannocist® (Laboratori Farmaceutici Krymi, Rome, Italy) twice daily for 3 days and then once a day for 10 days used in acute uncomplicated cystitis**
- **d-Mannose can also be used effectively as prophylaxis in combination with cranberry and plant based extracts**

7.1 Introduction and Mechanism of Action

D-Mannose is a monosaccharide simple sugar found within human metabolism. It was originally used in cats, dogs and horses to prevent UTIs in the past. However there are now increasing evidence for its use in humans [1].

D-Mannose is rapidly absorbed into the body within 30 minutes and excreted in the urinary tract where it exerts

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its effect. D-Mannose cannot be stored in the body as it cannot be converted into glycogen.

D-Mannose is thought to work by inhibiting the adherence of the bacteria to the urothelial cells found on the inner lining of the bladder. *E. coli* causes the vast majority of UTIs. This bacterium contains a virulence factor called FimH that aids in the binding of the bacteria to the bladder mucosa lining.

D-Mannose inhibits this binding by mimicking the bladder lining to attract the bacterial instead. This causes the bacteria to bind onto the D-Mannose in the urine instead of the bladder wall, trapping them within the urine itself and subsequently, when the patient voids, both are flushed out and removed.

This has been supported by laboratory based *in vitro* and *in vivo* experiments. In particularly, when rats were injected with D-Mannose, their urine grew significantly less bacteria compared to the control group [2].

7.2 Clinical Evidence

In 308 women, D-Mannose (2 g dissolved in 200 ml of water daily for 6 months) was compared against Nitrofurantoin (50 mg once a day) low dose prophylaxis and placebo. The study found a significant reduction in UTI recurrences with D-Mannose when compared with Nitrofurantoin and placebo with a risk reduction of 0.24 [1].

Smaller studies have also supported the beneficial use of D-Mannose in recurrent UTIs either as a stand-alone prophylaxis [3] or even combined with other non-antibiotic prophylaxis therapies such as cranberry [4] and plant based extracts [5].

A pilot study also found using D-Mannose may be effective in treating acute uncomplicated UTIs. Mannocist® (Laboratori Farmaceutici Krymi, Rome, Italy) is composed of D-Mannose (1.5 g), sodium bicarbonate, sorbitol and silicon dioxide. A 2016 study reported in 43 women with acute uncomplicated cystitis that the use of Mannocist® twice a day for 3 days and then once

a day for 10 days significantly improved cystitis symptoms and achieved UTI resolution, as well as significantly decreasing the risk of recurrence over the following 12 months. This study however was only a small pilot with no control group and the inability to control for the placebo effect, however the provisional results are promising [3].

The EAU guidelines currently state that D-Mannose therapy is **indicative but is not sufficient for a recommendation**. This is due to a lack of any high quality data. The EAU guidelines currently suggest the use of D-Mannose only within the frame of high quality clinical investigations.

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Chapter 8
Methenamine Hippurate (Hiprex)

Bob Yang and Steve Foley

- **Two active components—Methenamine salts which are hydrolysed to formaldehyde and hippuric acid which acidifies the urine**
- **Cochrane review 2012 showed Hiprex is effect in preventing recurrent UTIs**
- **Short term courses (1 week or less) also effective in decreasing number of symptomatic UTIs**
- **Hiprex is ineffective in the background of neurogenic bladders or patients with urinary tract abnormalities**
- **Hiprex is prescribed as 1 g twice a day for adult patients. If the patient has a catheter, this can be increased to three times a day.**

8.1 Introduction and Mechanism of Action

Since as early as the 1970s, Methenamine hippurate (Hiprex) has been used in the prevention of recurrent urinary tract infections [1]. Hiprex works via two pathways [2].

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- The methenamine salts component of Hiprex is excreted in the kidneys, whereupon a process called hydrolysis occurs, forming formaldehyde, a compound with bacteria killing properties.
- The Hippuric acid component of Hiprex are also excreted by the kidneys, causing urine to turn acidic, which can either kill or neuter the bacteria within it
- The acidic urine also provides the optimal environment to promote and increase the hydrolysis of the methenamine salts.

8.2 Clinical Evidence

Many small studies in pre and post-menopausal women have shown a beneficial effect of Hiprex as a method in preventing recurrent UTIs. Though when compared with antibiotic prophylaxis, Hiprex has been shown to be inferior to low dose nitrofurantoin (50 mg twice a day) but similar in efficacy to low dose trimethoprim (100 mg once a day) [3, 4]. In recent years, the use of Hiprex has lessened, though no overt reason for this is known.

There has been one large Cochrane review in 2012 [5]. This included 13 randomised control trials (RCTs) and involved 2032 patients. The review found:

- Hiprex reduced the risk of developing further recurrent UTIs episodes in symptomatic patients [relative risk reduction 0.24 (95% CI 0.07–0.89)].
- In patients with bacteriuria, Hiprex reduced the risk of developing further bacteriuria [relative risk reduction 0.56 (95% CI 0.37–0.83)]

When used as a short-term course (1 week or less), Hiprex was also found to be effective in reducing the number of symptomatic UTIs [Relative Risk reduction 0.14 (95% CI 0.05–0.38)].

Furthermore, the review reported that in the presence of neurogenic bladders or any underlying renal tract abnormali-

ties Hiprex was ineffective in preventing further UTI episodes. However the overall patient numbers were small so the strength of this conclusion is limited.

Overall, there were minimal adverse events or side effects were reported, and when also considering how easy it is to use, anecdotally, Hiprex is utilised in clinical practice in normal bladders, anatomical abnormalities and neurogenic bladder patients alike.

Currently the British National Formulary states Hiprex is to be prescribed at a dose of 1 g twice a day for adult patients. This can be increased to three times a day if the patient has a catheter. However current NICE guidelines does not list Hiprex as a potential prophylaxis therapy, stating weak evidence for its use.

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Chapter 9
Oestrogen Replacement Therapy

Bob Yang and Steve Foley

- **Loss of protective acidic vaginal environment after menopause due to low oestrogen levels**
- **Oestrogen replacement already in use in treating menopausal symptoms and atrophic vaginitis**
- **Vaginal oestrogen is effective in preventing UTIs—oral oestrogens have not been shown to be effective**
- **Oral oestrogens and vaginal high dose pessaries has shown higher levels of absorption systemically with more side effects**
- **Vaginal cream is effective (e.g. Vagifem 1 tablet daily for 2 weeks, then 1 tablet twice a week—administered vaginally)**

9.1 Introduction and Mechanism of Action

After menopause, oestrogen levels within a women's body decrease. The vagina is normally colonised with *Lactobacillus*, a type of "good bacteria", and their levels are maintained by

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oestrogen. *Lactobacillus* creates lactic acid, thus producing an acidic microenvironment within the vagina, protecting against harmful uropathogens from colonising. The loss of this oestrogen stimulation decreases the levels of *lactobacillus* within the vaginal wall epithelium, and thus the usual low pH acidic environment is lost, increasing the risk of UTIs in postmenopausal women.

Oestrogen replacement therapies are well established in treating menopausal and vaginal atrophy symptoms including dryness and dyspareunia (painful sexual intercourse) and systemic symptoms such as significant hot flushes. Their administration via the vaginal route has been shown both in cream and in ring pessary form to be effective at increasing blood oestrogen levels and combating menopausal symptoms.

9.2 Clinical Evidence

Their use in UTI prevention was reviewed in 2008 by a Cochrane study involving 3345 women. When comparing vaginal oestrogen and placebo, the authors reported vaginal oestrogen was effective at preventing recurrent UTIs, with a risk reduction of between 0.25 (95% CI 0.13–0.50) and 0.64 (95% CI 0.47–0.86) [1].

Preparations vary and often are dependent on clinician preference. Vaginal oestrogen can be applied in cream form (0.5 mg oestriol nightly for 2 weeks followed by twice a week for 8 months or even tablet form, such as Vagifem 1 tablet daily for 2 weeks, then 1 tablet twice a week) or as a pessary (a 12 weekly vaginal ring).

Side effects of vaginal oestrogen usage were mainly vaginal irritation (reported in 6–20% of women). Other side effects reported were breast tenderness, non-physiological discharge, burning and vaginal bleeding or spotting [2, 3].

Vaginal oestrogen replacement is currently recommended by both UK and EAU guidelines as a possible therapy in preventing UTI recurrences.

9.3 Oral Oestrogen

Until the late 1990s, oral oestrogen replacement (hormone replacement therapy) was the normal course of treatment for menopausal symptoms. However, later studies showed that this may actual cause more harm than good in patients, especially due to the significant side effects of high levels of oestrogen in the blood. These include higher risk of thromboembolic events (blood clots in legs, heart, lungs, etc.) and cancer.

Women in particular with underlying breast cancer or previous thromboembolic events should not be given oral oestrogen therapy due to increased risk of disease recurrence [4].

The above Cochrane review found that oral oestrogens did not reduce the risk of recurrent UTIs when used. Thus oral oestrogens are specifically NOT recommended in international guidelines in UTI prophylaxis [1].

From these findings, vaginal therapy gradually became the first line treatment and oral therapies were phased out.

Despite vaginal oestrogen replacement therapies inducing much lower (and safer) increases in blood oestrogen levels, patients with a history of breast cancer and clots often find the use of vaginal oestrogen replacement psychologically challenging.

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Chapter 10
Traditional Chinese Medicine

Cecilia Yu and Bob Yang

- **Traditional Chinese medicine (TCM), has over 2000 years of history of treating UTIs**
- **The Chinese herbal formulas used in treating UTIs are:**
  - ***Ba Zheng*** **(also known as Ba Zheng San UTflow™, 八正片)**
  - ***Er Xian Tang*** **(also known as Er Xian Wan, Menofine™, 二仙片)**
  - ***San Jin Pian*** **(also known as UTIGold™, 三金丸)**
- **A 2015 Cochrane review of TCM for recurrent UTIs found some preliminary supportive data for herbal interventions**
- **The studies were limited by small patient numbers, poor methodology, risk of bias and lack of standardisation in how to prepare the TCM itself**
- **Acupuncture has also shown potential as a prophylaxis for uncomplicated recurrent UTIs and may also reduce post void residuals in women**

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10.1 Introduction and Mechanism of Action

Traditional Chinese medicine (TCM) has over 2000 years of history in treating UTIs with recent research suggesting a potential role in the management of acute UTIs and as prophylaxis for recurrent UTIs.

TCM believes that the kidneys play a central role in the metabolism of the "water" within the body. All subsequent problems of the bladder, ureter and prostate are therefore related to the kidneys. UTIs in TCM are known as Lin Syndrome (淋证), with the main characteristics being painful urination and dribbling. The most common cause is the kidneys failure to regulate the 'dampness' and 'heat' of the bladder. Accordingly, the main treatment principle is to clear heat, remove dampness and promote urination. Chinese herbal formula *Ba Zheng* (also known as Ba Zheng San UTflow™, 八正片), *Er Xian Tang* (also known as Er Xian Wan, Menofine™, 二仙片) and *San Jin Pian* (also known as UTIGold™, 三金丸) have been widely used in China by TCM practitioners or as an over-the-counter formula to treat UTIs.

10.2 Formulations

Below we summarise the formations of *Ba Zheng* (Ba Zheng San UTflow™, 八正片), *Er Xian Tang* (Er Xian Wan, Menofine™, 二仙片) and *San Jin Pian* (UTIGold™, 三金丸).

Please note, there are often variabilities in the actual formation between different TCM practitioners if a bespoke medicine is made (Table 10.1).

10.3 Clinical Evidence

A large review in 2015 identified 542 women (of which 422 were post-menopausal in age) in seven RCTs that investigated the use of TCM in treating both the acute phase of the UTI and its ability to prevent recurrence [1, 2].

Table 10.1 Formulations for *Ba Zheng* (Ba Zheng San UTflow™, 八正片), *Er Xian Tang* (Er Xian Wan, Menofine™, 二仙片) and *San Jin Pian* (UTIGold™, 三金丸)

Er Xian Tang (二仙片)	**Ba Zheng (八正片)**	**San Jin Pian (三金丸)**
Curculigo orchioides Gaertn. (Xian Mao)	Plantago Seed (Che qian zi)	Radix Rosa laevigata Michx. (Jin Ying Gen), Rhizoma Smilax china L. (Ba Qia) Herba Lygodium japonicum (Thunb.) Sw. (Hai Jin Sha) Herba Centella asiatica (L.) Urb. (Ji Xue Cao), Lysimachia christinae Hance (Gold Coin Grass, Jin Qian Cao)
Epimedium grandiflorum var. thunbergianum (Miq.) Nakai (Xian Ling Pi)	Caulis Akebiae (Mu tong)	
Morinda officinalis F.C.How (Ba Ji Tian)	Herba Dianthi (Qu mai)	
Anemarrhena asphodeloides Bunge (Zhi Mu)	Polygonum herb (Bian xu)	
Phellodendron amurense Rupr. (Huang Bai)	Talcum (Hua shi)	
Angelica sinensis (Oliv.) Diels (Dang Gui)	Licorice (Gan cao)	
Taraxacum mongolicum Hand-Mazz. (Pu Gong Ying)	Gardenia Fruit (Zhi zi)	
Viola philippica Cav. (Zi Hua Di Ding)	Rhubarb (Da huang)	
	Juncus effusus pith (Deng xin cao)	

- Three RCT studies involving 282 women looked at TCM versus antibiotics in treating uncomplicated UTIs.
  - The results suggested that TCM had a higher rate of effectiveness in clearing an acute UTI (RR 1.21, 95% CI 1.11–33) than antibiotics and reduced recurrent UTI rates afterwards (RR 0.28, 95% CI 0.09–0.82).
- Two RCT studies involving 120 women compared TCM plus antibiotics versus antibiotics alone.
  - The results showed that that combined intervention was more effective in treating acute UTIs (RR 1.24, 95% CI 1.04–1.47) and resulted in lower rates of recurrent infection six months after the study (RR 0.53, 95% CI 0.35–0.80).

- Three RCT studies compared two different TCM treatments with each other.
  - ***Er Xian Tang*** (Er Xian Wan, Menofine™, 二仙片) was found to be more effective in treating acute infection in 80 post-menopausal women than ***San Jin Pian*** (UTIGold™, 三金丸) (RR 1.28, 95% CI 1.03–1.57)
  - Two RCT studies have showed that ***Er Xian*** treatment was associated with a reduced rate of recurrent infection compared with ***San Jin Pian*** at 6 months in 140 women (RR 0.40, 95% CI 0.21–0.77)

As the majority of study participants were post-menopausal, the results may not be applicable to pre-menopausal women.

Furthermore, the methodology and quality of all seven studies were found to be suboptimal. There were no report on assessor blinding, on allocation concealment, no power calculations or if sufficient numbers were recruited to claim statistical significance. There was significant loss of patients to follow up and there were failures to standardise how the actual TCM was prepared.

Only two of the seven studies mentioned side effects, of which none were reported.

More recently *Bazheng* powder (Ba Zheng San UTflow™, 八正片) has been investigated via a double-blinded trial in China in patients with recurrent UTIs [3]. 122 female patients received either *Bazheng* Powder for 4 weeks or antibiotics for 1 week, followed by 3 weeks of placebo. Clinical cure rate, microbiological cure rate (negative urine culture) and recurrence after treatment were evaluated.

Bazheng was found to be more effective than antibiotics in curing the acute UTI and preventing UTI recurrence, as shown in Table 10.2.

To date, all the clinical studies on the effectiveness of TCM in UTIs were performed in China. Currently a UK based trial in 80 women from the Wessex, South and Northwest London and the Brighton and Hove areas of the Clinical Research Network (CRN) on the effectiveness of

Table 10.2 Comparing the outcomes between Ba Zheng San UTflow™, 八正片 and antibiotic therapy in treating acute UTI and preventing UTI recurrence

	TCM formula Bazheng powder for 4 weeks	**Antibiotics for 1 week, followed by 3 weeks of placebo**
Clinical cure rate by the intention to treat approach	90.2% ($P < 0.05$)	82.0% ($P < 0.05$)
Microbiological cure rate	88.5% (54/61)	82.0% (50/61)
The recurrence rate in recovered patients at the 6-month follow-up	9.1% (5/61) ($P < 0.05$)	14.0% (7/61) ($P < 0.05$)

TCM in the treatment of recurrent UTIs is in the recruitment phase and we eagerly await their results [4].

10.4 Acupuncture

Acupuncture is a branch of TCM where fine needles are inserted at specific pressure points in the body for therapeutic purposes. TCM believes in Qi, a life force that flows through the body. In disease, the flow of Qi is disrupted and thus the correct application of acupuncture is believed to help restore the flow of Qi. Acupuncture is currently available in certain areas of the NHS, especially in chronic pain management and hospice care.

Two clinical studies [5, 6] in Norway have assessed the effectiveness of acupuncture treatment in the prevention of uncomplicated recurrent lower UTIs in adult women.

- The first study [5] was conducted in an acupuncture clinic in Norway in 1998. Sixty-seven women with a history of recurrent lower UTI had either acupuncture, "fake" sham acupuncture or no treatment. Patients were followed for 6 months.

  - In the acupuncture group, 85% were free of lower UTI during the 6-month compared with 58% in the "fake" sham group ($p < 0.05$), and 36% in the control group ($p < 0.01$).
- A further study [6] was also conducted in Norway in 2002 involving 94 women. Patients received acupuncture or no treatment. Outcomes were recorded in two areas. (1) how effective acupuncture was in preventing UTIs over 6 months and (2) residual urine was measured at 2, 4, and 6 months. Acupuncture was administered twice weekly for 4 weeks.
  - Following treatment, 73% of women in the acupuncture group were free of UTIs during the 6-month observation period, as compared with 52% of women in the control group ($P = 0.08$).
  - During the observation period, half as many UTI episodes per person-month occurred in the acupuncture group compared to the control group (RR = 0.45; 95% CI 0.23–0.86).
  - Women in the acupuncture group experienced a 50% reduction in residual urine after 6 months relative to baseline (35.4 vs 18.2 mL; $P \leq 0.01$), whereas women in the untreated group exhibited no significant change in residual urine (35.5 vs 38.8 mL).

Their findings are supportive of a potential role for acupuncture in this field. While more clinical studies are required, acupuncture could well one day be considered as a worthwhile alternative therapy as prophylaxis for uncomplicated recurrent UTI in women.

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Chapter 11
Intravesical Therapies

Cecilia Yu, Bob Yang, and Steve Foley

- **Antibiotic intravesical instillations can be used in the prevention of UTIs. The use of gentamicin, neomycin/polymyxin, neomycin and colistin has been reported in literature.**
- **Non-antimicrobial instillations, such as Cystistat® or lauril®, restores the bladder glycosaminoglycans (GAG) layer and can be used in UTI prophylaxis.**
- **Intravesical therapies bypasses the oral or intravenous route and thus minimises systemic side effects.**
- **The main limitations of intravesical therapy is that administration requires a course of in/out urinary catheterisation, which is invasive in nature and causes discomfort and its administration needs to be done in an outpatient clinical setting by a trained healthcare professional.**

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11.1 Introduction

Intravesical therapy is a localised treatment where a liquid drug is administered directly into the bladder via a urinary catheter, bypassing the oral or intravenous route and thus minimising side effects, as its effect is solely limited to the bladder where it needs to act. Intravesical therapies are already widely used in clinical practice as an adjuvant additional treatment for non-muscle invasive bladder cancer, following surgical endoscopic resection. In recent years, intravesical therapy has also been used to in the treatment of chronic cystitis and prophylactic treatment for recurrent UTIs. This involves either intravesical antibiotic irrigation or instillations of Cystistat® or Ialuril® to restore the bladder glycosaminoglycans (GAG) layer.

11.2 The Procedure Itself

Intravesical therapy involves urinary catheterisation into the bladder using a local anaesthetic lubricating gel. Once inserted and the bladder is emptied, the catheter can then be used to administer a liquid drug formulation directly to the bladder. After this, the catheter is removed and the patient is advised to refrain from passing urine in the next hour or so, to allow the medication enough time in the bladder to have an optimal effect.

Depending on the type of intravesical instillation agents and the underlying causes of recurrent UTIs, the frequency of treatments may vary.

Generally, the initial treatment regimen is once a week for 4 weeks, then every 2 weeks for two treatments. After this time, treatments are usually given once a month until patient's symptoms resolve, with a whole course lasting up to 6 months, or even 12 depending on local policies.

11.3 Intravesical Antibiotics (IVA)

Intravesical antibiotics (IVA) have been used for prophylaxis and treatment of recurrent UTIs since the 1960s, however there is still a lack of comprehensive evidence and consensus on its use.

11.4 Clinical Evidence

A recent 2018 review investigated the efficacy of IVA. They identified 285 patients in 11 clinical studies who received IVA either as treatment or as prophylaxis for UTIs.

The authors reported that the antibiotics used were mainly gentamicin, but also neomycin/polymyxin, neomycin or colistin. Furthermore, 78.2% (n = 223) of participants who underwent the antimicrobial instillation showed a beneficial response with reduction of symptomatic UTI, with success seen over 3–6 months in both the treatment (88% success) and prophylaxis (71% success) group.

Interestingly, the sensitivities of the organisms in the bladder also changed with IVA—either the multi-resistant organism was eradicated or antibiotics the bacteria were previously resistance to have now become effective and the bacteria has developed sensitivities. This occurred both in the treatment group (30% changed sensitivities) and prophylaxis group (23% changed sensitivities).

Importantly there were minimal side effects reported, with discontinuation rates of 5% and 8% in the treatment and prophylaxis group respectively. Gentamicin IVA patients had the lowest discontinuation rates of all the antibiotics.

Interestingly, the majority of patients had indwelling catheters, does intermittent self-catheterisation or had neurogenic bladders. This suggests IVA may be an effective treatment option in complex recurrent UTIs. Furthermore, the patient

already knowing self-catheterisation or has an indwelling catheter may eventually mean the more able patients may be able to self-administer this treatment at home once taught and supervised initially.

11.5 Non-antibiotic Instillations (GAG Layer Replacement)

In a healthy bladder there is a natural barrier, called the glycosaminoglycan (GAG) layer, which protects the bladder lining epithelial cells from the urine, preventing bacterial adherence. If GAG layer is damaged, urine comes into direct contact with the bladder epithelial cells. Over time this causes irritation and inflammation, which result in urinary symptoms such as pain, urgency and frequency, and increases the risk of infections due to easier bacterial adhesion and invasion.

One option to repair this damaged layer is instillations of Hyaluronic Acid (HA) or Chondroitin Sulphate (CS) via a catheter. Upon instillation, patients hold the treatments within their bladders for 2 hours before passing the urine/bladder instillation out and recommencing normal daily activities.

11.6 Clinical Evidence

HA +/− CS intravesical instillations have been shown to lower rates of UTI recurrence and increase duration of UTI-free time between acute attacks. Small studies have found intravesical therapies reduced cystitis recurrence when compared against antibiotics [1, 2], and placebo [3].

A larger European retrospective study in 276 women compared intravesical GAG replacement to “standard therapy”. This was defined as antibiotic prophylaxis, cranberry or probiotics. A 49% reduction in UTI risk was found in the 12-month follow up, with effectiveness correlating with increasing numbers of instillations. A bacterial recurrence

odds ratio of 0.81 was found in patients who underwent five or more instillations. If the patient had seven or more instillations, this dropped to 0.63 [4].

Cystistat® (Bioniche Life Sciences Inc., Belleville, Ontario, Canada) and Ialuril® (Aspire Pharma, UK) are a couple of commercially available HA + CS instillation options. Both have shown effectiveness in lowering rates of recurrent UTIs with minimal side effects.

Overall, the strength of the current evidence is limited by the small sample size in these studies. For this reason, the current EAU guidelines do not have any recommendation on GAG replacement and more large-scale trials and clinical data are required on this front.

11.7 Limitation of Intravesical Therapies

The main constraints for intravesical therapies are the need for in/out urinary catheters, an invasive process that can cause discomfort. Furthermore patients cannot self-medicate at home, rather the patient is required to regularly attend the specialist outpatient clinic where a trained healthcare professional is required to deliver this treatment.

Interestingly, Ialuril has recently developed a "catheter free" delivery method, which is a prefilled syringe with a unique adaptor that allows the reagent to be injected directly into the bladder to administer treatment without the need for a catheter. The process is very similar to injected Instillagel (a local lubricant anaesthetic) prior to a cystoscopy or catheterisation into the urethra. We eagerly await further clinical trials on this new delivery device and whether its use is taken up into routine clinical practice and negates the above limitations.

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Chapter 12
Fractional CO_2 Thermo-Ablative Vaginal Laser Therapy

Bob Yang and Steve Foley

- **Vaginal laser restores the vagina via superficial micro-trauma.**
- **Useful in treatment of women with atrophic vaginitis—similar to oestrogen therapy.**
- **Useful in patients who cannot tolerate oestrogen therapy (e.g. breast cancer patients).**
- **Three doses delivered in office setting without need for anaesthetics, one month apart for 3 months in total—effect lasts up to 12 months on average.**
- **Very early days in use in post-menopausal women with recurrent UTIs.**

12.1 Introduction and Mechanism of Action

CO_2 thermo-ablative lasers apply fractional micro-trauma to the lamina propria of the vaginal mucosa (the vaginal lining), causing immediate collagen fibre contractions, followed by

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inducing a repair and restoration of the vaginal architecture (initiation of new collagen and elastin synthesis), thus inducing a histologically confirmed restoration of the vagina.

Under the microscope, the thick squamous stratified epithelium is restored as well as the intracellular glycogen storage and synthesis of new components of the extra-cellular matrix. The limited penetration depth protects the underlying fibromuscular layers [1, 2].

Such lasers restore the vagina to a pre-menopausal state similar to topical oestrogen therapy and are currently in use in the treatment of atrophic vaginitis in post-menopausal women and are licensed for use in the UK [3].

The restoration of the vaginal "laxity" has also been used in treating women with stress urinary incontinence. Studies involving a series of patients show potential benefit in relieving mild urinary stress incontinence in women, however no high powered/high quality randomised control trial or comparison with placebo trials are available, meaning further trials are needed before any consensus can be reached in the use of vaginal lasers in stress incontinence [4].

Regarding UTIs, the restoration of the vaginal microenvironment replenishes the natural vaginal defences, in particular the acidic pH, which is likely a result of the increased presence of the commensal bacteria *lactobacillus* that synthesises lactic acid. Further, pH restoration is likely to also be aided by the repair of the vaginal architecture lost in menopause, restoring the normal moist conditions and vaginal secretions [5, 6].

The treatment is performed once a month for 3 months. Similar to a trans-vaginal ultrasound, a probe is inserted into the vaginal and the treatment applied. Apart from ample lubrication, no anaesthetic is needed and the whole treatment can be done in an outpatient setting. Prior to treatment, a vaginal swab, cervical smear and urine dipstick analysis is performed to exclude underlying active infection and exclude any evidence of cervical cancer.

12.2 Clinical Evidence

To date there has only been one prospective study [7] in the use of vaginal laser therapy in preventing UTIs, though with promising results. 12 post-menopausal UK women with recurrent UTIs received three courses of Vaginal CO_2 Laser (Femtouch™) at monthly intervals. The authors reported after 6 months since commencing treatment, 11/12 (92%) of patients remained UTI free. 75% of patients remained UTI free by 12 months.

This was associated with a concurrent restoration of the acidic vaginal microenvironment, from an average of pH 7 pre-treatment, to pH 5.4 by the end of the three courses. By 12 months, the pH has worsened to 6 but was still better than pre-treatment.

Furthermore, there was concurrent improvement in the Vaginal Health Index Score, which assess elasticity, Fluid, pH, integrity and moisture of the vagina. Any score <15 is defined as atrophic.

The VHIS score improved from 11 pre-treatment to 20 at dose 3. The effect is maintained and slowly wears off over the year and by 12 months, the score is down to 15, which is still better than before treatment.

Its benefit (in particular in patients with a previous breast cancer history who cannot tolerate oestrogen) is promising whilst at the same time restores the patients sex life (if they want it!).

However, there is currently no long-term data available for this therapy and therefore its use in UTI prophylaxis is still very much in its infancy.

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Chapter 13
Immunomodulation Vaccines

Bob Yang and Steve Foley

- **Induces the host adaptive immune system**
- **Uropathogens share similar surface antigens, which therefore allows for a broad-spectrum defence when the immune system is stimulated by antigen from one bacteria group**
- **RCT data available for:**
  - **Uro-Vaxom® (OM Pharma, Myerlin, Switzerland)—oral tablet**
  - **Urovac® (Solco Basel Ltd, Basel, Switzerland)—vaginal vaccine**
  - **ExPEC4V (GlycoVaxyn AG, Schlieren, Switzerland)—IM injection**
- **Uromune® (Syner-Med (PP) Ltd UK, Inmunotek S.L. Spain) is a newer sublingual (under the tongue) spray which is effective but has only prospective and retrospective trials published. No RCT available to date**

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13.1 Introduction and Mechanism of Action

Vaccines are the current hot topic in recurrent UTI prevention. These new immune-modulators stimulate the body's own immune system to more effectively fight off any bacterial invasion.

The urinary tract fights against uropathogens using both an innate and adaptive mucosal-immune system, which is part of a larger Mammalian lymphoid organ system. This system works by having receptors to recognise invading bacteria, binding onto them and stimulating the body's immune system to then kill it off. In the body, the mucosal immune system comprises of 80% of all immunocytes (cells used by the body to fight off infection).

Immunocytes transit throughout the body through various Mucosal associated lymphoid tissue (MALT), meaning stimulation and activation of the Toll-Like Receptors at one MALT site disseminates immunity to other MALT sites by allowing them to also recognise the surface antigens on the bacterium.

Vaccines work by introducing one or more common bacteria that cause UTI to the body's immune system. This can be done either with the bacteria's surface antigens or by using the whole inactivated bacterium, thus allowing for the induction of the host immune system without risking an actual infection. This exposure activates both the innate and (later on) the adaptive immune response.

This pre-sensitisation means when an actual virulent uropathogen attempts to invade the urinary tract, the body has already "learnt" previously how to deal with this bacteria and thus can mount a significantly faster adaptive host immune response, which when activated, promotes an more effective targeted immune reaction to clear the pathogen before any symptoms occur.

As most uropathogens share similar surface antigenic properties between themselves, stimulation with one (or more) uropathogens results in a broad-spectrum immune response against both the listed uropathogens and also other pathogens not solely limited to the bacteria within the vaccine itself [1].

13.2 Clinical Evidence

13.2.1 UroVaxom®

UroVaxom®, originally called OM-89, is an oral tablet composed of bacterial extracts from 18 strains of *Escherichia coli*. It is given daily in an oral tablet form for 90 days. Its use has been reported in the literature since 1986. Since then, there have been 6 RCTs, which on meta-analysis, found that UroVaxom® did reduce UTI recurrence rates (risk ratio [RR] 0.67, 95% CI 0.57–0.78). The maximal effect was seen by 3 months.

Current EAU guidelines recommend this treatment for immuno-prophylaxis in women with recurrent uncomplicated UTIs [2].

13.2.2 Urovac®

Urovac® is a vaginal suppository vaccine delivered as a weekly dose for 3 weeks. It is composed of ten inactivated uropathogen strains including six *E. coli* strains and one *Proteus mirabilis*, *Morganella morganii*, *Enterococcus faecalis* and *Klebsiella pneumoniae*. After the initial 3 week treatment period, three follow up booster doses are then given at 6, 10 and 14 weeks.

Urovac® has also been shown in a recent meta-analysis of 3 RCTs to effectively reduce UTI recurrence rates (RR 0.75, 95% CI 0.63–0.89) [2].

13.2.3 ExPEC4V

ExPEC4V is an intramuscular vaccine delivered as a single injection. It is composed of the O-antigens from four *E. coli* serotypes.

Whilst effective in initial trials, to date there has been only one published RCT, which in 93 women reported no reduction in UTI recurrence rates. (RR 0.82, 95% CI 0.62–1.10) However the trial did show ExPEC4V induced a significant host

immune response, with significant rises in the immunoglobulin (IgG) levels specific to all four O-antigens. A phase II trial is currently underway to investigate whether this rise in immunity translates to a clinical benefit in preventing UTIs [2].

13.2.4 Uromune®

Uromune® (Syner-Med (PP) Ltd. UK, Inmunotek S.L. Spain) is a newer immunomodulating vaccine which has reported good efficacy. However the lack of any published RCTs means to date, the EAU are unable to list this treatment in their guidelines.

Uromune® is a sublingual vaccine composed of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Enterococcus faecalis* in equal proportions. It is currently pre-licence.

Two large retrospective Spanish studies comparing Uromune® and antibiotic prophylaxis in 669 and 319 women found a significant decrease in UTI recurrence. [Risk reduction 90.28% (87.18–93.38)] The authors also reported no side effects [3, 4].

A recent 2018 prospective UK observational study found that in 77 women, after 3 months of daily administration, 78% of women developed no further UTIs in the 12-month follow-up period. For those who still developed UTIs despite treatment, proportionally more were seen in postmenopausal women, suggesting Uromune is more effective in pre-menopausal women, though it still displayed a marked effect in post-menopausal women too. [UTI free patients—Pre-menopause: 88%, Post-menopause 72%]. There were very few significant side effects with only one woman in the study stopping treatment due to a rash [5].

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Chapter 14
Urinary Tract Infections of the Neurogenic Bladder

Mostafa Ragab, Bob Yang, and Melissa Davies

- **High risk patient group for recurrent UTIs.**
- **Neurogenic lower urinary tract dysfunction increases the risk of UTIs due to a variety of factors including voiding dysfunction, catheters, stones, obstruction and bowel dysfunction.**
- **Classic symptoms of dysuria, frequency and urgency maybe absent in patients with neurogenic bladders due to the insensate nature of their body/urinary tract from their underlying neurological disorder.**
- **UTIs in neurogenic bladder patients are always deemed complicated UTIs therefore antibiotic treatment and duration should reflect this accordingly.**
- **•Non-antibiotic prophylaxis management options are similar to patients without neurogenic bladders.**

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Patients with neurogenic lower urinary tract dysfunction (NLUTD) are at increased risk of recurrent urinary tract infection (UTI), with much higher incidence reported compared with a "normal" population. As a result, this leads to increased utilisation of healthcare resources as well as morbidity and even mortality in some cases. As expected, the underlying cause, as well as the investigation and management of UTIs in this unique population is different to patients with a "normal" bladder and will be explored further by this chapter.

14.1 Pathophysiology

NLUTD has multiple causes which can be classified into;

Congenital—Bladder dysfunction is frequently seen in patients with spina bifida, with vesico-ureteral reflux present in up to 40% of children affected by 5 years of age and with up to 60.9% of young adults with spina bifida experiencing urinary incontinence [1, 2]. The spastic cerebral palsy population has an estimated 36% prevalence of NLUTD [3].

Acquired—traumatic injuries, such as spinal cord injury (SCI) or neurological conditions. In the United States, up to 40–90% of patients with multiple sclerosis, 37–72% of patients with Parkinson's disease, and 15% of patients with stroke have NLUTD [1, 4]. Less common causes of NLUTD may include diabetes mellitus with autonomic neuropathy, unintended sequelae following pelvic surgery, and cauda equina syndrome resulting from lumbar spine pathology [1].

The subsequent disruption of the micturition cycle give rise to LUT dysfunction. UTIs in NLUTD occurs either due to the LUTD (e.g. incomplete bladder emptying, stone formation) or because of treatment (e.g. intermittent/long term catheterisation).

14.1.1 Precipitating Factors

14.1.1.1 Voiding

Incomplete emptying of the bladder leading to stagnation of urine is a well-known risk for UTI, with as little as 20 ml of stagnant urine found to be linked to recurrent UTI [5–7]. Kim et al. reported that a post-void residual urine volume of more than 100 ml led to an increase chance of acquiring UTI by 4.87 times in stroke patients undergoing rehabilitation [8].

14.1.1.2 Catheters

There are data demonstrating that the bladder drainage method is the most important predictor of symptomatic UTIs, with indwelling catheters being the highest risk [9]. If patients are unable perform Clean intermittent self-catheterisation (CISC) alternative options include sphincterotomy in male patients (with a subsequent Convene sheath), ileovesicostomy and ileal loop urinary diversion.

14.1.1.3 Stones

Stones represent a nidus for persistent infection, either obstructing or non-obstructing. A retrospective study of patients with non-obstructing asymptomatic renal calculi and recurrent UTIs who underwent surgical removal, showed nearly 50% of the patients remained infection-free after the stone removal [10].

14.1.1.4 Obstruction

May occur as a result of Detrusor Sphincter Dyssenergia (involuntary contraction of the external sphincter and detrusor muscle simultaneously). Patients, who have undergone urinary diversion require monitoring with annual renal ultrasound.

Obstruction can occur at the level of the stoma (treated by gentle digitalisation, catheterisation for draining residual urine), or at the ureteroileal anastomosis level (which can be treated with revision surgery or ureteric stents). Loopogram studies looking for reflux is the best mean for evaluation of a urinary conduit.

14.1.1.5 Bowel Dysfunction

Is thought to cause UTI by perineal contamination and trans-colonic migration of bacteria. Intervention to address constipation or incontinence should be encouraged as part of the treatment plan for the UTI's [11].

14.2 Definition of UTI in NLUT

A UTI in patients with NLUTD is characterized by the new onset of sign(s)/symptom(s) [12];

- Fever (Highest specificity 99%, but 6.9% sensitivity)
- New onset or increase in incontinence, including leaking around catheter
- Increased spasticity
- Malaise, lethargy or sense of unease
- Cloudy malodourous urine
- Pyuria/Leukocyturia (Highest sensitivity 82.8%)
- Discomfort or pain over the kidney (costovertebral angle) or bladder or during micturition (dysuria)
- Autonomic dysreflexia (A medical emergency for SCI patients above T6 level, triggered by stimulation below the level of injury, mainly the genitourinary tract, causing abrupt sympathetic activity and leading to convulsion, cerebrovascular accidents and death if left untreated)

This is accompanied by laboratory findings of a UTI in urine analysis. It is important to note that often the classic symptoms of dysuria, frequency and urgency are absent due to the insensate nature of their urinary tract from their underlying disease.

14.2.1 Urine Analysis

Whilst setting their criteria for definition of the UTI the International SCI-UTI Basic Data Set used a study performed on SCI patients, which showed that combined nitrites and leucocyte esterase have a sensitivity and specificity of 0.79 and 0.99, respectively when compared with urine culture [13]. It is of note that when the National Institute on Disability and Rehabilitation Research (NIDDR) criteria was implemented [14], higher rates of overtreatment and lower rates of undertreatment were found when following the urine dipstick test as compared to positive bacteriuria [15]. One explanation is the inability of Enterococcus among other bacteria to reduce nitrates to nitrites. Hence, if there is an intention to treat an episode of UTI in SCI individuals, urine dipstick for nitrites and leucocyte esterase may be an initial indication, but should be followed by urine culture and sensitivity.

14.2.2 Positive Urine Culture

Urine for culture should ideally be collected as a clean catch midstream technique, which in NLUTD patients may be the urine from the insertion of a new urethral/suprapubic catheter. A growth of 10^3 CFU/mL is a reliable finding with standardised inoculation with 10 μL urine [16]. Having more than 2 species is not considered contamination, provided that the collection technique was sterile.

14.3 Clinical Evaluation of Neurogenic Bladder

1. Clinical history
   (a) History of the injury—Good history taking enables recognition of the level of injury, which allows for prediction of urological dysfunction.

   (b) Urological history—LUTS, urological symptoms including previous surgeries and red flag symptoms such as haematuria, that warrant further investigations.
   (c) Drug history
2. Bowels, erections, mobility, dexterity, cognition and comorbidity, family/social support and medical care that may influence bladder management need to be evaluated

14.3.1 Clinical Examination and Investigations

1. Neurological examination—Including mental status, strength, sensation, and reflexes
2. Rectal examination—anal tone, faecal impaction
3. 3-day bladder diary—records type and volume of fluid intake, incontinence episodes, number of pads used and a recorded chart of urinary frequency and voided urine volume (i.e. functional bladder capacity). Will also detect concomitant conditions such as nocturnal polyuria
4. Urine analysis/MSU
5. Urea and electrolytes, including VitB12 for patients with ileal loop urinary diversion
6. Renal ultrasound scan—to assess for obstructive uropathy, Uroflowmetry and Post-void residual urine volume
7. Video-Urodynamics (UDS). In clinical practice, SCI effects are variable from broad assumptions due to incomplete or multi-level injuries resulting in variable urodynamic findings. Video-UDS should be performed for evaluation of the type of NLUTD.
8. Cystoscopy—should be performed if red flag symptoms are present (Haematuria, recurrent UTI) to exclude underlying pathology in particular stones and bladder tumours. SCI patients have 16–28 times higher chance of developing bladder cancer, with a higher proportion of squamous cell carcinoma than transitional cell carcinoma [17]. This is mainly due to recurrent UTI and indwelling urinary catheters. Patients who have undergone reconstructive surgery using small intestine are predisposed to bladder cancer, which is mainly found at the line of anastomosis [18].

14.4 Treatment of Neurogenic Bladder and UTI in NLUTD

14.4.1 Antibiotic Treatment

There are some general rules that apply to the use of antibiotics in patients with NLUTD. As, by definition, UTIs in NLUTD patients are considered complicated UTI. Therefore, single-shot or short-term treatments (1–3 days) are not advised, based on the results of a meta-analysis, a 7–10 day treatment for UTI without fever, and 14 days in patients with fever is recommended [19]. In addition, if the infection involves parenchymal organs (e.g., pyelonephritis), the treatment duration should be extended [20]. It is important to avoid treating asymptomatic bacteriuria in patients with NLUTD and avoid the use of long-term prophylactic antibiotics for recurrent UTI due to the risk of developing resistance.

14.4.2 Preventive Measures Against UTI

14.4.2.1 Clean intermittent self-catheterisation (CISC) vs indwelling long term urethral catheter

Indwelling catheters poses the highest risk for UTI development in patients who cannot effectively empty their bladder [9]. Therefore, in the presence of good dexterity, consistent frequency or a 24-h carer, clean intermittent catheterisation is the standard of care [21]. It's often noted that patients on CISC resort to indwelling catheter in the case of developing recurrent UTI patients. It's important to encourage this group of patients to use CISC as often the cause of the UTI is not related to CISC [beyond ABX]. This is reflected in the US Centres for Disease Control recommendations to minimise the use of indwelling urinary catheters to decrease the incidence of catheter-acquired UTI (CAUTI) [22].

Techniques of CISC have been assessed for correlation with UTI, including single or multiple use catheters, exchange of multiple use catheters daily or weekly and coated vs uncoated

catheters. A Cochrane review and meta-analysis found no superior method to prevent UTIs [23]. For patients who rewash catheters, the authors recommend changing to a new catheter every week, washing with water and clear-rinsing dish soap, then drying the catheter in open air, it should be noted in rewashing that the catheter surface does eventually erode. A Cochrane review of three randomized control trials including a total of 107 patients did not find any difference between changing the catheter regularly and waiting until it was clinically indicated (symptomatic UTIs or obstruction) [24]. There is conflicting and scarce information regarding catheter irrigation with antimicrobial agents, thus NICE guidance recommends against its use [25].

14.4.2.2 Bladder Instillations

Bladder instillations of hyaluronic acid and chondroitin sulphate decreased UTIs frequency and improved quality of life [26]. These studies suggest that restoring the glycosaminoglycan bladder layer with nonantibiotic irrigation therapy may be an option to prevent recurrent UTIs, however have a limitation of retrospective approach.

It is of note that in case of when an indwelling catheter is indicated, a closed-catheter drainage system should be used to reduce UTIs and intraluminal biofilm development.

14.4.2.3 Cranberry

There are conflicting data regarding cranberry supplements for the prevention of UTIs and CAUTI in the NLUTD population [27]. In vitro studies showed proanthocyanidins inhibit *E. coli*'s P-fimbriae adherence to the urothelial cells and the fructose to block type 1 fimbriae [28, 29]. Only a single study has demonstrated a significant reduction in the incidence of UTI with cranberry prophylaxis in the NLUTD population. Patients were randomized to receive 6 months of cranberry extract tablet or placebo. The frequency of UTI was reduced to 0.3 UTI per year vs. 1.0 UTI per year while receiving placebo. However, this study has been criticized for its small sample size [30]. A double-blind randomized controlled trial,

investigating standardized proanthocyanidin extract for prevention of recurrent UTIs is currently in progress [31].

14.4.2.4 Probiotics

A multi-centre study in 2019 showed that in 207 patients with SCI, probiotic therapy with Lactobacillus reuteri RC-14 + Lactobacillus GR-1 (RC14-GR1) and/or Lactobacillus rhamnosus GG + Bifidobacterium BB-12 (LGG-BB12) was not effective in preventing UTI in NLUTD patients [32].

14.4.2.5 Ascorbic Acid

Ascorbic acid works by preventing the alkalinisation of urine. However, two studies in patients with SCI found a dose of 2–4 g of ascorbic acid daily did not result in statistically different changes in urine pH [33, 34].

14.4.2.6 Hiprex (Methenamine Hippurate)

Methenamine salts hydrolyse into ammonia and formaldehyde, whose antimicrobial effect is correlated to their concentration in urine. Therefore, in patients with NLUTD managed by indwelling catheters, the dwell time is reduced causing methenamine salts to be of limited use. A 2012 Cochrane review found that methenamine Hippurate did not appear to be effective long-term prophylaxis in patients with NLUTD, though the actual patient numbers were small [35]. However the ease of use, limited side effects and anecdotal evidence of its effectiveness means Hiprex is still often used in NLUTD patients with recurrent UTIs.

14.4.2.7 D-Mannose

D-Mannose is thought to work by inhibiting bacterial adherence to urothelial cells by binding to type 1 fimbriae [36]. One previous study has demonstrated that its use is safe in 22 patients with multiple sclerosis and NLUTD, and initial results regarding its efficacy were promising [37].

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Summary of Non-antibiotic Prophylaxis

Therapy	Target group	Evidence, guidelines and comments
Conservative management	All patients	**Recommended by the 2019 EAU guidelines** Lack of strong clinical evidence but actively encouraged due to simplicity with lack of harm from their implementation Patients should be advised on fluid intake, sexual hygiene, personal hygiene, voiding techniques and weight loss
Oestrogen replacement	Post-menopausal women	**Vaginal oestrogen is recommended by the 2019 EAU guidelines** Only vaginal preparations were effective in preventing rUTIs. Oral preparations not recommended Vagifem 1 tablet daily for 2 weeks, then 1 tablet twice a week—tablet administered vaginally

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Therapy	Target group	Evidence, guidelines and comments
Uro-Vaxom®	All patients	**Recommended by the 2019 EAU guidelines** in women with recurrent UTIs
		90 day course, one tablet a day oral therapy with good safety profile
D-Mannose	All patients	**Indicated by the 2019 EAU guidelines**, however no recommendations yet until higher quality clinical investigations available and recommends use as part of clinical trial
		As prophylaxis, 2 g dissolved in 200 ml water daily for 6 months, especially for patients with E. coli
		For acute uncomplicated cystitis, 1.5 g Mannocist® twice daily for 3 days and then once a day for 10 days
Cranberry (Proanthocyanidins)	All patients—especially for *E coli*.	Currently no longer recommended by NICE/EAU due to recent Cochrane review showing no efficacy against placebo—but may still be helpful in preventing uncomplicated UTIs in women
		No consensus on which formulation is best

Therapy	Target group	Evidence, guidelines and comments
Hiprex	All patients	Due to insufficient clinical data, no clinical recommendations are currently available. Potentially less effective in patients with neurogenic bladders or urinary tract structural abnormalities, however this has only been studied in a small number of patients
		Oral tablet 1 g twice a day for adult patients. If the patient has a catheter, can be increased to three times a day
Intra-vesical Instillation	All patients	Current EAU guidelines do not have any recommendation on GAG replacement and more large-scale trials and clinical data are required on this front
		Treatment requires in/out catheter and multiple rounds of treatment in the outpatient setting
		Can utilise either antibiotic instillation (namely gentamicin) or GAG replacement (Cystistat® or Ialuril®)

Therapy	Target group	Evidence, guidelines and comments
Urovac®	All patients	No EAU recommendations currently however meta-analysis of 3 RCTs shows significant risk reduction
		Vaginal suppository vaccine, 3 weekly courses followed by booster at 6, 10 and 14 weeks
ExPEC4V	All patients	Only one phase 1 RCT published which showed elevated immune response to treatment but no reduction in UTIs. Currently awaiting results from phase 2 trials
		Delivered as one single intramuscular injection
Uromune®	All patients	No recommendations yet due to lack of randomised control trials. Spanish and UK studies show significant benefit
		Daily sublingual spray for 3 months with good safety profile
CO_2 thermo-ablative vaginal laser	Post-menopausal women	Only one prospective trial in 12 women, which did show a benefit. No long term or large volume data yet. Utilised already by gynaecologists to treat vaginal atrophy
		1 transvaginal treatment per month delivered in outpatient setting for 3 months

Therapy	Target group	Evidence, guidelines and comments
Traditional Chinese Medicine	Main evidence in post-menopausal patients	*Ba Zheng* (Ba Zheng San UTflow™, 八正片), *Er Xian Tang* (Er Xian Wan, Menofine™, 二仙片) and *San Jin Pian* (UTIGold™, 三金丸) have evidence for their use in treating acute infection and preventing recurrence
		However quality of the trials are suboptimal and the majority of patients were post-menopausal in age
Acupuncture	All patients with uncomplicated recurrent UTIs	Evidence to show acupuncture is effective in preventing recurrent UTIs and decreasing post-void residual volumes
		However, there are only 2 reliable studies available to date on its use in UTI prevention

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