Guidelines for Primary Care management of Recurrent Urinary Tract Infections in Adults: Antibiotic Prophylaxis

Definition of recurrent lower urinary tract infection:

The symptoms of a lower urinary tract infection include: frequency, dysuria, urgency and suprapubic pain. Recurrent lower urinary tract infection (rUTI) is defined as:

2 or more episodes of lower urinary tract infection in the last 6 months, OR
3 or more episodes of lower urinary tract infection in the last 12 months[1].

Recurrent lower urinary tract infection (rUTI) does not include asymptomatic bacteriuria, which refers to the presence of bacteria in the urine without any accompanying symptoms, or in catheterised patients. Asymptomatic bacteriuria should not be screened for or treated, unless prior to urological surgery or in pregnancy (positive cultures in pregnancy should be confirmed with a second culture confirming the same organism prior to treating)[2].

1. Consider whether referral is required for patient with recurrent UTIs:

Consider referring the patient to a specialist based on the following factors[,4]:

1.1 Red Flags for Referral to Urology:

- Referral to urology is recommended for all men
- Frank haematuria, even in the context of confirmed UTI (refer to current ‘2 week wait’ guidelines for further information)
- Neurological disease e.g. spinal cord injury, spina bifida
- Pneumaturia or faecaluria
- Proteus on repeat urine cultures
- Suspected stone
- Obstructive symptoms, or structural/functional abnormality, causing >200ml residual urine on bladder scan

In pregnancy:

- All rUTIs in pregnancy should be discussed with the Obstetrics team

Based on “Guidelines for Recurrent Urinary Tract Infections in Adults” by Authors: Dr Amelia Joseph, Mr Richard Parkinson and Dr Jane Coleman GP.
http://www.nottsapc.nhs.uk/media/1217/uti-prophylaxis-guideline.pdf

1.2 Consider risk factors:

A sexual history and investigations for sexually transmitted infections should be performed if appropriate. In peri- and post-menopausal women, atrophic vaginitis may cause urinary symptoms and may increase the risk of bacteriuria.

1.3 Microbiological confirmation:

Patients with rUTIs should have a mid-stream urine (MSU) sample sent for culture **prior** to antibiotics being initiated, in order to confirm infection and guide antibiotic therapy[3]. Patients should be counselled on how to provide a specimen to minimise the chance of contamination. http://patient.info/health/midstream-specimen-of-urine-msu

Urine cultures sent in the absence of symptoms are unlikely to be helpful, may detect asymptomatic bacteriuria and lead to inappropriate antibiotic use. Antibiotic treatment of asymptomatic bacteriuria is more likely to be harmful than beneficial[4].

2. Management of initial presentation of recurrent UTI in <u>non-pregnant females</u>

The following conservative measures should be tried prior to antibiotic prophylaxis:

2.1 Self-care measures:

- Encourage better hydration if necessary and more frequent voiding if patient only visits the lavatory infrequently.
- Patients can be advised to try D-mannose and / or Cranberry tablets (available without prescription) but there is very limited evidence of benefit. (Both are available without prescription).
- For sexually active women:
  - Advise post-coital voiding
  - Avoid use of contraceptive diaphragm and spermicide
- Avoid using feminine hygiene products (e.g cosmetic bath products and feminine douches).
- Perineal hygiene i.e. wiping front to back.
- Avoid using flannels. A clean non scented disposable wipe is preferable.
- Offer TARGET - Treat Your Infection Urinary Tract infection Patient Information Leaflet

2.2 Vaginal oestrogens:

Current NICE guidelines state that vaginal oestrogens [unlicensed indication] can be used for postmenopausal women with recurrent UTIs at the lowest effective dose if behavioural and personal hygiene measures alone are not effective or appropriate. The prescriber should follow relevant professional guidance, taking full responsibility for the decision.

Discuss the following with the woman to ensure shared decision-making:

- The severity and frequency of previous symptoms
- The risk of developing complications from recurrent UTIs
- The possible benefits of treatment, including for other related symptoms, such as vaginal dryness
- The possible adverse effects such as breast tenderness and vaginal bleeding (which should be reported because it may require investigation)
- The uncertainty of endometrial safety with long-term or repeated use
- Preferences of the woman for treatment with vaginal oestrogen.

Choosing which option to have is a highly preference-sensitive decision. It involvestrading-off the benefits against the risks of the different treatment options. Should vaginal oestrogens be considered, local experience and published evidence[5] suggests using once each night for two weeks followed by twice-weekly applications for 4 weeks initially. Consideration should be given to continuing them for 3-6 months and then review treatment within 12 months, or earlier if agreed with the woman

3. Antibiotic prescribing strategies

The relative risks and benefits of the following antibiotic prescribing strategies should be discussed with the patient. These strategies should be in addition to conservative measures.

3.1 Standby antibiotics

- If the patient is able to wait, infection should first be confirmed by MSU prior to commencing standby antibiotics .
- Offer TARGET – Treat Your Infection Urinary Tract infection Patient Information Leaflet.

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- A patient advice sheet and boric acid container for pre-antibiotic MSU should be provided to the patient.
- A 'self-start' course of antibiotics, prescribing an agent according to previous known sensitivities and choosing the narrowest spectrum agent available.
- Safety-net with advice to seek medical attention if they develop fever, loin pain, or symptoms are not improving by 48 hours.
- This option limits antibiotic exposure and risk of resistance emerging and may be the more suitable option for patients with <1 UTI per month.

3.2 Post coital antibiotics

- For rUTIs that are triggered by sexual intercourse, confirm that the patient passes urine after intercourse. If this is the case post coital antibiotic is as effective as continuous antibiotic prophylaxis[6,7], and limits antibiotic exposure and risk of resistance emerging.

3.3 Continuous antibiotic prophylaxis

- Longer term antibiotic prophylaxis is strongly associated with the development of antimicrobial resistance.
- A **trial** of low-dose continuous antibiotic treatment may be beneficial if rUTIs are occurring ≥1 per month and are not triggered by sexual intercourse. Review antibiotic prophylaxis for recurrent UTI at least every 6 months.
- Patients should be counselled at an early stage that antibiotic prophylaxis is not usually a lifelong treatment although they are necessary for some patients. Documenting and triggering a review date in the patient's record, and on the repeat prescription, is strongly advised to avoid prolonged courses of antibiotics without review.

Choice of agents[6,7]:

Choice of antibiotic should be based on **confirmed culture and sensitivity results** (wherever possible), and consider the patient's co-morbidities, renal function and any contra-indicating factors.

Nationally for England, resistance of E. coli (the main causative organism of lower UTIs) in laboratory-processed urine specimens to the following antibiotics is:

- nitrofurantoin: 2.5% (varies by area from 2.0 to 3.6%)
- trimethoprim: 30.3% (varies by area from 27.1 to 33.4%)
- pivmecillinam: 7.5% (varies by area from 4.1 to 15.7%)
- cefalexin: 9.9% (varies by area from 8.1 to 11.4%).

(Public Health England. Antimicrobial resistance quarterly surveillance: March 2018).

Trimethoprim and nitrofurantoin are licensed for the prophylaxis of rUTIs. Nitrofurantoin is the first line choice for antibiotic prophylaxis.

The risk of adverse effects (see box below), as well as common side-effects such as rashes, oral/vaginal thrush and gastro-intestinal upset, should be discussed with the patient. Nitrofurantoin induced lung toxicity appears to occur in less than 1 in 1000 exposures. The spectrum of **nitrofurantoin induced pulmonary toxicity** includes acute or chronic interstitial pneumonia, pulmonary hemorrhage, bronchoconstriction, anaphylaxis, and pleural effusion. Acute pulmonary reactions are probably underestimated. The incidence has been estimated to be anywhere from 1 in 550 to 1 in 5400 individuals. Acute toxicity is nearly 10 times more common than chronic. Toxicity can occur at relatively small doses, and does not appear to be dose-related.[8]

If resistance to trimethoprim and nitrofurantoin, other agents may be considered after discussion with Urology, Urogynaecology and/or Microbiology. Broader spectrum agents such as cefalexin, ciprofloxacin and co-amoxiclav have a higher risk of *C.difficile* diarrhoea and should not be routinely used for prophylaxis. In addition MHRA have issued an alert restricting the use of fluoroquinolone antibiotics e.g. ciprofloxacin

Antibiotic	Dose	Cautions and Monitoring
Nitrofurantoin **First line**	100mg immediate release One dose post-coital (off label) Or 50 to 100mg at night	• Avoid if renal function eGFR <45ml/min. Consider checking renal function prior to commencing continuous prophylaxis, especially in the elderly. • Avoid if G6PD deficiency. • Use with caution in anaemia, diabetes, vitamin B or folate deficiencies. • Monitor full blood count, renal function and liver function tests every 3-6 months • **Advise the patient on the risk of pulmonary and hepatic fibrosis, and the symptoms (such as chronic cough) to report if they develop during treatment. Reactions can develop acutely or insidiously. The incidence has been estimated to be anywhere from 1 in 550 to 1 in 5400 individuals.** • Advise the patient on the risk of peripheral and optic neuropathy, and the symptoms to report if they develop during treatment.
Trimethoprim	200mg One dose post-coital (off label) Or 100mg at night	• Hyperkalaemia: caution when prescribing with drugs such as spironolactone, ACE inhibitor or angiotensin inhibitors. • Renal Impairment: Avoid if eGFR <15ml/min. Discuss with renal physician if eGFR <30ml/min. May increase serum creatinine. • Patients should be counselled on the risk of blood disorders and advised to seek attention if fever, sore throat, purpura, mouth ulcers, bruising or bleeding occurs.

Amoxicillin	500mg single dose when exposed to a trigger (off label indication) Or 250mg at night if no improvement or no identifiable triggers (off label indication)	• Avoid if history of anaphylaxis, urticaria or rash immediately after previous penicillin administration
Cefalexin	500mg single dose when exposed to a trigger Or 125mg at night if no improvement or no identifiable triggers	• Contra-indicated in patients with cephalosporin hypersensitivity • Patients with a history of immediate hypersensitivity to penicillin and other beta-lactams should not receive a cephalosporin

NB Chose antibiotics according to recent culture and susceptibility results where possible. Consideration must be given to causative organism and resistance reporting. Broad spectrum antibiotics (e.g. co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow spectrum antibiotics are ineffective.

4. Managing a patient who has had a prolonged course of prophylactic antibiotics:

4.1 Identifying patients for review:

- Review antibiotic prophylaxis for recurrent UTI **at least every 6 months.**
- Patients who have urine cultures confirming resistance to the prophylactic agent they are on, should have their prophylaxis stopped (exposure to antibiotic without benefit) and a clinical review to discuss ongoing management and/ or need for referral.

4.2 Stopping continuous prophylaxis:

- The proportion of patients who will return to suffering rUTIs after stopping continuous prophylaxis may be around 50%.[6]
- This means a significant number of patients are able to stop continuous prophylaxis without a return of symptoms and therefore avoid the risks of resistance emerging and side-effects.
- One option is to provide 'standby' antibiotics when stopping continuous prophylaxis which may give sufficient reassurance to patients for a trial off antibiotics.
- Consider referring patients who relapse after stopping continuous prophylaxis, if not already been investigated.
- Longer term prophylaxis may be helpful in those patients whose UTIs are suppressed when on prophylaxis and recur when prophylaxis is discontinued.

5. Managing 'breakthrough' UTIs in patients on antibiotic prophylaxis:

- The first breakthrough infection should be treated according to culture and sensitivity results, with the original prophylaxis being re-started once the infection has resolved <u>if the culture confirms it is still sensitive to the prophylactic agent.</u>
- If the culture shows resistance to the prophylactic agent, or multiple breakthrough UTIs occur (≥2 UTIs in 6 months), prophylaxis has proved ineffective and should be stopped.
- Consider alterative prophylactic agent based on identification and sensitivity of the organism
- In absence of sensitivity data liaise with consultant microbiologist from acute Trust
- Consider referral to Urology or Urogynaecology at this point if not already been investigated.

6. Recurrent UTIs associated with urinary catheters[9]:

- Cloudy or offensive urine alone does not merit treatment or investigation for UTIs in patients with urinary catheters.
- Do not use dipsticks to diagnose UTIs in patients with urinary catheters as symptomatic UTIs cannot be differentiated from asymptomatic bacteriuria on the basis of dipstick urinalysis.
- Look for associated localising or systemic features including flank pain, and exclude other potential sources of infection in catheterised patients who present with fever.
- In general, antibiotic prophylaxis does not significantly decrease symptomatic infections

and increases the risk of antimicrobial resistance. It is therefore not usually recommended to reduce the frequency of UTIs in patients with urinary catheters.

- Seek explicit guidance from a microbiologist before commencing antibiotic prophylaxis in patients with a urinary catheter.
- Obtain a urine sample from the sampling port of the catheter using an aseptic technique (in line with the NICE guideline on healthcare-associated infection) and send for culture and susceptibility testing.
    - ➢ If the catheter has been changed, obtain the sample from the new catheter.
    - ➢ If the catheter has been removed obtain a midstream specimen of urine.

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Summary of Management of Recurrent Lower UTIs (in non-pregnant adults):

≥ 3 symptomatic lower UTIs / 12 months or

≥2 symptomatic lower UTIs / 6 months

Consider red flag indications for Urology referral

Advice on conservative measures

Postmenopausal women
Consider vaginal oestrogens. Discuss treatment option with the woman to ensure shared decision making

Consider risks and benefits with the patient of:

1. **Stand-by antibiotics**
2. **Post-coital antibiotics (if associated with intercourse)**
3. **Trial of continuous antibiotics**

For stand-by or post-coital antibiotics:

Review repeat prescriptions at least every 6 months to assess benefit and if any resistant urine cultures

Patients on continuous antibiotic prophylaxis

Trial of nightly antibiotics. Base on susceptibility and pt. history of drug allergy

Breakthrough UTI whilst on continuous prophylaxis

If more than one breakthrough UTI or the urine cultures are resistant to the prophylactic agent:

- Antibiotic prophylaxis has failed and therefore should be stopped
- Consider alterative prophylactic agent based on identification and sensitivity of the organism
- In absence of sensitivity data liaise with consultant microbiologist from acute Trust

No breakthrough UTIs

Review at least every 6 months, stop antibiotics

- Around half will have recurrent UTI symptoms after stopping
- Consider offering stand-by antibiotics if patient concerned
- Ensure access to treatment rapidly if symptoms of UTI recur

If recurrent UTIs return after stopping, consider referral.

Self-Management and stand-by pack advice sheet

You have been provided with a red-top urine sample pot and a stand-by pack of antibiotics.

What to do if you experience urinary tract infection symptoms:

1. Collect a mid-stream sample of your urine in the sample pot provided.
2. Place the pot of urine in a sealed plastic bag and hand in to the GP reception straight away. If there is a delay, store in the fridge and hand in on the next working day.
3. Take the first dose of the antibiotic supplied.
4. Follow the instructions for taking the full course of antibiotics.
5. Contact your GP practice to discuss the results of the urine culture (usually available 24-72 hours after handed into the practice), and to obtain a new sample pot and stand-by pack of antibiotics. The GP will check whether the same antibiotics are still appropriate for your next stand-by pack (if the antibiotic will still work against the bacteria in the urine).

What to do if the symptoms of urinary tract infection do not improve:

Your symptoms should start to improve once you start taking the antibiotics. If you have not improved within 48 hours, or the symptoms have got worse, or you feel feverish, develop new back pain or feel generally unwell, contact the GP practice, or call 111 if the GP practice is shut.

Urinary Infections Diary

	Date of start of symptoms	Date urine sample provided	Date of start of antibiotics (if given)	Date symptoms settled
1				
2				
3				
4				
5				
6				
7				
8				

Based on "Guidelines for Recurrent Urinary Tract Infections in Adults" by Authors: Dr Amelia Joseph, Mr Richard Parkinson and Dr Jane Coleman GP. http://www.nottsapc.nhs.uk/media/1217/uti-prophylaxis-guideline.pdf