Guidelines for Recurrent Urinary Tract Infections in Adults: Antibiotic Prophylaxis

Definition

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

Two or more episodes of lower urinary tract infection in the last 6 months, or
Three or more lower urinary tract infection episodes in the last 12 months[1].

It does not include bacteriuria in the absence of symptoms or catheterised patients, i.e., asymptomatic bacteriuria. 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 treatment)[2].

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

Consider whether the patient requires a specialist referral for the following factors[1,3].

Red Flags for Referral to Urology:

- 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 recurrent UTIs in pregnancy should be discussed with the Obstetrics team.

Consider risk factors:

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. Due to low oestrogen levels in post-menopausal women with recurrent UTIs, consider using intravaginal oestrogens[4].

Microbiological Confirmation:

Patients with rUTIs should have a mid-stream urine (MSU) sample sent for culture before antibiotics are initiated 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

In symptomatic patients with pyuria and a negative culture who do not respond to antibiotics as expected, consider whether an alternative diagnosis may be relevant. Sterile pyuria can occur in a number of infective conditions, including sexually transmitted diseases (e.g., Chlamydia), infections with organisms that are difficult to grow on standard culture, and renal tuberculosis, as well as non-infectious causes.

It is important to note that a negative urine culture in symptomatic patients with pyuria does not rule out infection[5]. Symptomatic patients with persistent sterile pyuria (persistent presence of white blood cells in the urine that repeatedly do not grow any organisms on routine culture) and symptoms strongly suggestive of urinary tract infection should be discussed with the duty microbiologist.

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].

'Clearance' cultures are not recommended if symptoms have resolved.

2. Management of Initial Presentation of Recurrent UTI in non-pregnant females- see flow chart

The following conservative measures may be advised however, the evidence is poor quality or inconclusive:

Conservative Measures:

- Drink plenty
- Avoid use of scented washes/wipes
- For sexually active women:
  - Advise post-coital voiding
  - Avoid use of contraceptive diaphragm and spermicide
- Perineal hygiene i.e., wiping front to back.
- Avoid using flannels. A clean unscented disposable wipe is preferable.
- Over-the-counter products – limited evidence but some women may find useful:
  - D-mannose (1g twice daily. Available without prescription)
  - Cranberry tablets (Follow individual product instructions. Available without prescription. Contraindicated in patients on Warfarin)[6]

Recurrent UTI Prophylaxis Prescribing Strategies

The relative risks and benefits of the following recurrent UTI prophylaxis prescribing strategies should be discussed with the patient. These strategies should be in addition to the conservative measures detailed above and are based on the patient's history and risk factors.

Summary of Prescribing Strategy Options	
Consider prescribing a vaginal oestrogen in peri- and post-menopausal women.	
Standby Antibiotics	A 'self-start' course of antibiotics if <1 episode per month
Post Coital Antibiotics	For rUTIs that are triggered by sexual intercourse
Continuous Antibiotic Prophylaxis	Continuous low-dose antibiotic prophylaxis
Continuous Urinary Antiseptic Prophylaxis	Continuous prophylaxis with methenamine hippurate as a first-line alternative to continuous antibiotic prophylaxis

- **Standby Antibiotics**
    - This option limits antibiotic exposure and risk of resistance emerging and may be the more suitable option for patients with <1 UTI per month. A Patient Advice Sheet and boric acid container for pre-antibiotic MSU should be provided to the patient. A urine specimen should be obtained when the patient becomes symptomatic, but patients can self-initiate antibiotics whilst awaiting the culture results.
    - Prescribe a 'self-start' antibiotic according to previously known sensitivities and choose the narrowest spectrum agent available[7]. Refer to Nottinghamshire APC Antibiotic Guidelines for more information.
    - Safety-net with advice to seek medical attention if they develop fever, loin pain, or symptoms are not improving by 48 hours.

- **Post Coital Antibiotics**
    - For rUTIs triggered by sexual intercourse, this strategy is as effective as continuous antibiotic prophylaxis[8] and reduces antibiotic exposure and the risk of resistance emerging.

- **Continuous Antibiotic Prophylaxis**
    - Continuous antibiotic prophylaxis is strongly associated with the development of antimicrobial resistance.

- A **6-month trial** of a low-dose nightly antibiotic may be beneficial if rUTIs are occurring ≥1 per month and are not triggered by sexual intercourse.
- Patients should be counselled at an early stage that antibiotic prophylaxis is not usually a lifelong treatment. Documenting and triggering a review date in the patient's record and on the repeat prescription is recommended to avoid prolonged courses of antibiotics without review.

- **Continuous Urinary Antiseptic Prophylaxis (Methenamine hippurate)**

  - Methenamine hippurate is a urinary antiseptic agent that is converted to formaldehyde in an acidic urine environment which is directly toxic to bacteria
  - A randomised control trial in 2022 demonstrated methenamine hippurate was non-inferior to prophylactic antibiotics for reducing the incidence of symptomatic UTIs over a 12-month period[9]
  - Continuous methenamine prophylaxis avoids the risks of long-term prophylactic antibiotic treatment, including the development of antibiotic resistance and adverse effects such as *C. difficile* infection
  - Methenamine may now be offered as a first-line alternative to continuous antibiotic therapy for UTI prevention in women. It may be initiated in primary care in women without urinary tract abnormalities or neuropathic bladder (Amber 3 classification).
  - Methenamine should **NOT** be used for the treatment of UTIs.
  - There is some evidence that methenamine works in an acidic urine environment. In the ALTAR study, the value of urinary acidification was not explored. Therefore, routine dipstick testing is currently not advised in this guideline until further evidence is available.

Choice of Agents for Prophylaxis[6,10]:

The choice of agent should be based on patient preference, consideration of the patient's co-morbidities, renal function and any contra-indicating factors. If prescribing antibiotics, the choice of antibiotic should be based on **confirmed culture and sensitivity results** (wherever possible). The antibiotics licensed for the prophylaxis of UTIs are trimethoprim and nitrofurantoin.

The risk of adverse effects (see box below), as well as common side-effects such as rashes, oral/vaginal thrush, and gastrointestinal upset, should be discussed with the patient.

First-line antibiotic options

Antibiotic	Dose	Cautions and Monitoring
Trimethoprim	200 mg one dose post-coital (off-label) or 100 mg nightly	• Hyperkalaemia: caution when prescribing medications such as spironolactone, ACE inhibitor or angiotensin inhibitors. • Renal Impairment: Avoid if eGFR <15ml/min. Discuss with a renal physician if eGFR <30ml/min. It 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.
OR:		
Nitrofurantoin	100 mg immediate release one dose post-coital (off-label) Or 50 mg nightly	• 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 to report if they develop during treatment. Reactions can develop acutely or insidiously. • Advise the patient on the risk of peripheral and optic neuropathy and the symptoms to report if they develop during treatment.

Or

Methenamine as an alternative to antibiotics

Antiseptic	Dose	Cautions and Monitoring
Methenamine	1 g twice a day	• Check baseline LFTs, U&Es and eGFR. • Not for the treatment of UTI. • Avoid in patients with a history of febrile UTI or previous urosepsis. • Contra-indications: Gout, metabolic acidosis, severe dehydration. • Renal impairment: Avoid if eGFR <10ml/min. • Hepatic impairment: Avoid. • Pregnancy: Preferable to avoid as inadequate evidence of safety. • Uncommonly can cause epigastric discomfort and skin reactions.

Second-line antibiotic options on urology or infection specialist advice only

If resistance to first-line antibiotics and methenamine, used as single agents, is not tolerated or contra-indicated, other antibiotic agents may be considered after discussion with Urology and/or an Infection Specialist if the patient is not under urology. Broader spectrum agents such as cefalexin, ciprofloxacin and co-amoxiclav have a higher risk of *C. difficile* diarrhoea and selection for resistance, so they should not be routinely used for prophylaxis and be reviewed with a trial of stopping after 6 months. In addition, MHRA has issued an alert restricting the use of Fluoroquinolone antibiotics, e.g. ciprofloxacin.

Second-line antibiotic options on urology or infection specialist advice only. Trial of stopping after 6 months.		
Antibiotic	**Dose**	**Cautions and Monitoring**
Cefalexin	500 mg one dose post-coital **or** 125 mg nightly	• Higher risk of selection for resistant infections • Higher risk of *C. difficile* infection
Pivmecillinam	200 mg one dose post-coital **or** 200 mg nightly	• Unknown safety profile and potential carnitine deficiency with prolonged use [10] • Note the BNF pivmecillinam dosing for "chronic or recurrent bacteriuria" is not applicable for recurrent symptomatic urinary tract infections.

3. Managing 'breakthrough' UTIs on a continuous prophylactic agent

Antibiotic prophylaxis

- The first breakthrough infection should be treated according to culture and sensitivity results if available, with the original prophylaxis being held and then restarted once the infection has resolved if the culture confirms susceptibility to the prophylactic agent
- If the culture shows resistance to the prophylactic agent, or multiple breakthrough UTIs occur (≥2 UTIs in 6 months), prophylaxis has therefore proved ineffective and should be stopped or changed to an alternative prophylactic agent (antibiotic or methenamine)
- Consider referral to Urology at this point if you have not already been referred

Methenamine prophylaxis

- The breakthrough infection should be treated according to culture and sensitivity results if available
- Methenamine prophylaxis should be continued alongside the antibiotic course for the breakthrough infection if there has been a good response
- If multiple breakthrough UTIs occur (≥2 UTIs in 6 months), methenamine should be stopped or changed to an alternative prophylactic agent (antibiotic)
- Consider referral to Urology at this point if not already been investigated

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

Antibiotic prophylaxis

Identifying patients for review:

- Patients should be reviewed after 6 months of prophylactic antibiotics with a view to stopping
- 12 months is a suggested trigger for audit purposes for patients on long-term antibiotic prophylaxis
- 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 the need for referral

Methenamine prophylaxis

Identifying patients for review:

- Patients should be reviewed after 6 months of prophylactic methenamine with a view to stopping
- If the patient starts to suffer from recurrent UTIs again and methenamine was effective previously, this can be restarted. Consider referral for investigation (if the patient has not already been investigated)

Stopping continuous prophylaxis:

It is understandable for patients to be anxious about a return to frequent UTIs after stopping continuous prophylaxis. However, a prolonged period of a prophylactic agent may allow bladder epithelial healing, reducing the risk of future UTIs when antibiotics are then stopped.

- The proportion of patients who will return to suffering recurrent UTIs after stopping continuous prophylaxis may be around 50%[8].
- 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 prophylaxis.
- Consider referring patients who relapse after stopping continuous prophylaxis, if not already been investigated.
- Longer term prophylaxis with an antibiotic or methenamine may be helpful in those patients whose UTIs are suppressed when on prophylaxis and recur when prophylaxis is discontinued after 6 months.

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

≥ 3 symptomatic lower UTIs / 12 months or

≥2 symptomatic lower UTIs / 6 months

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Consider red flag indications for Urology referral (see page 1)

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Advice on Conservative Measures (see page 2)

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Consider risks and benefits with the patient of:

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

→ **For Stand-by or Post-coital antibiotics:**

Review repeat prescriptions at 6 month to assess benefit and if any resistant urine cultures

Choice dependent on factors outlined on page 4

Continuous antibiotic prophylaxis

Trial of 6 months of nightly antibiotics (see page 3)

No breakthrough UTIs →

After 6 months, stop prophylaxis

Around 50% will not return to recurrent symptoms.

Consider offering stand-by antibiotics if patient concerned.

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If recurrent UTIs return after stopping, restart and consider referral

Breakthrough UTI whilst on prophylaxis →

If ≥2 breakthrough UTIs, or the urine cultures are resistant to the prophylactic agent:

Antibiotic prophylaxis has failed and should be stopped or changed

Consider referral if not already investigated

Continuous methenamine prophylaxis

Trial of 6 months of methenamine (see page 3)

No breakthrough UTIs →

After 6 months, stop prophylaxis

Around 50% will not return to recurrent symptoms.

Consider offering stand-by antibiotics if patient concerned.

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If recurrent UTIs return after stopping, restart methenamine and consider referral

Breakthrough UTI whilst on prophylaxis →

If ≥2 breakthrough UTIs:

Methenamine prophylaxis has failed and should be stopped or changed

Consider referral if not already investigated

References

1. Grabe, M., Bjerklund-Johansen, T. E., Botto, H., Çek, M., Naber, K. G., & Tenke, P. (2015). Guidelines on urological infections. European Association of Urology.
2. Nicolle, L. E., Bradley, S., Colgan, R., Rice, J. C., Schaeffer, A., & Hooton, T. M. (2005). Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clinical Infectious Diseases*, 643-654.
3. NICE Clinical Knowledge Summaries: https://cks.nice.org.uk/urinary-tract-infection-lower-women#!scenario:2 accessed June 2022.
4. Scottish Intercollegiate Guideline Network. A national clinical guideline 160. Management of suspected bacterial urinary tract infection. Updated September 2020.
5. Public Health England. UK SMI B41i8.7. Updated January 2019.
6. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD001321. DOI: 10.1002/14651858.CD001321.pub5
7. Public Health England. Diagnosis of UTI. Quick Reference Guide for Primary Care. Updated May 2020.
8. Albert X, Huertas I, Pereiro I, Sanfélix J, Gosalbes V, Perrotta C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD001209. DOI: 10.1002/14651858.CD001209.pub2
9. Harding C, Mossop H, Homer T, et al. Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial. BMJ. 2022;376:e068229. Published 2022 Mar 9. DOI:10.1136/bmj-2021-0068229
10. Urinary tract infection (recurrent): antimicrobial prescribing NICE guideline [NG112] Published date: October 2018: https://www.nice.org.uk/guidance/ng112 accessed online June 2022