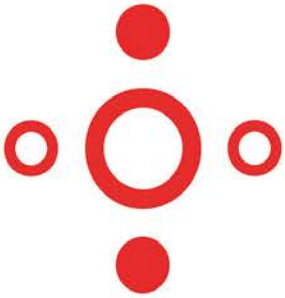
Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group



Management of Recurrent Symptomatic Urinary Tract Infection in Adult Women

March 2022

(July 2022 – updated 'Non-antimicrobial therapies' section with additional information on open-label trial for methenamine hippurate)

This document has been prepared by the All Wales Antimicrobial Pharmacist Group (AWAPG) and the All Wales Antimicrobial Guidance Group (AWAGG), with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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Acknowledgements
This guidance has been adapted from:

- Swansea Bay University Health Board. Primary Care Antimicrobial Guidelines. Recurrent (symptomatic) UTIs. March 2021. RxGuidelines 2021 – Horizon Strategic Partners – 2.0.0.0. Available from: https://viewer.rx-guidelines.com/SBUHB/abx#content,mb65dDoX4o.
- Hywel Dda University Health Board. Primary Care Antimicrobial Guidelines. Recurrent UTIs. December 2018. MicroGuide 2021 – Horizon Strategic Partners – 2.0.0.0. Available from: https://viewer.rx-guidelines.com/HDUHB/Abx#content,9032c8f5-bb50-45d0-8c21-fc52644b736b.

1.0 Background

This guideline is aimed at all community and non-specialist medical, nursing and pharmacy staff involved in the prescribing and management of recurrent urinary tract infections (UTIs). This guideline is intended for non-pregnant, non-catheterised women aged 16 years and over.

2.0 Definition

Recurrent lower urinary tract infection is defined as[1]:

- three or more episodes of lower urinary tract infections in the last 12 months; **or**
- two or more episodes of lower urinary tract infections in six months.

3.0 Referral

Referral or seeking specialist advice from the most appropriate specialty on further investigation and management is recommended for:

- men aged 16 years and over[2].
- people who are catheterised, so as to ensure appropriate catheter care and reduce the risk of infection[3].
- people with recurrent upper UTI[2] (more than two episodes within 12 months).
- people with recurrent lower UTI when the underlying cause is unknown[2].
- people who do not respond to prophylactic antibiotics, including two or more episodes of UTIs returning after stopping prophylactic antibiotics[4].
- recurrent UTI in women with previous radiation treatment or pelvic cancer (as they are at risk of fistula formation)[4].
- pregnant women.
- children and young people under 16 years in line with the NICE guideline on urinary tract infection in under 16s[2].
- people with suspected cancer in line with the NICE guideline on suspected cancer: recognition and referral[2].
- people with structural abnormalities e.g. renal stones[5].
- people with neurological disease e.g. spinal cord injuries[1].

Also consider whether the patient requires specialist referral for the following “red flag” factors:

- Patient over 60 years with persistent non-visible new haematuria and dysuria/bladder pain or raised white cell count (WCC) on blood test[4].
- Visible haematuria in the absence of positive culture or persists after treatment of UTI[4].
- Pneumaturia (bubbles in urine)[4].

When referring patients to secondary care, please ensure referral is made to the most appropriate specialty (e.g. obstetrics, gynaecology, urology, urogynaecology, paediatrics).

4.0 Non-antimicrobial therapies

The following agents may be used as part of an antimicrobial sparing regime.

Vaginal (not oral) oestrogen:

- Consider use for postmenopausal women if behavioural and personal hygiene measures (see Self Care section below) not effective or appropriate, as they can reduce the risk of UTI[1,2,6]. Vaginal oestrogen products are not licensed for preventing recurrent UTI, so this use would be off-label.
- Review treatment within 12 months, or earlier if agreed with the woman[2].

Methenamine hippurate[2,7]:

- Conflicting advice for use in recurrent UTIs
- Does not appear to be effective in patients with neuropathic bladder or in patients who have renal tract abnormalities.
- Limited evidence that it may prevent UTI in the short term in patients without renal tract abnormalities.
- Review ongoing therapy after six months.
- BNF lists methenamine as a medication less suitable for prescribing, although they acknowledge that it may have a role in the prophylaxis and treatment of chronic or recurrent uncomplicated lower UTIs[8].
- In 2022, the outcomes of an open-label trial demonstrated non-inferiority when comparing methenamine hippurate to standard antimicrobial prophylaxis in women with a history of recurrent UTI[9].

Over the counter, purchasable options (not available on prescription):

- Some women with recurrent UTI may wish to try D-mannose if they are not pregnant[1,2].
- Some women with recurrent UTI may wish to try cranberry products if they are not pregnant (evidence of benefit is uncertain and there is no evidence of benefit for older women)[1,2].
    - Patients taking warfarin should be advised to avoid cranberry products due to potential interactions[10].
- Be aware that evidence is inconclusive about whether probiotics (lactobacillus) reduce the risk of UTI in people with recurrent UTI[2].

5.0 Self care

Give advice to people with recurrent UTI about behavioural and personal hygiene measures and self-care treatments that may help to reduce the risk of UTI[6]. Select the appropriate advice for your patient depending on co-morbidities:

- Ensure adequate hydration to pass pale coloured urine regularly during the day and to avoid feeling thirsty, especially during hot weather. Encourage water, decaffeinated drinks and avoid fizzy drinks.
- Encourage urge-initiated voiding and post-coital voiding.
- Avoid delay of habitual and post-coital urination.
- Encourage good vulval hygiene. Consider use of soap substitutes to avoid skin irritation.
- Wipe from front to back after defaecation.
- Showers are preferred to baths[4].
- Wear loose, comfortable clothing made from natural fibres[5].
- Avoid douching and occlusive underwear.
- Avoid constipation.

- Consider alternative to spermicide-containing contraceptives as these can increase the risk of UTIs[11].
- Some experts may also advise timed voiding in the elderly; forward pelvic tilting during voiding; pelvic floor relaxation techniques; avoidance of tampons or vaginal pessaries in favour of alternatives; avoidance of perfumed soaps that may reduce natural mucosal barriers[12].

6.0 Assessment

- Arrange urine culture to check for resistant or atypical organisms.
- If appropriate, exclude chlamydia
- Consider referral to urology/urogynaecologist, if recurrent UTI in women with history of:
  - pelvic cancer or pelvic radiotherapy
  - complex pelvic surgery
  - urinary incontinence or prolapse procedures with surgical mesh.

Take a careful history and distinguish between a persistent UTI (same organism with small gaps between treatment) or a recurrent UTI (different organisms or resolution of symptoms and significant gaps between episodes) as each of these will require different management strategies.

Persistent infection

Consider a prolonged course of antibioitcs to eradicate the infection from the bladder and allow the urothelium to heal (this should initially be for a total of 6 weeks initially). Antibiotic choice should be based on cultures and sensitivities. **This should not be confused with prophylaxis**.

All patients with persistent infection should be referred to a urologist.

Recurrent infection

Recurrent UTI is defined as two or more episodes of lower UTI in the last six months or three or more episodes of lower UTI in the last 12 months.

Recurrent infection

Take a careful history to look for trigger factors* for UTI. If a trigger factor is found, consider:
steps to reduce the risk from the trigger factor and/or consider single dose prophylaxis given at the time of the trigger factor (e.g. sexual intercourse).

If this does not help, recurrent UTIs should be treated with provision of rescue antibiotic treatment in preference to long-term prophylaxis whenever possible.

If no other strategy works, and a 3–6 month trial of daily prophylaxis is deemed appropriate, then choose the most appropriate antibiotic based on culture and sensitivity and patient characteristics. Monitor closely and review regularly. Stop after six months and monitor for anv recurrence.

* Triggers include: intercourse, menstruation, menopause, constipation and diabetes (new or poorly controlled).

7.0 Trigger antibiotics

Prescribe antibiotics and advise that a single dose is to be taken when exposed to a trigger.

Triggers may include:

- intercourse
- menstruation
- constipation.

Note: Post-coital antibiotic prophylaxis should be taken within two hours of coitus.

Other triggers may include menopause and diabetes (new or poorly controlled). Consider treating underlying issues before starting antibiotics.

Treatment choice must be made with consideration of recent culture and sensitivity results if available.

First choices[2]:

- Nitrofurantoin 100 mg single dose when exposed to a trigger (if estimated glomerular filtration rate [eGFR] ≥ 45 ml/minute)
  or
- Trimethoprim 200 mg single dose when exposed to a trigger.

Second choice[2]:

- Cefalexin 500 mg single dose when exposed to a trigger.

8.0 Rescue antibiotics

Patients should be trialled with 'trigger' or 'rescue' antibiotic treatment in preference to long-term prophylaxis whenever possible. This reduces the total exposure to antibiotic therapy, reduces the risk of exposure to sub-therapeutic doses of antibiotic therapy and thereby slows the development of a resistance.

- Choice of antibiotic should be made with consideration of recent culture and sensitivity results if available or in line with the recommendations for 'Lower UTI' made in the AWMSG All Wales Primary Care Antimicrobial Guidelines.
- **Do not** issue as a repeat prescription.
- Frequent requests should trigger a clinical review. If there are any trigger factors for UTI, take steps to reduce risks and manage underlying conditions before starting antibiotics.

Rescue antibiotics should be taken at the first sign of urinary tract infection. This strategy is likely to be effective in patients that have clear symptomatology. Provide patient with urine sample pot to collect a sample prior to initiation of antibiotics.

9.0 3–6 month prophylaxis course

- **3–6 month UTI prophylaxis is generally not recommended and should only be used in patients with either a temporary reason for requiring extended prophylaxis or in cases where alternative strategies have failed and the risk of infection is deemed to clearly outweigh the risk of development of antimicrobial resistance**.
- When prescribing prophylactic antibiotics, factors that should be considered include:
    - risk profile of antibiotic
    - suitability of antibiotic (allergy, renal function, other comorbidity or risk factors)
    - microbiology results
    - propensity to cause *Clostridioides difficile*.
- Whenever possible prophylactic agent with a low propensity to cause disruption to the faecal microbiome should be chosen (e.g. nitrofurantoin).
- Cycling of antibiotics is not encouraged. It is common for patients receiving UTI prophylaxis to subsequently become colonised with bacteria that are resistant to the antibiotic being given and develop infections with resistant bacteria. The act of cycling antibiotics during prophylaxis will tend to result in colonisation with multi-drug resistant bacteria.
- It is likely that there will still be some patients for whom 3–6 month UTI prophylaxis is appropriate. However, use of 3–6 month UTI prophylaxis should be the exception rather than the rule, and the decision to provide prophylaxis should be regularly reviewed. It should only be tried if alternative strategies have been unsuccessful.

9.1 Antibiotic choice

When starting UTI prophylaxis offer a 3–6 month course of low-dose continuous antibiotic treatment.

- Before any prophylaxis regimen is initiated, eradication of a previous UTI should be confirmed by a negative urine culture 1–2 weeks after treatment.
- Patients should be made aware that this is a 3–6 month course only. The antibiotic will be reviewed at three months and stopped after a maximum of six months and the patient monitored for recurrence and /or offered alternative strategies.

The choice must be made with consideration of recent culture and sensitivity results.

First choices[2]:

- Nitrofurantoin 50–100 mg at night (if eGFR ≥ 45 ml/minute)
  or
- Trimethoprim 100 mg at night

Second choice[2]:

- Cefalexin 125 mg at night

10.0 Reviewing and monitoring prophylaxis

Following initiation, the patient should be reviewed for a clinical response after three months and after stopping the antibiotics at six months.

When reviewing antibiotic prophylaxis, confirm the effectiveness of the strategy (is the frequency of UTI significantly lower when on prophylaxis) and check for the development of resistance.

Development of a single UTI with a resistant bacteria is not necessarily an indication to change the prophylaxis as a change is likely to only result in further resistance. The measure of success of any prophylaxis, regardless of the presence of resistant bacteria, is whether or not it reduces the frequency of UTI.

After six months of prophylaxis is complete, discuss behavioural and personal hygiene measures and self-care with the patient, and discuss alternative strategies for management and prevention.

No break-through UTIs in last six months

Stop prophylaxis or offer standby antibiotics if patient concerned – ensure patient is counselled on simple self-care measures.

Monitor for any recurrences.

Two or more break-through UTIs (in last six months) or urine culture resistant to prophylactic agent

Consider alternative strategies for management/prevention and **stop** prophylactic antibiotic.

Consider referral.

11.0 Monitoring for adverse effects

Please refer to the BNF[8] and the Summaries of Product Characteristics (SPCs)[13,14] for full prescribing details and monitoring information.

11.1 Nitrofurantoin[8,13,15]

Tests prior to starting

- Full Blood Count
- Liver Function Tests
- Renal Function - urea and electrolytes, creatinine
  (Nitrofurantoin is ineffective at an eGFR of less than 45 ml/minute and there is also a risk of an increased incidence of adverse effects).

Tests during treatment

- Liver Function Tests (due to a risk of cholestatic jaundice and hepatitis)
- Renal Function - urea and electrolytes, creatinine.

These should be measured ‘periodically’. More frequent monitoring is required when the patient’s condition is fluctuating.

Note that the onset of hepatotoxicity can be insidious and symptoms can be non-specific (e.g. nausea, rash, headache, flu-like symptoms). Cholestatic jaundice is generally associated with short-term therapy (usually up to two weeks) whereas chronic active hepatitis, occasionally leading to hepatic necrosis, is generally associated with long-term therapy (usually after six months).

Clinical Monitoring during treatment
If prescribing prolonged courses for prophylaxis, then liver function and the appearance of neurological or pulmonary symptoms should be monitored and, if these or other evidence of toxicity arise, therapy should be stopped. The main risk factor for adverse drug reactions is impaired renal function[13].

Pulmonary
The incidence of pulmonary disease is hard to assess but can be fatal. The severity of chronic pulmonary reactions and their degree of resolution appear to be related to the duration of therapy after the first clinical signs appear. Elderly patients should be monitored closely. It is therefore important to recognise symptoms as early as possible. Note that minor symptoms such as fever, chills, cough and dyspnoea may be significant[13]. Pulmonary function may be impaired permanently, even after stopping treatment. There are three types of pulmonary disease:

- Acute pneumonitis syndrome which is an allergic reaction; symptoms are chills, fever, dyspnoea, cough, cyanosis and there is a rapid resolution after withdrawal of drug.
- Subacute pneumonitis. Symptoms are dyspnoea, orthopnoea, cough, pulmonary infiltrates and pleural effusions may be present.
- Chronic interstitial fibrosis may occur after six months of treatment. Symptoms are dyspnoea, non-productive cough. There is a good prognosis if nitrofurantoin is discontinued promptly.

Nitrofurantoin must be withdrawn at the first sign of pulmonary damage.

Neurological
Peripheral neuropathy is seen with long-term therapy and associated with renal failure not necessarily severe enough to raise blood urea. Symptoms are paraethesia beginning in extremities, ascending bilaterally and symmetrically followed by paralysis of varying extent. In most patients, it occurs within 45 days of starting and patients should be advised to report paraethesia[8,13].

11.2 Trimethoprim[8,14]

Tests prior to starting
- Full Blood Count
- Renal Function (urea, electrolytes and creatinine). Adjust dose according to renal function.

Tests during long-term treatment
- Full Blood Count - every six months (see below)
- Renal Function (urea, electrolytes & creatinine) - every six months.

Clinical monitoring during treatment

Folate deficiency: There is a theoretical risk of folate deficiency with long-term use of trimethoprim. Caution should be exercised in patients with a predisposition to folate deficiency (e.g. elderly patients) and adding a folate supplement should be considered. The manufacturer recommends blood counts on long-term therapy[14], but evidence of practical value is unsatisfactory. Megaloblastic anaemia has been reported but is rare and usually mild, except in pre-existing folate deficiency. If interference in haematopoiesis is seen folinic acid should reverse the effect[14].

Blood disorders:

Patients and their carers should be told how to recognise signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. Manufacturer recommends monitoring full blood counts[14].

Hyperkalaemia:

Close monitoring of serum electrolytes is advised in patients at risk for hyperkalaemia. Hyperkalaemia is a very common adverse effect of trimethoprim treatment[14].

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