Management of recurrent urinary tract infection (rUTI) in non-pregnant adult females (≥16 years old)

Recurrent UTI is common in women of all ages and has a significant impact on quality of life. A number of interventions that reduce the number of episodes experienced by affected women are available. **Non-antimicrobial options can be highly effective if applied consistently** and minimise both the risk of antimicrobial-related adverse drug effects and the risk of antimicrobial resistance.

Antimicrobial prophylaxis should only be offered to suitable women after non-antimicrobial prevention has been found to be ineffective. Continuous single-agent antimicrobial prophylaxis for a maximum of 6 months should be used as a last resort option, and be reviewed after every episode of UTI while prophylaxis continues.

The following document is based on recommendations from the Scottish Intercollegiate Network (SIGN) Guideline 160: Management of suspected bacterial lower urinary tract infection in adult women

This document does not apply to

- **children under the age of 16**
- **males (of any age)**
- **women ≥16 years old who are pregnant or have a long-term urinary catheter**

In these patient groups management of rUTI should be discussed with an appropriate specialist, and antimicrobial prophylaxis started only under their guidance.

Reference: ADTC 337/2 **Supersedes**: ADTC 337/1
Written by: Dr Ursula Altmeyer, on behalf of the Antimicrobial Management Team (AMT)
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1. Evaluating prophylaxis options for women with rUTI

Step 1 – Are diagnostic criteria for rUTI met?	Yes	No
≥2 episodes in 6 months or ≥3 episodes in 12 months?		
For each separate episode, did the following apply?		
≥2 recognised symptoms of UTI		
Urinalysis positive for nitrates and leucocytes?		
Vaginal discharge absent		

The accepted clinical symptoms of UTI are **dysuria, frequency, urgency, visible haematuria, and nocturia**. A diagnosis of UTI should be made based on presence of **≥2 of these symptoms AND - in pre-menopausal women - a urinalysis positive for nitrites and leucocytes**.

In patients with ≥2 recognised symptoms of UTI, but a urinalysis that is *negative* for nitrates or leucocytes, **consider urine culture as an additional diagnostic test**. **Culture from a mid-stream sample of urine** is not necessary for patients presenting with a first-ever UTI, but **should be sent for every episode of rUTI** to monitor for development of antimicrobial resistance.

Diagnosis of UTI in post-menopausal women can be challenging and should not be made based on a change in appearance or smell of urine, positive urinalysis, or growth of bacteria in a urine culture without recognised symptoms of UTI. The Scottish Antimicrobial Prescribing Group has developed a useful decision aid.

To count as separate episodes, urinary symptoms should have settled completely (with or without treatment) before onset of the next episode of UTI.

The following patients should not be diagnosed with UTI:

- Patients with symptoms of UTI and new vaginal discharge
- Patients with a positive urine culture but no typical urinary symptoms – **this is asymptomatic bacteriuria and should not be treated.**

If the answer to any of the above is "NO", do not continue with the evaluation, as the criteria for rUTI have not been met for this patient.

Urology advise the following investigations for any woman that fulfils rUTI criteria:

- Check of renal function and blood glucose
- Clinical examination of abdomen and genital tract
- Renal tract ultrasound imaging

If renal tract USS shows dilated renal tract or residual bladder volume of >300mls after voiding OR renal function is impaired, refer URGENTLY to urology.

If renal tract USS shows no abnormality, proceed to step 2.

The following measures should be used for prevention of rUTI in the first instance:

Step 2 - Non-antimicrobial options for prevention of rUTI	Discussed
Increase fluid intake to 2.5 litres or 6-8 mugs of fluid /day	
Urge-prompted voiding, i.e. not "holding on"	
Timed voiding, e.g. every 2-3 hours even if no urge	
Wiping "front-to-back" after using the toilet	
Washing genitals with plain water before and after sexual intercourse	
Voiding within 15 minutes of sexual intercourse	
Stopping use of spermicidal contraception	
Intra-vaginal oestrogens (post-menopausal patients only)	
D-mannose (only if rUTI caused by *E.coli*)	
Methenamine hippurate + vitamin C	

Material that helps patients assess whether their oral fluid intake is sufficient is available on the National Hydration Campaign website.

Patient leaflets are available from the Royal College of General Practitioners, the British Association of Urological Surgeons (BAUS), and Public Health England.

D-mannose is a metabolically inert sugar that is available to buy without prescription in powder and tablet form. **It has no effect on blood sugar levels.** The proposed mechanism of action is inhibition of bacterial adherence to mannose on urothelial cells by binding uropathogenic *E.coli* to D-mannose present abundantly in urine. D-mannose is available from a variety of on-line stockists, pharmacies, or from health shops. BAUS recommend a daily dose of 2g. D-mannose is not a medicine and cannot be prescribed on the NHS. It costs approximately £15 for 30 tablets. As patients will have to purchase D-mannose themselves this is an option that will not be affordable or suitable for some patients.

Methenamine hippurate is converted to formaldehyde and ammonia in acidic urine and can be used as a urinary antiseptic. It is usually taken with vitamin C to adequately acidify the urine.

Do not proceed to step 3 unless non-antimicrobial measures have been ineffective at preventing further episodes of UTI.

For **women who experience UTI after sexual intercourse, and in whom self-care measures in step 2 have failed to be effective, offer post-coital single dose antimicrobial prophylaxis** (to be taken within 2 hours of intercourse) with either

- Nitrofurantoin 100mg stat post-coital dose (off-label use) **OR**
- Trimethoprim 200mg stat post-coital dose (off-label use)

For women without a clear trigger for rUTI in whom self-care measures have not been effective, **consider whether the patient would be able to adhere to instructions for stand-by antimicrobials**. If the patient is deemed suitable, supply them with

- A **red top boric acid urine container**, so sampling can be undertaken at home at the onset of urinary symptoms
- **Instructions on submitting a mid-stream sample of urine before the antimicrobial is taken**

- A **3 day course of an appropriate antimicrobial** based on susceptibilities for the isolate grown during the most recent episode of UTI. **If no resistance is reported, nitrofurantoin or trimethoprim should be supplied preferably.** The choice of agent must be reviewed regularly with available culture results.

Step 3 – Intermittent and stand-by antimicrobials	**Suitable**	**Failed**	**Not suitable**
Single-dose post-coital antimicrobial			
Stand-by 3 day course of antimicrobial			

If patients are unsuitable for either of the interventions in step 3 or they have failed to be effective, proceed to step 4.

Step 4 – Time-limited continuous antimicrobial prophylaxis in addition to non-antimicrobial measures	**Accepted by patient/carer**	**Not accepted by patient/carer**
Risk of drug-related side effects and adverse events		
Need for monitoring for adverse events (see cautions below)		
Risk of resistant infections		
Time-limited nature of intervention - 3-6 months		
Importance of ongoing non-antimicrobial measures (See step 2)		

Single daily dose antimicrobials, usually taken at night, are effective at reducing the number of UTIs experienced while prophylaxis is ongoing. **The number needed to treat (NNT) to prevent 1 episode of UTI in women with rUTI under the age of 65 is 2.2, but it is 8.5 in those over the age of 65.**

The **potential risks and benefits should be discussed and weighed up very carefully** in any patient for whom continuous prophylaxis is considered, and **particularly in those over the age of 65**, as they may be at increased risk of adverse events due to age, comorbidities, and polypharmacy.

Continuous antimicrobials should only be used for 3-6 months. The hypothesis is that an infection-free period allows the bladder to "heal" which will make future UTI less likely. There is no evidence that prophylaxis has any additional benefits if continued for more than 6 months, and the risk of adverse events and resistance development increases with increasing durations of exposure. Life-long continuous prophylaxis is no longer recommended. **It is important to explain the time-limited nature of the intervention at the outset, and ideally a stop date should be agreed in advance to help manage patient expectations.**

Due to its lack of systemic effect and high concentration in the urine, oral **nitrofurantoin 100mg at night is the preferred agent for continuous prophylaxis**. Alternatively, oral trimethoprim 100mg at night can be used.

Due to the risk of *C.difficile* infection associated with cephalosporin use, cefalexin should not be offered for prophylaxis.

Cautions

Avoid nitrofurantoin if eGFR <45ml/min, or patient at increased risk of peripheral neuropathy. **Long-term nitrofurantoin** is associated with pulmonary fibrosis, hepatitis, and peripheral neuropathy. Patients receiving continuous prophylaxis, especially those >65, should have liver and renal function monitored and undergo lung function testing. Discontinue nitrofurantoin if the patient develops any deterioration in lung function or signs of possible peripheral neuropathy.

Long-term trimethoprim can cause hyperkalaemia; avoid use alongside other drugs affecting potassium homeostasis, e.g. spironolactone, ACE inhibitors or angiotensin II inhibitors. Patients on long-term trimethoprim should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develops. Manufacturer recommends monitoring of full blood count with long-term use, especially in those at risk of folate deficiency.

Checklist: Evaluating prophylaxis options for women with rUTI

Step 1 – Are diagnostic criteria for rUTI met?	Yes	No
≥2 episodes in 6 months or ≥3 episodes in 12 months?		
For each separate episode, did the following apply?		
≥2 recognised symptoms of UTI		
Urinalysis positive for nitrates?		
Vaginal discharge absent		

If the answer to any of the above is "NO", do not continue with this checklist, as the criteria for rUTI have not been met.

Assess need for urgent urology referral before proceeding to step 2 (see page 2).

Step 2 - Non-antimicrobial options for prevention of rUTI	Discussed
Increase fluid intake to 2.5 litres or 6-8 mugs of fluid /day	
Urge-prompted voiding, i.e. not "holding on"	
Timed voiding, e.g. every 2-3 hours even if no urge	
Wiping "front-to-back" after using the toilet	
Washing genitals with plain water before and after sexual intercourse	
Voiding within 15 minutes of sexual intercourse	
Stopping use of spermicidal contraception	
Intra-vaginal oestrogens (post-menopausal patients only)	
D-mannose (only if *E.coli* UTI)	
Methenamine hippurate + vitamin C	

Do not proceed to step 3 unless the above non-antimicrobial measures have been ineffective at preventing further episodes of UTI.

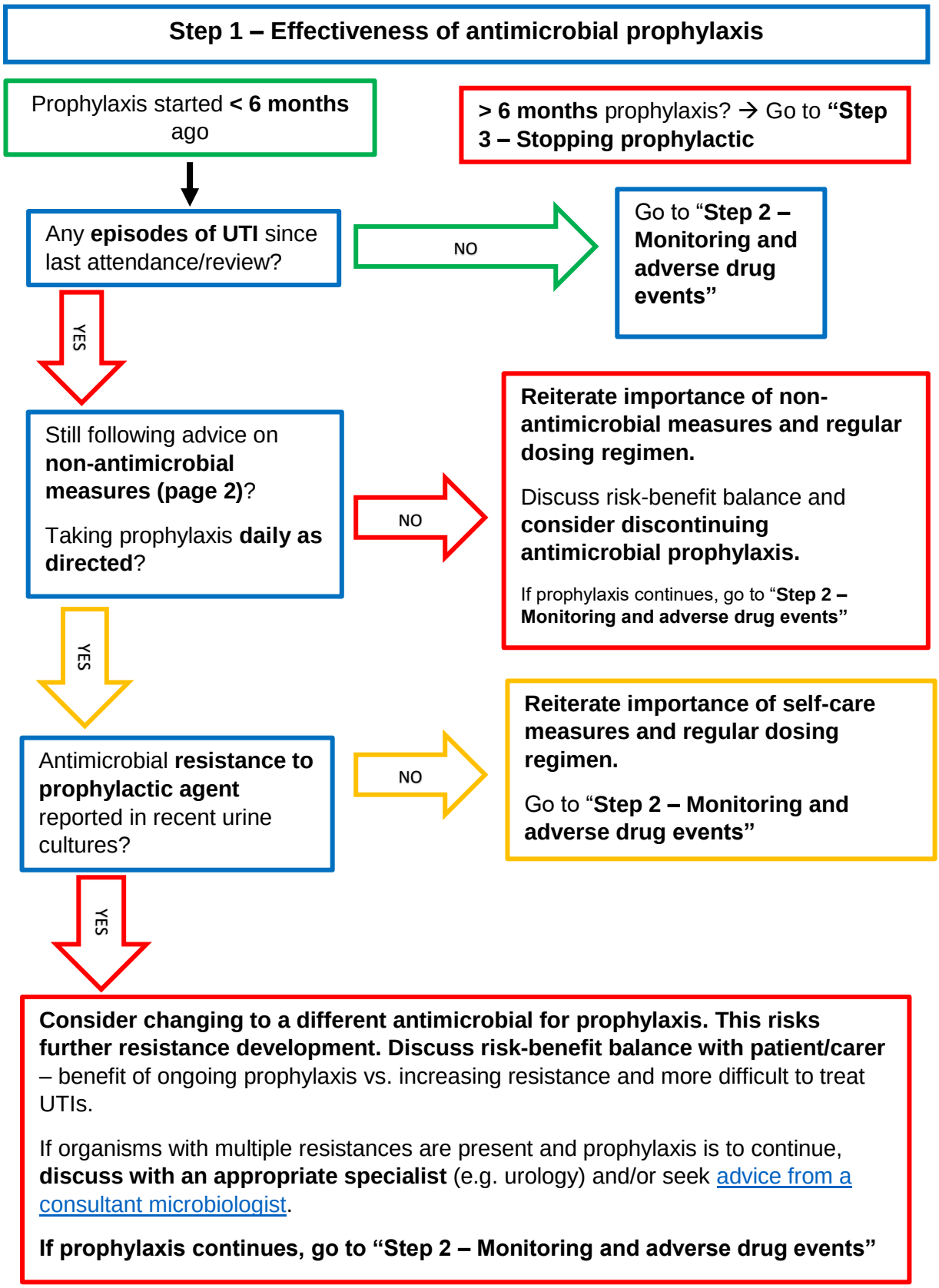
Step 3 – Intermittent and stand-by antimicrobials	Suitable	Failed	Not suitable
Single-dose post-coital antimicrobial			
Stand-by 3 day course of antimicrobial			

If patients are unsuitable for either of the interventions in step 3 or they have failed to be effective, proceed to step 4.

Step 4 – time-limited continuous antimicrobial prophylaxis in addition to non-antimicrobial measures	Accepted by patient/carer	Not accepted by patient/carer
Risk of drug-related side effects and adverse events		
Need for monitoring for adverse events		
Risk of resistant infections		
Time-limited nature of intervention – 3-6 months		
Continue non-antimicrobial measures (page 2)		

2. Review of women receiving antimicrobial prophylaxis for rUTI

Women on time-limited antimicrobial prophylaxis should be reviewed regularly to assess effectiveness of the intervention and to monitor for drug-related adverse events.



Adverse events related to antimicrobials are common, and become more likely the longer the antimicrobial is taken for. Nitrofurantoin in particular commonly causes side-effects severe enough to discontinue treatment (RR 1.83). **Both nitrofurantoin and trimethoprim have a number of potentially severe side effects for which patient education and regular monitoring are required (see cautions on page 4).**

Step 2 – Monitoring and adverse drug events

Have there been serious adverse events related to the prophylactic antimicrobial?

Allergic reactions (any agent): severe rash or anaphylaxis

Nitrofurantoin: evidence of deteriorating lung function, deranged liver function tests, evidence of peripheral neuropathy

Trimethoprim: neutropenia or thrombocytopenia, hyperkalaemia

YES

Discontinue agent immediately.

Discuss risk-benefit balance and consider switch to alternative agent or stopping prophylaxis. **If prophylaxis is stopped, reiterate non-antimicrobial measures (page 2).**

If patient has **contra-indications/severe adverse events with both nitrofurantoin and trimethoprim and prophylaxis is to continue**, discuss with an appropriate specialist (e.g. urology) and/or seek advice from a consultant microbiologist.

NO

Have there been any other side effects, e.g. GI upset?

Are they severe enough for the patient to want to stop taking their current prophylactic agent?

YES

Discuss risk-benefit balance and consider switch to alternative agent or stopping prophylaxis altogether.

If prophylaxis is stopped, reiterate non-antimicrobial measures (page 2).

NO

Should any monitoring tests be repeated?

Nitrofurantoin: lung function tests, renal function, liver function

Trimethoprim: full blood count

Remind patient of time-limited nature of the intervention and agree when prophylaxis will stop. There is no additional benefit from antimicrobial prophylaxis that is continued for more than 6 months.

3. Stopping antimicrobial prophylaxis

If antimicrobial prophylaxis has been effective and well tolerated, patients may express a wish to continue with the intervention indefinitely. **Agreeing a defined course length at the outset will help manage the patient's expectations.**

Limiting continuous prophylaxis to a maximum of 6 months both **prevents development of antimicrobial resistance**, especially accumulating resistances to different classes of antimicrobials caused by "cycling" prophylactic agents over a long period of time, **and limits the risk of severe drug-related adverse events**, particularly that of lung fibrosis secondary to long term nitrofurantoin use.

Patients who have been started on antimicrobial prophylaxis for rUTI in the past and have continued with prophylaxis for more than 6 months without an agreed stop date should be invited for review and discussion.