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:

- **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**\(^1\).

It does **not** include bacteriuria in the absence of symptoms or in 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 treating)\(^2\).

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

Consider whether the patient requires 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:

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.

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.\(^4\)

‘Clearance’ cultures are not recommended if symptoms have resolved, with the exception of pregnant women.

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

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

### Conservative Measures:

- Drink plenty
- D-mannose is worth trying (1g twice daily. Available without prescription)
- Cranberry tablets are worth trying (Follow individual product instructions. Available without prescription)
- Avoid use of feminine hygiene products
- 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 non scented disposable wipe is preferable.

### Intra-vaginal oestrogens:

- For post-menopausal women with recurrent UTIs, consider intravaginal oestrogens\(^4\).
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. Some patients may find cranberry juice or products helpful, however the evidence for their benefit is variable and compliance is low, so they are not routinely recommended\(^6\). It is also contraindicated in patients on Warfarin.

- **Standby Antibiotics**
  - If the patient is able to wait, infection should first be confirmed by MSU prior to commencing standby antibiotics.
  - 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\(^5\). 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.
  - This option limits antibiotic exposure and risk of resistance emerging, and may be the more suitable option for patients with <1 UTI per month.

- **Post Coital Antibiotics**
  - For rUTIs that are triggered by sexual intercourse, this strategy is as effective as continuous antibiotic prophylaxis\(^7\), and limits antibiotic exposure and risk of resistance emerging.

- **Continuous Antibiotic Prophylaxis**
  - Longer term antibiotic prophylaxis is strongly associated with the development of antimicrobial resistance.
  - A 6 month trial of low-dose continuous antibiotic treatment 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 strongly advised to avoid prolonged courses of antibiotics without review.
**Choice of Agents**: 

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. Trimethoprim and nitrofurantoin are licensed for the prophylaxis of UTIs.

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.

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<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Cautions and Monitoring</th>
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| Trimethoprim   | 200mg One dose post-coital (off label) or 100mg nightly | • 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. |
| Nitrofurantoin | 100mg immediate       | • Avoid if renal function eGFR <45ml/min.                                               |

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 antibiotic treatment 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%.  
- 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 after 6 months.
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.

Second line options

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

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<tr>
<td></td>
<td>Cefalexin</td>
<td>125 mg One dose post-coital or Or 125mg nightly</td>
<td>• Higher risk of selection for resistant infections • Higher risk of <em>C. difficile</em> infection</td>
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<tr>
<td></td>
<td>Pivmecillinam</td>
<td>200 mg One dose post-coital or Or 200 mg nightly</td>
<td>• On urology advice only , noting unknown safety profile and potential carnitine deficiency with prolonged use⁹ • Stop after 6 months</td>
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</table>

The BNF pivmecillinam indication and dosing for "chronic or recurrent bacteriuria" is not applicable for recurrent urinary tract infections.
Methenamine

A Cochrane review in 2007 assessed the benefits of a urinary antiseptic agent, methenamine hippurate\textsuperscript{8}. This is converted to formaldehyde in the acidic urine environment, which is directly toxic to bacteria. It concluded that in a sub-group of women without urinary tract abnormalities or neuropathic bladder, it may be of benefit in preventing rUTIs in the short-term but long-term benefit was not demonstrated. The studies were of poor quality and there was insufficient evidence to recommend its routine use. Methenamine may be advised by:

- Urologists or Infectious Diseases physicians (Amber 2 classification), if there are no suitable alternative therapies, due to:
  - Multi-resistant organisms
  - Allergies, contraindications, or side-effects with prophylactic antibiotics.
  - High-risk patients for whom prophylactic antibiotics are not appropriate e.g. \textit{C.difficile} carriage

\textbf{Treatment should stop after 6 months and patient should be referred back to the advising Specialist if relapses or side-effects occur.}

Please refer to BNF for dosing advice.

3. 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 if the culture confirms it is still sensitive 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.
- Consider referral to Urology at this point if not already been investigated.
4. Managing a patient who has had a prolonged course of prophylactic antibiotics:

Identifying patients for review:

- Patients should be reviewed after 6 months of prophylactic antibiotics with a view to stopping (refer to ‘Stopping Continuous Prophylaxis’ page 4).
- 12 months is a suggested trigger for audit purposes for patients on long-term 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 need for referral.
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 (see page 1)

Advice on Conservative Measures (see page 2)

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 6 month to assess benefit and if any resistant urine cultures

Patients on continuous antibiotic prophylaxis:
- Trial of 6 months of nightly antibiotics (see page 3)

After 6 months, stop antibiotics.
- Around half will not return to recurrent symptoms
- Consider offering stand-by antibiotics if patient concerned

If more than one breakthrough UTI, 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

If recurrent UTIs return after stopping, consider referral.
References

9. Urinary tract infection (recurrent): antimicrobial prescribing NICE guideline [NG112] Published date: October 2018 accessed online https://www.nice.org.uk/guidance/ng112 July 2019

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