Urinary tract infections in women: recurrent

The following is summarised from a clinical review article in the BMJ (BMJ 2013;346:f3140).

This applies to NON-PREGNANT WOMEN with recurrent urinary tract infections.

**Recurrent UTI statistics and definitions**

- Recurrent UTIs are defined as:
  - 2 or more infections in 6m or
  - 3 or more infections in a year.
- Uncomplicated cystitis occurs in 50–80% of women in the general population at some point. Of these, 30–44% will experience a recurrence.
- Recurrence within 2w is usually a relapse of the initial infection, and should prompt culture of urine to check antibiotic sensitivities.

**Risk factors for and causes of recurrent UTI**

The risk factors differ between pre- and postmenopausal women.

<table>
<thead>
<tr>
<th>Pre-menopausal risk factors</th>
<th>Post-menopausal risk factors</th>
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<tbody>
<tr>
<td>Sexual activity (especially &gt;9 episodes of intercourse per month).</td>
<td>Incontinence.</td>
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<tr>
<td>Use of spermicides.</td>
<td>Post-micturition residual volume.</td>
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<td>First UTI before age 15y.</td>
<td>Pre-menopausal UTIs.</td>
</tr>
<tr>
<td>Maternal history of UTI.</td>
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There is also probably a genetic predisposition linked to binding of bacteria to uroepithelial cells – there is a lot of work in this area, but, at present, it is not clinically relevant to primary care.

*E. coli* is the most common causative organism, and it has been observed that the same *E. coli* strain can cause recurrence 1–3y later; this suggests that some women may have a vaginal or rectal reservoir of the causative bacteria, or that the bacteria can invade the bladder urothelium and subsequently re-emerge.

Interestingly, factors that neither increase nor reduce risk include: fluid intake, douching, post-coital voiding, caffeine intake, cotton underwear, BMI and bubble baths. *So much for all my well-intended advice!!*

**Investigating recurrent UTI**

For recurrent UTI, send a urine culture to confirm the diagnosis and determine antibiotic sensitivity. Recurrent LUTS symptoms and negative urine cultures should prompt consideration of alternative diagnoses (e.g. overactive bladder).

**Imaging and referral**

There are no UK evidence-based guidelines or RCTs which have looked at the benefits of referral for further investigation, or indeed which women benefit most. Therefore, the BMJ makes its recommendations on the basis of expert consensus.

One small observational study of 100 women with recurrent UTI referred for cystoscopy found no abnormalities in any of them, except cystitis. A retrospective database study found anomalies in 8%, and, in this study, if ultrasound and CT were negative, there was no additional benefit to cystoscopy.

Consider imaging and referring women with the following:

- History of urinary tract surgery.
- Known anatomical abnormality.
- Renal calculi.
- Multi-drug resistant bacteria.
- Persistent visible or non-visible haematuria after treatment of infection.
- Pneumaturia/faecaluria (suggestive of fistula).

NICE recommends URGENT referral via the cancer pathway for:

- Any woman ≥45y with:
  - Unexplained visible haematuria without UTI.
  - Visible haematuria that persists or recurs after successful treatment of UTI.
- Any woman ≥60y with unexplained non-visible haematuria AND:
- EITHER dysuria.
- OR raised white cell count.

NICE recommends NON-URGENT referral of any woman aged ≥60y with recurrent/persistent UTI that is unexplained (NICE 2015, NG12).

### Management of recurrent UTI

NICE has issued guidelines on antimicrobial prescribing for recurrent UTI (NG112, 2018) which is summarised below. There are two issues here:

- Treatment of the acute infection (see the article *Urinary tract infections in women: acute* for guidance).
- Prevention of future episodes.

#### Preventing recurrence

There are several options for reducing the impact of recurrent UTIs, and this is something which can be discussed and agreed with the individual woman. The aim is to minimise her symptoms while also minimising antibiotic exposure and side-effects (e.g. candida).

Note: NICE recommends a different antibiotic should be used for prophylaxis if an acute UTI is being treated at the same time.

<table>
<thead>
<tr>
<th>First line</th>
<th>Second line</th>
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</table>
| **Advise simple measures and self-care** | - Maintain hydration.  
- Symptom relief, e.g. ibuprofen.  
- Don’t delay urination (including post-coitally).  
- Wipe front to back after defaecation.  
- Avoid douching and tight underwear.  
- Some women may wish to try D-mannose, cranberry products or probiotics (although see below for evidence). |

| Topical oestrogens | **Patient-initiated antibiotics** 
*Note: trimethoprim should be avoided:*  
- In pregnancy (contraindication).  
- If it has been prescribed in the past 3m.  
- In areas of high-resistance (especially in residential homes). |

| **Single-dose antibiotic prophylaxis to women exposed to a trigger (e.g. post-coital UTI)** | - Women have a home supply of antibiotics which they can take at first sign of symptoms.  
- Unless organism resistant, NICE suggests either:  
  - Nitrofurantoin 100mg twice daily for 3d.  
  - Trimethoprim 200mg twice daily for 3d.  
- Patients should have a clear understanding of red flags and when to seek help.  
- Shown to be safe and effective – likely best strategy for women with relatively few recurrences.  
- Review after 6m and consider stopping. |

| **Third line** | - For women who temporally relate recurrences to a specific trigger (e.g. sexual intercourse).  
- Unless organism resistant, NICE suggests:  
  - 200mg trimethoprim stat post-exposure OR  
  - 50–100mg nitrofurantoin (if eGFR ≥45mL/min).  
- Second-line options are:  
  - Amoxicillin 500mg stat OR  
  - Cefalexin 500mg stat.  
- Review after 6m. |
Duration of antibiotic treatment

NICE does not give specific recommendations but suggests that, at the 6m review, we should consider stopping, continuing or changing regime based on individual circumstances.

Recurrent UTI in the elderly

How should we manage recurrent UTI in our elderly patients?

A large retrospective cohort study based in UK primary care looked at this question (Age & Ageing 2019;48:228).

Researchers examined the medical records of patients over the age of 65y with a history of recurrent UTI for evidence of prophylactic antibiotic prescriptions and read-codes for incidence of UTI.

- They found that use of prophylactic antibiotics reduced the risk of recurrent UTI by 51% in women and 43% in men compared with no prophylaxis.
- In men, this had a corresponding effect of a 22% reduction in UTI-related hospital admission, but this was not seen in women.
- Only about 14% of people with recorded read-codes for recurrent UTI were given prophylactic antibiotics.
- Of those who did get antibiotics, more than 50% took them for over 2 years!

This study did not look at antibiotic-related adverse events or at rates of resistant bacteria in urine, and the data is reliant on accurate read-coding of UTI diagnoses in primary care, so we cannot comment on the possible harms of prophylactic antibiotics for recurrent UTI in the elderly from these results.

Alternatives to antibiotics in recurrent UTI

Alternatives to antibiotics have the advantage of preventing recurrent urinary infection without the adverse effects of prolonged antibiotic usage.

But do they work?

A recent ‘Practice’ article in the BMJ considers the evidence, and concludes that the answer isn’t yet clear, and that (BMJ 2017;359:j5193):

- Based on current evidence, prophylactic antibiotics remain first-line preventative treatment for recurrent UTI.
- Most alternative agents appear to be well-tolerated, with few adverse side-effects, so may provide a suitable strategy for individual patients who are allergic, intolerant or do not wish to take antibiotics.

Alternative treatments and the evidence behind them are summarised in the table below:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Mode of action</th>
<th>Effective?</th>
<th>Where do I get it?</th>
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<tbody>
<tr>
<td>Methenamine Hippurate</td>
<td>Hydrolysed to formaldehyde in the presence of acidic urine, and exerts a bactericidal effect on E.coli.</td>
<td>reduction in UTIs and recurrent UTIs in small trials. Low rates of adverse events were reported.</td>
<td>Available on the NHS as Hiprex 1g; take one tablet twice daily (60 tablets cost £19.74). Avoid if renal/hepatic impairment. Review after 6m.</td>
</tr>
<tr>
<td>D-mannose oral powder</td>
<td>This is a sugar compound which concentrates in the bladder and inhibits bacterial adhesion to uroepithelial cells.</td>
<td>One RCT suggests it may be as effective as nitrofurantoin.</td>
<td>Available in healthfood shops.</td>
</tr>
</tbody>
</table>
| **Topical oestrogens** | Improve atrophy, increasing vaginal lactobacilli, which change vaginal pH, suppressing bacterial growth. | • Benefit in postmenopausal women in 2 small trials.  
• Side-effects include breast tenderness, vaginal bleeding and discharge. | Available as prescription-only creams, tablets and a ring. |
| **Chinese herbal medicine (Er Xian Tang, Bai Tou Weng Tang, and San Jin Wan)** | Not known. | Small studies, in postmenopausal women only, show benefit. | Chinese herbalist. |
| **What probably doesn’t work…** |  |  |  |
| **Urinary alkalisation (e.g. potassium citrate)** | Reduce the acidity of urine to reduce dysuria. | • Inconclusive evidence.  
• Side-effects include gastrointestinal symptoms (e.g. nausea/flatulence) and mild diuresis. | Available over the counter in pharmacies and online. |
| **Probiotics (lactobacillus)** | Organisms establish a barrier against infectious pathogens ascending the urinary tract, reducing pathogen adherence and colonisation. | • Limited evidence of benefit.  
• Possible side-effects may be vaginal discharge, genital irritation and diarrhoea. | Healthfood shops and online. |
| **Cranberry products** | Prevent bacteria (particularly E coli) from adhering to the uroepithelial cells. | • No better than placebo/no treatment.  
• Many studies reported low compliance and high dropout rates, due to palatability of products. | Pharmacies and healthfood shops. |
| **What might be available in the future…** |  |  |  |
| **Hyaluronic acid** | Replenishes surface glycosaminoglycan layer of the urothelium, preventing bacterial adherence. | Significant evidence of benefit. | Administered intravesically, so a secondary care option. |
| **Oral immunostimulants** | These contain serotypes of heat killed/inert uropathogens designed to upregulate the patient’s immune response to urinary infections. | Mixed evidence, but European Association of Urology supports their use. | Likely to be available in secondary care only. |
| **Vaccines** | These are either:  
• Vaginal immunogens applied mucosally, OR  
• Sublingual vaccines containing inactivated uropathogens. | More research needed! |  |
Recurrent urinary tract infections

- Make this diagnosis in non-pregnant women with 2 or more UTIs in 6m, or 3 or more in 1y.
- Culture urine if this has not been done before.
- The majority of women do not need any further imaging or investigations. However, investigate and refer those with persistent visible or non-visible haematuria after treatment, history of urological surgery, multi-drug resistant bacteria or symptoms of fistula.
- Treat each acute episode as per any UTI, e.g. 3d nitrofurantoin.
- Discuss with women self-initiated antibiotics, or prophylaxis (either continuous or post-coital) – this discussion should balance inconvenience of symptoms with risk of candida/resistance.
- Review at 6m.
- Non-antibiotic strategies may be a suitable alternative for some patients, although the evidence is weak.

Recurrent urinary tract infections

We make every effort to ensure the information in these articles is accurate and correct at the date of publication, but it is of necessity of a brief and general nature, and this should not replace your own good clinical judgement, or be regarded as a substitute for taking professional advice in appropriate circumstances. In particular check drug doses, side-effects and interactions with the British National Formulary. Save insofar as any such liability cannot be excluded at law, we do not accept any liability for loss of any type caused by reliance on the information in these articles.
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