UTIs: recurrent infections in non-pregnant women

Here we are considering specifically recurrent urine infections in non-pregnant women - the situation with men and children is different. There is an article about UTI in children in the online handbook.

Sometimes a nice straightforward UTI consultation can be just what the doctor ordered at the end of a busy surgery, but here is a reminder to ensure that we manage these women in the best way possible and consider the more unusual!

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

**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 post-menopausal women.

<table>
<thead>
<tr>
<th>Pre-menopausal risk factors</th>
<th>Post-menopausal risk factors</th>
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<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>
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<td>Maternal history of UTI</td>
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There is also probably a genetic pre-disposition linked binding of bacteria to uroepithelial cells - there is a lot of work in this area but at present it is not clinically relevant to GPs.

*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 suggesting 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**

Simple sporadic UTIs do not require any specific investigation and even routine urine culture is not necessary in the presence of a suggestive history and positive dipstick.

- 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 or interstitial cystitis (see later in chapter).

**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 their 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).

Management of recurrent UTI

There are two issues here - treatment of the acute infection and prevention of future episodes.

Managing the acute episode

- Use the same antibiotic regimens and the same duration of treatment as a single episode of simple cystitis, e.g.
  - nitrofurantoin 100mg bd 5d (remember ineffective for patients if eGFR <45 as reduced concentration in urine, supposed to be given for 5d but in practice most seem to use it for only 3d!)
  - trimethoprim 200mg bd 3d
  - as indicated by sensitivities.
  - The article recommends giving diabetics 7d of treatment but acknowledges there is limited evidence to support this.

Antibiotic update: pivmecillinam

In October 2014 Public Health England published an update to their management of infection guidance for primary care (PHE publications gateway number: 2014378). Pivmecillinam is a PENICILLIN antibiotic that has been used in Scandinavia for years. It is now recommended as a first line treatment option for UTI in adults with no fever or flank pain.

- Consider pivmecillinam in those with risk factors for resistant bacteria (including recurrent UTI).
- It can be used instead of nitrofurantoin in those with eGFR <45ml/min.
- The dose for women is 400mg STAT then 200mg three times a day for 3d.
- The PHE guidance does not recommend pivmecillinam for treatment of UTI in children or pregnancy or as prophylaxis for recurrent UTI.
- BNF Jan 2015: it is contraindicated in infants <3m and those taking valproate. The manufacturers advise that it is avoided in pregnancy but it is appropriate to use in breast-feeding women.

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 whilst also minimising antibiotic exposure. The options are as follows.

- Patient initiated antibiotics
  - Women have a home supply of antibiotics which they can start at first sign of symptoms.
  - Trimethoprim or nitrofurantoin are preferred unless previous resistance.
  - Patients should have a clear understanding of red flags and when to seek help.
  - Been shown to be safe and effective - likely best strategy for women with relatively few recurrences.

Continuous antibiotic prophylaxis

- This can be daily or 3 times weekly.
- Regimens include trimethoprim 100mg at bedtime or nitrofurantoin 50-100mg at bedtime.
- This has consistently been shown to reduce recurrences with an NNT of 2.2 to give an 85% reduction in recurrence.
- There is, however, an increased risk of resistant bacteria and candida.
- Try this for 6m and then withdraw and reassess.
- Occasionally, years of nitrofurantoin use can lead to reversible pulmonary toxicity.

Post-coital antibiotic prophylaxis

- For women who temporally relate recurrences to sexual intercourse.
- Either 100mg trimethoprim or 100mg nitrofurantoin post-coitaly.

Treating asymptomatic bacteriuria has not been shown to reduce the incidence of recurrent UTI so there is no advantage in screening urine samples in the absence of symptoms. It should only be treated in pregnant women.

Non-antibiotic interventions

Cranberry products

- Mixed evidence - Cochrane review showed no benefit whereas another meta-analysis showed a reduction in recurrent events.
- There are no harms.

Vaginal oestrogens

- Show modest benefits in post-menopausal women in contrast with oral oestrogens which have no effect.
**Future possibilities**

The DTB reviewed the evidence for strategies to prevent recurrent UTIs and it drew the same conclusions regarding antibiotics, cranberry products and vaginal oestrogens as the BMJ review above (DTB 2013;51(6):69). However, it also considered future interventions which have shown benefits in small trials:

- *E. coli* immunostimulation.
- Hyaluronic acid and chondroitin bladder infusions.

Watch this space!

**Community pharmacy instigated treatment for UTI**

“Doc, I’ve been taking those sachets from the chemist for days but it still burns when I pee!” Many patients seek assistance from pharmacies for cystitis symptoms and yet the available over the counter remedies have minimal evidence to support their efficacy.

This BJGP cross-sectional study proposed the hypothesis that allowing pharmacies to issue trimethoprim for symptomatic lower UTIs under a patient group directive (PGD) could improve patient access to treatment and reduce GP workload (BJGP 2013;63:187). There was a strict symptom-based protocol though interestingly they didn't include a urine dipstick test! They interviewed patients and pharmacists about their experiences.

They found that:

- Pharmacists issued trimethoprim according to protocol.
- Patients unanimously expressed preference to get their UTI treated at the pharmacy rather than GP because of easier access and "not wanting to bother their doctor".
- Pharmacists were universally in favour of this.

This was a small study but is food for thought when considering service redesign.

**How useful is the MSU culture in cystitis?**

For the majority of cases of simple cystitis, we will use urine dipsticks as our first line diagnostic test. In recurrent or complicated cases we sometimes resort to MSU cultures to establish that there is infection and to look at sensitivities.

We have known for a long time that it is not a gold standard test because of the risk of contamination - the purity of growth and the number of colony forming units have been used by labs to determine whether a culture is positive or not. This microbiological study looked at how good the MSU is at predicting bladder bacterial colonisation by taking paired MSU and fresh catheter samples on more than 200 women presenting with uncomplicated cystitis (NEJM 2013;369:1883). They found:

- Uropathogens were present in 70% of catheter specimens and 78% of MSUs (8% false positive rate).
- If *E. coli* was the cultured organism there was high agreement between catheter and MSU specimens, even if the number of colony forming units were low.
- If enterococci or group B streptococcus were identified on MSU, they were not predictive of bladder bacteriuria at any colony count.

Beware false positive results when an MSU grows enterococci or streptococcus - in this study they did not seem to cause cystitis when isolated alone. If *E. coli* is present, even at low counts in a symptomatic woman, it is reasonable to treat.
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 trimethoprim, nitrofurantoin or pimecillinam first line.
- 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.
- If using prophylaxis, try for 6m then withdraw and reassess.
- There is mixed evidence for the efficacy of cranberry products but vaginal oestrogens may be helpful in post-menopausal women.
- Only treat asymptomatic bacteriuria in pregnant women.

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