Antibiotic Management of Recurrent Urinary Tract Infections in Adults

April 2016

Background

This document gives guidance on the management of adults with recurrent lower UTIs recurrent UTI (rUTI) is a common problem affecting many women of various ages.

rUTI is defined as **'three or more episodes of urinary tract infection in the last 12 months or 2 or more episodes of UTI in 6 months'**[(1)] and is accepted as a symptomatic UTI that follows resolution of an earlier episode, usually after appropriate treatment, and may be due to relapse or re-infection (most are thought to represent re-infection with the same organism). It is therefore important to clarify whether relapse or reinfection is occurring, since the management of these situations are different.

It **does not** include episodes of bacteriuria without UTI symptoms (asymptomatic bacteriuria) which appears to play a protective role in preventing symptomatic recurrence so should not be treated (EXCEPT in pregnant women).

Prophylactic use of antibiotics

- is recognised as a potential area for improvement to reduce unnecessary use of antibiotics and also to tackle resistance which inevitably develops with long-term use of antibiotics, therefore the cautious use of antibiotics and use of other initial therapies should be considered where possible.[(2)]

It is important that the prescriber feels confident in the following areas when managing recurrent UTI:

- When it is appropriate to commence long-term antibiotic prophylaxis; and what should be considered prior to antibiotic prophylaxis
- What the local first-line antibiotic choices are for antibiotic prophylaxis
- When it is appropriate to stop long-term antibiotic prophylaxis
- What action to take if the patient relapses after cessation of prophylaxis

The Management of Recurrent UTI will be considered in THREE sections:

1. **History and physical factors to identify patients for further investigations ('RED FLAGS').**
2. **How to manage the initial presentation of recurrent UTI.**
3. **How to manage the patient who has had a prolonged course of prophylactic antibiotics.**

Relapse vs Reinfection[(29)]

A relapse is defined as:

- a recurrent infection with the same organism, despite adequate therapy at less than 2 weeks and should be thoroughly investigated as it may indicate structural abnormalities and may require referral - *see* **RED FLAGS**.

A re-infection is defined as:

- a recurrent UTI caused by a different bacteria isolate or
- a recurrent UTI caused by the previous isolated bacteria after a negative intervening culture or
- a recurrent UTI caused by the previous isolated bacteria after an adequate time period (more than 2 weeks) between infections.

E.coli is the most common causative organism and it has been observed that the same *E.coli* strain can cause recurrence 1 to 3 years later.

1. History and Physical Factors to Identify Patients for Further Investigation

Complication	Examples
Anatomical abnormality	Cystocele, diverticulum, fistula
Iatrogenic	Indwelling catheter, nosocomial infection, surgery
Voiding dysfunction	Vesicoureteric reflux, neurological disease, pelvic floor dysfunction, high post void residual, incontinence
Urinary tract obstruction	Bladder outlet obstruction, ureteral stricture, ureteropelvic junction obstruction
Other	Pregnancy, urolithiasis, diabetes or other immunosuppression

FURTHER INVESTIGATIONS / SPECIALIST REFERRAL [1]

Several studies have demonstrated a low incidence of anatomical abnormality in patients with recurrent UTI it is recommended that the following groups are referred for further evaluation to a consultant urologist or other specialist with an interest in UTI.

RED FLAGS

Indications for further investigation of recurrent UTI [1,13]

- All men
- Prior urinary tract surgery or trauma
- All patients with Gross (visible) haematuria
- Previous bladder or renal calculi
- Obstructive symptoms (straining, weak stream, intermittency, hesitancy), low uroflowmetry or high post void residual
- Urea-splitting bacteria on culture (e.g., *Proteus* sp.) which may cause formation of struvite (infection) stones
- Bacterial persistence after sensitivity-based therapy
- Prior abdominopelvic malignancy
- Diabetes or otherwise immunocompromised
- Pneumaturia, faecaluria, anaerobic bacteria or a history of diverticulitis
- Repeated pyelonephritis (fever, chills, vomiting, costovertebral angle tenderness)
- New onset of recurrent UTI in a post-menopausal women
- Asymptomatic haematuria after resolution of infection should be managed as per Renal Association guidelines
  http://www.renal.org/docs/default-source/guidelines-resources/joint-guidelines/Haematuria_-_RA-BAUS_consensus_guideline_2008.pdf?sfvrsn=2

2. How to Manage the Initial Presentation of Recurrent UTI [8 22 32]

There are several options for reducing the impact of recurrent UTIs which should be discussed and agreed with the patient. The aim is to minimise symptoms while also trying to minimise antibiotic exposure.

NB

- A UTI diagnosed before or whilst the patient is awaiting a referral appointment should be treated appropriately.
- Except in pregnancy, asymptomatic bacteruria should **not** be treated with an antibiotic.

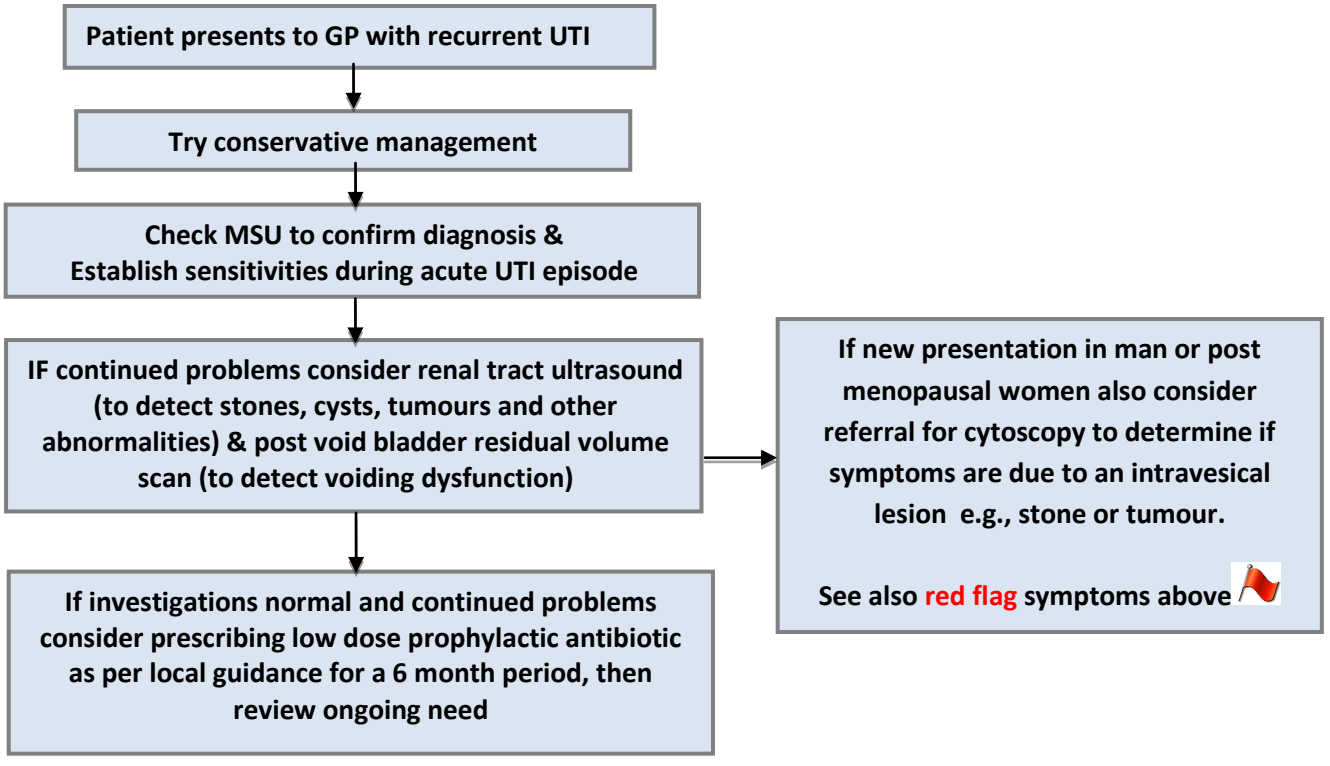
Assessment should include urine analysis (particularly for haematuria) and consideration of screening for sexually transmitted infection and vaginal infection.

It is recommended that the following simple measures are tried before starting antibiotic prophylaxis:

Conservative Management

- Encourage better hydration to ensure more frequent urination.
- Encourage urge-initiated voiding and post-coital voiding.
- Advise sexually active women that diaphragm and spermicide use are risk factors for cystitis and discuss alternative contraception.
- There is conflicting evidence to support the use of cranberry products to reduce recurrence, however, patients may choose to obtain and try cranberry products, e.g., high strength cranberry extract capsules may be more effective & acceptable than juice.[11 12, 28]
  (cranberries should be avoided in patients taking warfarin)[6] *(and avoided if history of kidney stones)* [34]
- For post-menopausal women with risk factors such as atrophic vaginitis consider prescribing intravaginal or oral oestrogens .[22, 23, 24 ,25]
- For post-menopausal women with no obvious risk factors, consider referral to urology for further investigations, particularly if recurrent UTI is a recent problem.

If these simple measures fail to improve then follow the flow chart below



Use of prophylactic antibiotics

- If conservative management advised has not resolved the situation to the satisfaction of the patient, prophylactic antibiotics may be considered as a last resort.
- Long-term antibiotic prophylaxis is strongly associated with the development of antimicrobial resistance.
- There is no strong evidence for or against rotation of antibiotics in this situation; therefore; long-term use with switching of antibiotic to theoretically reduce risk of resistance is not recommended.
- There is no ideal antibiotic for UTI prophylaxis as all are associated with problems of resistance and/or adverse effects, however, nitrofurantoin and trimethoprim are the usual first line agents for UTI prophylaxis but consult recent urine culture results to confirm sensitivities.

Counselling prior to initiation of prophylaxis.

- The patient should be counselled at an early stage that antibiotic prophylaxis is not usually a life-long treatment.
- Antibiotics are given in this way to allow a period of bladder healing which makes UTI much less likely.
- There is no evidence they have any additional benefit beyond 6-12 months treatment, therefore the treatment should be discontinued ideally after 6 months. [2]

URINARY TRACT INFECTIONS-refer to PHE UTI guidance for diagnosis information
https://www.gov.uk/government/publications/managing-common-infections-guidance-for-primary-care

IN NON-PREGNANT WOMEN, THE USUAL FIRST LINE AGENTS FOR UTI PROPHYLAXIS

Recurrent UTI in non-pregnant women ≥ 3 UTIs/year	To reduce recurrence first advise simple measures including hydration, cranberry products. Then standby or post-coital antibiotics Nightly prophylaxis reduces UTIs but adverse effects and long term compliance poor	*Antibiotics:* nitrofurantoin *or* trimethoprim	50–100mg 100mg	*Post coital* stat (off-label) *Prophylaxis* OD at night review at 6 months

Treatment options

1. **A Self-start /Standby 3 day course [10 19 20 28] may be considered**
   - **Trimethoprim 200mg twice daily or Nitrofurantoin MR 100mg twice daily**
2. **Continuous antibiotic prophylaxis[2 10 19 20]**
   - **Trimethoprim 100mg at bedtime or Nitrofurantoin (immediate release) 50mg - 100mg at bedtime**
3. **Post coital antibiotic prophylaxis [19 20 27 28]**
   - **Trimethoprim 100mg or Nitrofurantoin 100mg to be taken within 2 hours of intercourse (off-label use) (Use of condoms (without spermicidal), post coital voiding and good hydration are all important non-pharmacological prophylactic measures to help prevent RUTIs. Avoiding use of spermicidal products may help to prevent RUTIs)**

As *E.coli* bacteraemia in the community is increasing ALWAYS safety net and consider risks for resistance

- Advise the woman to collect and submit a mid-stream sample of urine before starting the treatment and to seek medical advice if symptoms have not resolved within 48 hours.
- Patients should have a clear understanding of red flags and when to seek help.
- Prophylaxis should not be initiated until eradication of active infection is confirmed by a negative culture at least 1-2 weeks (preferably 2 weeks) after treatment has been discontinued.

CAUTIONS AND CONTRA-INDICATIONS [4, 5, 6, 16, 17, 18]

Nitrofurantoin: *Drug Safety Update September 2014 vol 8, issue 2: A3*.

Nitrofurantoin is now contra-indicated in patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min. However, a short course (3 to 7 days) may be used with caution in certain patients with an eGFR of 30 to 44 ml/min. Only prescribe to such patients to treat lower UTI with suspected or proven multidrug resistant pathogens when the benefits of nitrofurantoin are considered to outweigh the risks of side effects.

Additional MHRA and BNF Advice for health professionals [6, 16]

- Nitrofurantoin, if suitable and tolerated, appears to be associated with less resistance problems than trimethoprim.
- Nitrofurantoin should **not** be used to treat sepsis syndrome secondary to UTI or suspected upper UTIs.
- Consider checking renal function when choosing to treat with nitrofurantoin, especially in the elderly.
- **Patients should be monitored closely for signs of hepatitis (particularly in long term use)**
- **Close monitoring of the pulmonary conditions of patients receiving long-term therapy is warranted (especially in the elderly)**
- **Discontinue treatment with nitrofurantoin if otherwise unexplained pulmonary, hepatotoxic, haematological or neurological syndromes occur**
- Avoid in G6PD deficiency, upper UTI / pyelonephritis & near term
- Please advise women who are taking nitrofurantoin not to take alkalinising agents such as potassium citrate

***Costs:** Nitrofurantoin 100mg generic capsules are most cost-effective prep, followed by 50mg generic capsules Nitrofurantoin suspension is much more expensive; only prescribe if needed e.g. swallowing difficulties*

Long Term Trimethoprim [17]

- can contribute to hyperkalaemia; exercise caution when concurrently prescribed with drugs which may potentiate this e.g., spironolactone, ACE inhibitors or angiotensin II inhibitors.
- Renal impairment-BNF recommends *half-normal dose if eGFR 15-30ml/min/1.73m^2*.
- **Avoid if eGFR less than 15ml/min/1.73m^2.**
- **Avoid trimethoprim in renal impairment - may cause increase in serum creatinine and hyperkalaemia; use only after discussion with renal physician.**
- Patients should also be told how to recognize 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 develops.

NB. If a patient has received trimethoprim within the previous 2 months, use nitrofurantoin as patient is more likely to have a resistant organism (if nitrofurantoin is not suitable, use appropriate antibiotic with lowest risk of *C difficile* infection)

Please refer to summary of product characteristics for further information on Precautions and special warnings
https://www.medicines.org.uk/emc/search

If resistance to these first line agents is confirmed other agents may be considered

e.g., co-trimoxazole (see BNF restrictions on use) 480mg once daily and potentially cephalexin 250mg once daily or ciprofloxacin 250mg once daily; when there is good bacteriological evidence of sensitivity.
Risks that need to be considered are that co-trimoxazole may cause Steven Johnson syndrome and ciprofloxacin may cause synovitis and tendon damage and should be used with caution in patients with a history epilepsy or conditions that predispose to seizures. (see BNF for cautions) [17].
The broad spectrum antibiotics co-amoxiclav, ciprofloxacin and cephalosporins should not be used for prophylaxis unless no there is no alternative, due to risk of *C. difficile* and in addition for quinolones induction of resistance including MRSA [18].

If prophylaxis fails during the initial 6 month period

A urine sample should be sent for culture and sensitivity testing. Uncomplicated UTI should be treated with a 3-day course of a suitable antibiotic based on the urine culture results and the prophylactic antibiotic resumed following completion of the course with a different antibiotic if appropriate. A longer course of antibiotics may be necessary in patients with impaired renal function, immunosuppressed or with abnormal urinary tract. These patients should be reviewed and assessed by a specialist.

3.How to Manage the Patient who has had a Prolonged Course of Prophylactic Antibiotics

Identifying patients for review

Ideally patients should be reviewed after 6 months of prophylactic antibiotics [19] with a view to stopping them and it may be helpful to document a review date in the medical notes and also on the prescription. For audit purposes and retrospective review, 12 months is suggested as a suitable trigger for prolonged duration.

Discussing patient concerns

The risks of long term antibiotics in terms of vulvovaginal side effects, *Clostridium difficile* and increased likelihood of infection with resistant organisms are also important considerations for the doctor and patient and should be fully discussed.

It is understandable for patients to feel anxious about returning to suffering recurrent UTIs. However after a prolonged period of antibiotic treatment in most cases this has allowed the bladder wall to 'heal' making UTI's less likely.

Offering advice about trial of cranberry products [11, 12] and 'stand by' antibiotics [19] to be taken at the first symptoms of UTI can sometimes give sufficient reassurance to the reluctant patient. They should also be given appropriate advice regarding continuation of simple measures to prevent UTI. [10]

Recurrence of UTI after stopping prophylaxis

It is important to ensure the patient is complying as far as possible with the simple measures outlined previously. If they have not already had a renal tract ultrasound and post void bladder residual volume scan now is a good time to consider doing this.

In post-menopausal women consider the possibility of atrophic vaginitis as a risk factor for UTI and manage appropriately. If recurrent UTI is a relatively 'new' problem in a post-menopausal woman consideration should also be given to referral for cystoscopy. [22]

However, if appropriate investigations have already been done and shown no abnormality and there are no other concerning 'red flag' symptoms and cranberry extract has already been tried (or is inappropriate, e.g., if the patient is on warfarin) then a further course of prophylaxis can be considered.

The ongoing need for antibiotic prophylaxis should be reviewed after 6 months. For patients continuing on prophylaxis beyond 6 months the ongoing need should be discussed on an annual basis as part of the standard repeat medication review.

Antibiotic Management of Lower RUTIs (in non-pregnant females) - Choice & duration of prophylaxis

Important –Antibiotic prophylaxis should not be initiated until eradication of active infection is confirmed by a negative culture

(at least 1-2 weeks after treatment has been discontinued)

Cephalosporins (or quinolones,in particular) should not be used for prophylaxis unless no alternative, due to ↑ risk of *C difficile*, MRSA and resistant UTIs. Obtain microbiology advice if needed.

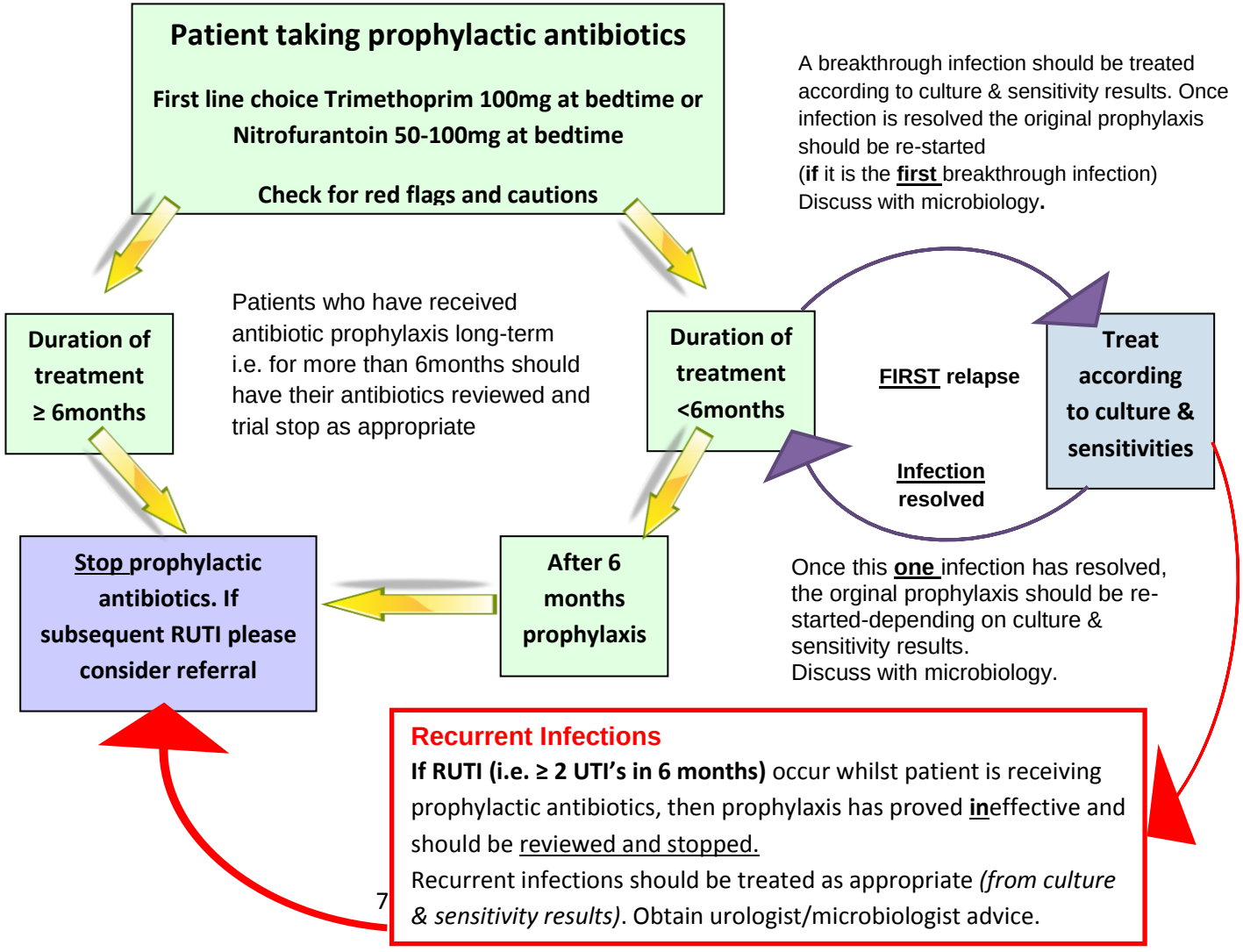
IMPORTANT-antibiotic risk of association with *C. difficile*

Highest risk

Clindamycin (1st)
Quinolones (2nd)
Cephalosporins and Co-amoxiclav.

Moderate risk
Macrolides & Amoxicillin

Lower risk
Tetracyclines, Trimethoprim & Penicillin V
Note Risk ↑ with longer duration and multiple courses



A breakthrough infection should be treated according to culture & sensitivity results. Once infection is resolved the original prophylaxis should be re-started
(**if** it is the **first** breakthrough infection)
Discuss with microbiology**.**

Once this **one** infection has resolved, the orginal prophylaxis should be re-started-depending on culture & sensitivity results.
Discuss with microbiology.

References

1. European Association of Urology: Guidelines on urological infections 2014 http://www.uroweb.org/guidelines/online-guidelines/

2. Albert, X., Huertas, I., Pereiro, I., et al.(2002) Antibiotics for preventing recurrent urinary tract infections in non-pregnant women (Cochrane Review). *The Cochrane Library*, **(2)** Chichester, UK: John Wiley & Sons Ltd.

- *Nightly prophylaxis: pooled data from 10 RCTs of poor methodological quality calculated a Relative Risk of having one microbiological recurrence (MR) was 0.21 (95% CI 0.13 to 0.34), favouring antibiotic and the NNT was 1.85. over 6–12 months. But adverse effects do occur and 30% of women did not adhere to treatment. The benefit is lost as soon as prophylaxis stops. Post-coital antibiotics: one study of post-coital ciprofloxacin compared with ciprofloxacin prophylaxis found no significant difference between regimens on the rate of UTIs.*

2. Dason, S., Dason, J., Kapoor, A. (2011). Guidelines for the diagnosis and management of recurrent urinary tract infection in women. *Canadian Urological Association Journal,* **(5),** 316-22

3. Geerts A,. et al. (2013). Ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care. *Eur J Clin Pharmacol.* **69(9)**, 1701-7

4. Oplinger , M., Andrews, C. (2013). Nitrofurantoin contraindication in patients with a creatinine clearance below 60 mL/min: looking for the evidence*. Ann Pharmacother*, **47(1)**, 106-11

5. Nitrofurantoin summary of product characteristics http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/?IdcService=SS_GET_PAGE&nodeId=%3C%25%3D+nodeId+%25%3E&searchFiled=nitrofurantoin

6. Drug Safety Update September 2014 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON452539

7. Antibiotic Management of recurrent Urinary Tract Infections in Adults-County Durham and Darlington NHS Foundation Trust http://www.cddmedicinesmanagement.nhs.uk/documents/Prescribing/Guidelines/Infections/Antibiotic_management_of_recurrent_UTIs_in_adults.pdf

8. CKS NICE guidance Recurrent urinary tract infection(lower) in women http://cks.nice.org.uk/ Urinary tract infection (lower) in women -Preventing Recurrent UTI

9. CKS NICE Guidance Supporting Evidence on regular prophylactic antibiotics for preventing recurrent UTI http://cks.nice.org.uk/urinary-tract-infection-lower-women#!supportingevidence1:10

10. Scottish Medicines Consortium. Guidance to improve the management of recurrent lower urinary tract infection in non-pregnant women. SAPG/2014 available at:- http://www.scottishmedicines.org.uk/files/sapg/Management_of_recurrent_lower_UTI_in_non-pregnant_women.pdf

11. Jepson, R., Williams, G., Craig, J. (2012) Cranberries for presenting urinary tract infection (Cochrane review). *The Cochrane Library,*Chichester, IK: John Wiley & Sons Ltd. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001321.pub5/abstract

- *This review identified 24 studies (4473 participants) comparing cranberry products with control or alternative treatments. There was a small trend towards fewer UTIs in people taking cranberry product compared to placebo or no treatment but this was not a significant finding. Many people in the studies stopped drinking the juice, suggesting it may not be an acceptable intervention. In the long term cranberry products (such as tablets or capsules) were also ineffective (although had the same effect as taking antibiotics), possibly due to lack of potency of the 'active ingredient'.*
- *However, four of the five studies in women with recurrent UTI (594 participants) which included a placebo group provided data that could be combined in a meta-analysis (Kontiokari 2001; Barbosa-Cesnik 2011; Stothers 2002; Sengupta 2011). Results showed a small, non-significant reduction in risk of repeat symptomatic UTI with cranberry treatment compared to placebo or no treatment (RR 0.74, 95%CI 0.42 to 1.31). Two studies in women with recurrent UTI (McMurdo 2009; NAPRUTI Study 2011) and one study in children (Uberos 2010) compared cranberry product with antibiotic prophylaxis. All three studies used either cranberry capsules or syrup, rather than cranberry juice. Analysis of the two studies in women*

showed that cranberry product compared to antibiotic were equally as effective in reducing the risk of repeat UTI in women (RR 1.31, 95% CI 0.85 to 2.02) The study in children also showed that the cranberry product.continued…

- *Cranberry juice has been found to potentially prevent infection by interfering with the attachment of bacteria to urepithelial cells. There are many other compounds found in cranberries that have yet to be explored for their potential adherence activity, but A-type proanthocyanidins (PACs) have been shown to potentially inhibit the adherence of P-fimbriated Escherichia coli to the urogenital mucosa. Without adhesion, E.coli cannot infect the mucosal surface of the urinary tract.*
- *There have been two recent systematic reviews examining the evidence for cranberry products for recurrent UTI. A 2012 Cochrane review of 24 studies (4473 participants) found a small trend towards fewer urinary tract infections in people taking cranberry juice or other products compared to placebo or no treatment but this was not significant (Jepson et al., 2012). Chi-Hung et al (Arch Intern Med 2012) examined 10 trials (1494 subjects, 9 community based) : cranberry-containing products were significantly more effective in women with recurrent UTIs (RR, 0.53; 95% CI, 0.33-0.83) (I2 = 0%), female populations (RR, 0.49; 95% CI, 0.34-0.73)but there was substantial heterogeneity across trials*
- *Many people in the Cochrane review studies stopped drinking the juice, suggesting it may be difficult to continue long term. Cranberry capsules may be more convenient than juice and high strength capsules may be most effective.*
- *Thus women should be advised about the relative benefits and risks of daily prophylactic antibiotics, versus post-coital antibiotics, versus stand by antibiotics and cranberry products, so they can make an informed decision. Advise patients taking warfarin to avoid taking cranberry products unless the health benefits are considered to outweigh any risks.*

12. Stothers, L., Urol, C. (2002). A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. **9(3),** 1558-62. http://www.ncbi.nlm.nih.gov/pubmed/12121581
13. Renal Association guidelines http://www.renal.org/docs/default-source/guidelines-resources/joint-guidelines/Haematuria_-_RA-BAUS_consensus_guideline_2008.pdf?sfvrsn=2
14. North East and Cumbria Antibiotic guideline for Primary Care Nov 2014. http://www.networks.nhs.uk/nhs-networks/nhs-cumbria-ccg
15. Perrotta, C., Aznar, M., Mejia, R., Albert, X., Werne Ng, C. (2008). Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. Cochrane library, Chichester, IK: John Wiley & Sons Ltd. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005131.pub2/abstract
Nine studies (3345 women) were included. Oral oestrogens did not reduce UTI compared to placebo (4 studies, 2798 women: RR 1.08, 95% CI 0.88 to 1.33)
- *Vaginal oestrogens versus placebo reduced the number of women with UTIs in two small studies using different application methods. The RR for one was 0.25 (95% CI 0.13 to 0.50) and 0.64 (95% CI 0.47 to 0.86) in the second. Two studies compared oral antibiotics versus vaginal oestrogens (cream (1), pessaries (1)).*
- *There was very significant heterogeneity and the results could not be pooled. Vaginal cream reduced the proportion of UTIs compared to antibiotics in one study and in the second study antibiotics were superior to vaginal pessaries. Adverse events for vaginal oestrogens were breast tenderness, vaginal bleeding or spotting, nonphysiologic discharge, vaginal irritation, burning and itching.*
- *Based on only 2 studies comparing vaginal oestrogens to placebo, vaginal oestrogens reduced number* of UTIs in postmenopausal women with RUTI, however this varied according to type of oestrogen used and treatment duration

16. *BNF,* 68**,** September2014-March 2015
17. Trimethoprim summary of characteristics https://www.medicines.org.uk/emc/medicine/24188
18. PHE guidance; Managing common infections: guidance for primary care

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/377509/PHE_Primary_Care_guidance_14_11_14.pdf

19. CKS NICE guidance- http://cks.nice.org.uk/urinary-tract-infection-lower-women -Empirical antibiotic choice for recurrent UTI

20. Pfau, A., Sacks, T. (1992). Effective prophylaxis for recurrent urinary tract infections during pregnancy. *Clin Infect Dis*, 14;(4), 810-4 http://www.ncbi.nlm.nih.gov/pubmed/1576275*http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005131.pub2/abstract*

21. Christophides, A., Swallow, T., Parkinson, R. (2013). Contemporary management of recurrent UTI in adult females. *Journal of Clinical Urology,* **6**, 140pp. article on Management of RUTIs - http://uro.sagepub.com/content/early/2013/02/18/2051415812472433

22. SIGN 88 guidelines: The management of suspected bacterial urinary tract infection in adults in 2012. (http://www.sign.ac.uk/pdf/sign88.pdf).

They do not recommend oestrogens for routine prevention of recurrent UTI in postmenopausal women although acknowledge that treatment with oestrogens may still be appropriate for some women.They included the following:

- *Genitourinary atrophy may increase the risk of bacteriuria and the role of oestrogen therapy in reducing the risk of symptomatic UTI has been investigated.*
- *Evidence for the efficacy of oestrogen in comparison with placebo is inconsistent. There is good evidence that this treatment is less effective than antibiotic prophylaxis.*
- *A trial comparing nine months treatment with oral nitrofurantoin versus estriol pessaries in postmenopausal women reported a significantly reduced risk of symptomatic UTI with nitrofurantoin.91 Two systematic reviews of vaginal oestrogen administration both reported considerable unexplained heterogeneity of results with some studies reporting significant reduction in risk of recurrent UTI while others report no significant effect or even a trend towards harmful effects.*

Use of Eostrogens:Conclusions and Implications for practice

- *In postmenopausal women with RUTI ass**ocia**ted with a lack of oestrogens and signs and significant symptoms of vaginal atrophy, vaginal oestrogens are a potentially valid intervention. However, women should be advised that the evidence is based on only a few small studies.*
- *The type of oestrogens to use is less clear. Vaginal rings need to be changed periodically and have to be placed by an experienced doctor, however they could be an option in women who have difficulties in applying a cream or used in nursing home residents.*
- *Vaginal creams are a cheaper and possibly a more efficient option but women should be advised about adverse events (itching and burning, occasionally spotting)*
- *The studies comparing vaginal oestrogens to antibiotics were inconclusive due to the significant heterogeneity between the two studies.*

***CKS guidelines on UTIs in women (last revised in 2013)** advises the following: Oestrogen products (for postmenopausal women) are not recommended for use as preventive treatment in primary care because there is evidence from a **Cochrane ystematic review** (2008) that oral oestrogens are no more effective than placebo in reducing recurrent UTIs in postmenopausal women, and there is conflicting evidence from two small trials on intravaginal oestrogen.*

23. Raz, R., Colodner, R., Rohana, Y., Battino, S., Rottensterich, E., Wasser, I., et al. (2003). Effectiveness of estriol-containing vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in postmenopausal women. *Clin Infect Dis*, **36(11),** 1362-8

24. Cardozo, L., Lose, G., McClish, D., Versi, E., de Koning Gans, H. (2001). A systematic review of estrogens for recurrent urinary tract infections: third report of the hormones and urogenital therapy (HUT) committee. *Int Urogynecol J Pelvic Floor Dysfunct,* **12(1),** 15-20

25. Rozenberg, S., Pastijn, A., Gevers, R., Murillo, D. (2004). Estrogen therapy in older patients with recurrent urinary tract infections: a review. *Int J Fertil Womens Med* , **49(2),** 71-4

26. Stapleton, A., Latham, RH., Johnson, C., Stamm, WE. (1990). Postcoital antimicrobial prophylaxis for

recurrent urinary tract infection. A randomized, double-blind, placebo- controlled trial. *JAMA*, **264(6),** 702-706

- *This small (n = 27) RCT found that the relative risk of symptomatic recurrence was lower with post-coital co-trimoxazole (RR 0.15, 95% CI 0.04 to 0.58). Adverse event rates were low and not significantly different between antibiotic and placebo.*

27. Grabe, M., Bishop, M., Bjerkland-Johansen, T., Botto, H., Cek, M., Lobel, B., Naber, K., Palou, J., Tenke, P., Wagenlehner, F. (2009). Guidelines on Urological Infections. *European Association of Urology* , 1-110.

- *. Standby antibiotics: expert opinion, based on one open prospective trial, is that standby antibiotics may be suitable if the rate of recurrences is not too common. Post-coital antibiotics: expert opinion is that the same antibiotics and same doses as for nightly prophylaxis can be used as a stat dose for post-coital prophylaxis of UTI.*

28. Chi-Hung, W., Cheng-Chung, F., Nai-Chuan, C., Shi-Hung Liu, S., Ping-Hsun, Y., Tao-Yu, W., et al. (2012). Cranberry-containing products for prevention of Urinary Tracy Infections in susceptible populations. *Arch Intern Med*, **172(13),** 988-996

- *This systematic review with meta-analysis of randomised controlled trials included 1494 subjects in the qualitative analysis in 10 review trials, with all but one of the trials following subjects living in the community. Administration of cranberry-containing products differed significantly in form, daily dosage, PAC content, and dosing frequency. Results: cranberry-containing products seemed to be more effective in women with recurrent UTIs (RR, 0.53; 95% CI, 0.33-0.83) (I2 = 0%), female populations (RR, 0.49; 95% CI, 0.34-0.73) (I2 = 34%), children (RR, 0.33; 95% CI, 0.16-0.69) (I2 = 0%), cranberry juice users (RR, 0.47; 95% CI, 0.30-0.72) (I2 = 2%), and people using cranberry-containing products more than twice daily(RR, 0.58; 95% CI, 0.40-0.84) (I2 = 18%). The results suggest that cranberry-containing products are associated with protective effect against UTIs. However, this result should be interpreted in the context of substantial heterogeneity across trials.*

29. Turck, M., Ronald, A., Peterdorf, R. (1968). Relapse and reinfection in chronic bacteriuria II: The correlation between site of infection and pattern of recurrence in chronic bacteriuria. *N Engl J Med,* **278**, 422-7pp. http://www.medscape.com/viewarticle/718176_8

32 Management of Recurrent UTIs(RUTIs) in Adult Females. www.derbyshiremedicinesmanagement.nhs.uk/

33 Patient .co uk http://www.patient.co.uk/health/recurrent-cystitis-in-women

34 Cranberry information. http://www.nlm.nih.gov/medlineplus/druginfo/natural/958.html

For further information please contact:
Name: Melanie Graham
E-mail: Melanie.Graham@cumbria.necsu.nhs.uk
Tel: 07909 890754

Guidance produced: April 2016
Guidance expiry: April 2018