PRACTICE

UNCERTAINTIES

Non-antibiotic options for recurrent urinary tract infections in women

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Recurrent urinary tract infection in women is a common problem. There is no universally accepted definition, but most clinicians would classify recurrent UTI as being two episodes of infection in six months, or three episodes in one year.¹ The annual incidence of a single UTI is 30 per 1000 women,² with 44% experiencing recurrence within 12 months.³

Guidelines from the Scottish Intercollegiate Guidelines Network⁴ and the European Association of Urology¹ recommend the use of low dose prophylactic antibiotics for preventive treatment of recurrent UTI. The largest systematic review and meta-analysis of the effect of prophylactic antibiotics on recurrence rates includes 19 randomised controlled trials with data from 1120 women⁵ and reports an 85% reduction in the incidence of symptomatic UTI compared with placebo (relative risk 0.15, 95% confidence interval 0.08 to 0.28). This review examined data from girls and women over 14 with a history of at least two episodes of uncomplicated UTI and calculated that the number needed to treat with prophylactic antibiotics to prevent recurrence over a 6-12 month period was 1.85⁵ (however, the authors commented that the quality of the included studies was poor).

Prolonged antibiotic use in women has resulted in the emergence of resistant organisms in their urine. A randomised controlled trial of 252 women who had been through menopause showed that if resistance develops, it is often to multiple antimicrobial agents and not just the primary drug that the patient has been prescribed.⁶ This trial, comparing antibiotic prophylaxis against urinary tract infections with an oral *Lactobacillus* preparation, found that in the antibiotic arm (trimethoprim), resistance to other antibiotic agents such as amoxycillin and co-trimoxazole doubled over a period of one month.⁶ Resistant micro-organisms can develop after just a few weeks of treatment. A prospective cohort study involving 136 students (no ages given) who were given trimethoprim for two weeks found resistance to at least four antibiotics in 96% of *Escherichia coli* from faecal isolates.⁷ Consequently, other treatment options are of interest.

Emerging potentially efficacious non-antibiotic treatments (table 1⇓) for prevention of recurrent UTI could minimise the development of antimicrobial resistance in bowel reservoirs but there is a paucity of high level evidence to demonstrate their effectiveness.

What is the evidence for uncertainty?

Despite the existence of several up to date Cochrane meta-analyses on the subject of recurrent UTI prevention, uncertainty remains because of the lack of good quality comparative head to head trials. Consequently, precise quantification of the risks and benefits of prolonged non-antibiotic treatments is yet to be established.”

Urinary alkalisation

A meta-analysis examining the efficacy of urinary alkalisation for prevention of recurrent UTI screened 172 randomised controlled trials, all of which failed to meet the inclusion criteria because of poorly defined study populations, interventions, and a lack of comparators (table 1⇓). No recommendations could be made, therefore, for the use of urinary alkalisation.⁸ No comment can be made regarding the risks or adverse events of urinary alkalisation, but recognised side effects include gastrointestinal symptoms such as nausea and flatulence and mild diuresis.

Probiotics

Probiotics in recurrent UTI were the subject of a recent Cochrane systematic review and meta-analysis including nine randomised controlled trials of 735 patients.⁹ No statistically significant benefit (relative risk 0.82 v placebo [95% confidence interval 0.6 to 1.12]; relative risk 1.12 v antibiotics [95% confidence interval 0.95 to 1.33]) was shown for probiotics over placebo or no treatment, but the authors concluded that a benefit cannot be ruled out as the number of patients was small, and the trials had poor methodological reporting because of high reporting and attrition bias. Reported side effects of probiotics included

What you need to know

- After treating the acute infection, low dose antibiotics given for 6-12 months are the most evidence based preventive measure for recurrent urinary tract infections (UTIs) in women, and are recommended by national and international guidelines as the standard of care
- There is evidence of antimicrobial resistance development with prolonged low dose antibiotics and this has led to the investigation of non-antibiotic alternatives to prevent UTIs
- Evidence for non-antibiotic treatments is variable: vaginal oestrogens, D-mannose, immunotherapy, and methenamine look most promising

When to investigate further

Most women presenting with recurrent UTI have uncomplicated infections (defined as no structural or functional urinary tract abnormalities).¹ Current international guidelines do not recommend routine investigations of women with recurrent UTI because of their low diagnostic yield.¹ Symptoms such as persistent loin pain, haematuria, or the presence of atypical infection would necessitate referral to secondary care, where further tests (renal tract ultrasound/computed tomography, flexible cystoscopy, and urine flow studies/post-void urine estimation) can be carried out.

Sources and selection criteria

We searched only level 1a evidence in October 2016: systematic reviews (with homogeneity) of randomised controlled trials. We performed a digital search of the most recent issue of the Cochrane Database of Systematic Reviews via the Cochrane Library using the following MeSH terms: "urinary tract infection," "recurrent urinary tract infection," "bacterur*," "urin* infection," "preventing urin* infection" and "preventing urin*." The results generated for each MeSH search were then evaluated and the systematic reviews relevant to the adult female population were selected. We also performed a literature search of PubMed, Embase, and Medline using the MeSH terms outlined above. We identified relevant randomised controlled trials or other systematic reviews that had been conducted since the Cochrane Systematic Reviews were published. We have not referenced them in this article, as they showed a vast heterogeneity of the sample groups, assessment criteria, and outcome measures assessed. Despite the existence of several up to date Cochrane meta-analyses on the subject of recurrent UTI prevention, uncertainty remains because of the distinct lack of good quality comparative head to head trials. Consequently, precise quantification of the risks and benefits of prolonged non-antibiotic treatments is yet to be established.

What are the non-antibiotic treatment options?

Urinary alkalisation

Urinary alkalisation is the administration of oral medications, such as potassium citrate, to reduce the acidity of urine. By raising the pH of urine, it is postulated that the severity of dysuria experienced by the patient is reduced.

Probiotics

Probiotic organisms (eg, *Lactobacillus* spp) are thought to establish a barrier against infectious pathogens ascending the urinary tract and subsequently causing infection. They modulate host defences by reducing pathogen adherence, growth, and colonisation.

Chinese herbal medicine

According to a 2015 Cochrane review, the Chinese herbal medicines most commonly used are Er Xian Tang, Bai Tou Weng Tang, and San Jin Wan.

Methenamine hippurate

Methenamine hippurate¹¹ is hydrolysed to formaldehyde in the presence of acidic urine and exerts a bactericidal effect on *E coli*.

Cranberry

It is postulated that cranberries prevent bacteria (particularly *E coli*) from adhering to the uroepithelial cells.¹²

Topical oestrogen

Topical application of vaginal oestrogen improves vaginal atrophy and increases vaginal lactobacilli. These promote a change in vaginal pH, suppressing Gram negative bacterial growth.

Hyaluronic acid

Intravesical hyaluronic acid aims to replenish the surface glycosaminoglycan layer of the urothelium and can prevent bacterial adherence.

Oral immunostimulants

Oral immunostimulants contain serotypes of heat killed/inert uropathogens designed to upregulate the patient's immune response to urinary infections. Immunostimulants work by increasing the activity of components of the immune system, rather than providing an acquired immunity to a specific pathogen, like a vaccine does.

vaginal discharge, genital irritation, and diarrhoea, but these only affected 23 out of 735 women.

Chinese herbal medicine

In a 2015 Cochrane review, meta-analysis of three randomised controlled trials involving 282 women that looked at Chinese herbal medicine compared with antibiotics suggested that the Chinese herbal medicine reduced recurrent UTI rates (relative risk 0.28, 95% confidence interval 0.09 to 0.82), but the authors advised caution because of the small study sizes, the high risk of bias, and the lack of evidence in the premenopausal

population. Only two studies reported on adverse events, and neither found any change in liver or kidney function. It was not explained in the review how this was assessed.

Methenamine hippurate

In a 2012 Cochrane review, methenamine hippurate¹¹ was associated with a reduction in risk of UTI in patients with normal renal tracts (relative risk 0.24, 95% confidence interval 0.07 to 0.89) and was found to be well tolerated. However, only one of the trials—of 30 patients—included in this review looked specifically at people with recurrent UTI, and found that

methenamine was associated with a reduction in UTI (relative risk 0.46). Low rates of adverse events were reported across all included studies. Nausea was the most common symptom, and was noted in 12 of 3032 people. Single instances of rash, diarrhoea, sore throat, and bladder “stinging” were also described. Given the demonstrable benefit of methenamine hippurate and its excellent side effect profile, it is one of the most promising non-antibiotic treatments for recurrent UTI, and is currently subject to an ongoing multicentre UK randomised controlled trial.¹⁴

Cranberry

A Cochrane review in 2008¹⁵ found a reduction in the incidence of recurrent UTI (relative risk 0.65, 95% confidence interval 0.46 to 0.9), but since the dropout rates for several of these studies was high, there was a high risk of bias. An updated 2012 Cochrane review including an additional 14 studies and 4473 participants (table 1) suggested that cranberry juice was less effective than previously indicated; cranberry products (juice or dietary supplements based on fruit extracts) did not statistically significantly reduce the occurrence of symptomatic UTI overall (relative risk 0.86, 95% confidence interval 0.71 to 1.04) compared with placebo or no treatment. The subgroup analysis for women with recurrent UTIs also showed no difference (relative risk 0.74, 95% confidence interval 0.42 to 1.31). The authors concluded that cranberry juice could not be recommended for the prevention of UTI.

Although adverse events from taking cranberry products, such as gastrointestinal disturbance, were similar to those of placebo/no treatment, many studies reported low compliance and high dropout rates, which were attributed to palatability of the products.

Oral immunostimulants

A meta-analysis in 2009 (four randomised controlled trials, 891 patients) of oral immunostimulants looking at their effectiveness showed a benefit in decreasing recurrent UTI (relative risk 0.61, 95% confidence interval 0.48 to 0.78).¹⁶ However, a later randomised double blind trial (2015) involving 451 women with recurrent uncomplicated UTI found no benefit of oral immunostimulants compared with placebo.¹⁷ Guidelines from the European Association of Urology¹ support their use.

Topical oestrogen

Topical vaginal oestrogen, when used primarily as a treatment for recurrent UTI, was shown to be beneficial in reducing the incidence of infection in women who have been through menopause in a meta-analysis of five randomised controlled trials.¹³ The included populations were well defined as women with an existing diagnosis of recurrent UTI who were more than 12 months from their last menstrual period. The two randomised controlled trials analysed contained only small patient numbers with differing results (relative risk 0.25, 95% confidence interval 0.13 to 0.50, and relative risk 0.64, 95% confidence interval 0.47 to 0.86), and therefore no robust recommendations can be made on the basis of such small scale trials. Adverse events for vaginal oestrogens were breast tenderness, vaginal bleeding or spotting, non-physiological discharge, vaginal irritation, burning, and itching. These side effects were reported in a minority of participants, but exact numbers were not described.¹³

Is ongoing research likely to provide relevant evidence?

More than 190 studies on recurrent UTI are listed on clinicaltrials.gov.¹⁸ Emerging non-antibiotic prophylactic agents such as intravesical agents,¹⁹ vaccines,¹⁷ and D-mannose²⁰ show promise in reducing the risk of recurrent UTI, but have yet to be evaluated in robust randomised controlled trials. Further research is necessary to enable meaningful comparisons with prophylactic antibiotics.

A small meta-analysis of intravesical hyaluronic acid included four studies (two randomised, two non-randomised, 143 patients) looking at the use of this treatment in recurrent UTI, showing a statistically significant improvement in the rates of recurrent UTI (mean difference –3.4 episodes per patient year, 95% confidence interval –4.3 to –2.5).¹⁹

Vaginal vaccines (vaginal immunogens applied mucosally) have also been shown (three randomised controlled trials, 220 patients) to convey some benefit (relative risk 0.81, 95% confidence interval 0.68 to 0.96)²¹ in reducing the risk of recurrent UTI, especially if the initial inoculation is followed up with booster doses. Smaller studies examining sublingual vaccines²⁰ and the use of D-mannose oral powder¹⁴ have also shown promising results and have been compared directly with the current standard of prophylactic antibiotics.

What should we do in the light of the uncertainty?

Based on the currently available evidence, prophylactic antibiotics remain the first line preventive treatment for uncomplicated recurrent UTI in women, and this is reflected in practice guidelines (Cochrane reviews, detailed in this article, have concluded that there is insufficient evidence to make a conclusive recommendation for many of the non-antibiotic treatments described).

Nonetheless, increased awareness of antimicrobial resistance has led patients and clinicians to seek alternatives. It has been noted that non-antibiotic prophylactic agents seem generally well tolerated, with few adverse events or side effects reported in the preliminary work described. Some of the non-antibiotic treatments—for example, vaginal oestrogens and probiotics, have been used extensively for other indications and therefore there are no concerns regarding their safety. As a result, there might be a case to support the use of non-antibiotic prophylactic agents, on an individual patient basis, for those who do not wish to take, or have an allergy or intolerance to, antibiotics.

Conflicts of Interest: CH reports speaker fees from Astellas, Pfizer, Ferring, Allergan, Medtronic, and is a member of the advisory boards for American Medical Systems and Pierre Fabre Pharmaceuticals. JB and RV have no conflicts to report.

Patient consent not applicable.

Provenance and peer review: commissioned, externally peer reviewed.

- 1 Bonkat G, Pickard R, Bartoletti R, et al. *Urological Infections*. European Association of Urology Guidelines, 2017.
- 2 Laupland KB, Ross T, Pitout JD, et al. Community-onset urinary tract infections: A population based assessment. *Infection* 2007;35:150-3.
- 3 Ikäheimo R, Siitonen A, Heiskanen T, et al. Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. *Clin Infect Dis* 1996;35:91-9. doi:10.1093/clinids/22.1.91 pmid:8824972.
- 4 Scottish Intercollegiate Guidelines Network. Management of suspected bacterial urinary tract infection in adults. Edinburgh. SIGN; 2012. <http://www.sign.ac.uk>
- 5 Albert X, Huertas I, Pereiró II, Sanfeliú J, Gosálbez V, Perrota C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database Syst Rev* 2004;359:CD001209, pmid:15266443.

Sublingual vaccines and D-mannose

In a multicentre observational trial involving 319 women with recurrent UTI, the efficacy of a sublingual vaccine containing a suspension of inactivated *E coli*, *Klebsiella*, *Proteus*, and *Enterococcus* was examined. In the patients receiving vaccine there was a 75% reduction in mean number of infections compared with those receiving daily trimethoprim (0.36 v 1.6 episodes at 3 months).²⁰ The efficacy of D-mannose has been studied in a recent three arm randomised controlled trial comparing D-mannose with nitrofurantoin with no prophylaxis.¹⁴ Overall, 98 patients (31.8%) had recurrent UTI: 15 (14.6) in the D-mannose group, 21 (20.4) in nitrofurantoin group, and 62 (60.8) in no prophylaxis group, with the rate statistically significantly higher in the no prophylaxis group compared with the active groups. There was no statistically significant difference in the efficacy of D-mannose when compared with prophylactic antibiotics.

Recommendations for future research

Population: Female patients with recurrent UTI

Intervention: Prophylactic treatments to reduce/prevent infection

Comparison: Prophylactic antibiotics (current gold standard)

Outcome: Reduction in infection episodes, side effects of treatments, health economic analysis of cost effectiveness

Many of the studies in progress are small, and further research with larger numbers of participants is needed before any firm conclusions for prevention of recurrent UTI can be made. Specifically, new studies should be designed to examine patient reported outcomes and quality of life indices, as well as more conventional endpoints such as bacterial eradication. In addition, the use of current standard treatment of prophylactic antibiotics as a comparator should be encouraged, and studies should be designed to look at other endpoints such as antimicrobial resistance development as well as clinical benefit.

Education into practice

When a patient presents with recurrent UTIs, ask yourself:

- Have I addressed all modifiable risk factors for this patient—eg, adequate fluid intake, diabetic control, oestrogen depletion, and constipation, before recourse to preventive measures?
- Do I need to perform further investigations in this patient, or am I happy that this is an uncomplicated recurrent UTI?
- Have I discussed the potential risks and benefits of the standard treatment of prophylactic antibiotics with the patient? Should we consider the use of a non-antibiotic alternative in the light of the evidence presented?

What to tell patients

- Most women with recurrent UTI will have a structurally and functionally normal urinary tract, therefore treatment is based on prevention and reducing infection frequency
- Low dose antibiotics for 6-12 months carry the highest chance of success in reducing the frequency of UTI
- Avoiding the development of antibiotic resistance is best achieved with non-antibiotic measures, but it is unclear how effective these are

How patients were involved in this article

There was no patient involvement from the authors when constructing this article. However, the patient reviewer highlighted the importance of patient reported outcome measures in any future or planned trials in addition to traditional microbiological tests.

- Beerepoot MA, ter Riet G, Nys S, et al. Lactobacilli vs antibiotics to prevent urinary tract infections: a randomized, double-blind, noninferiority trial in postmenopausal women. *Arch Intern Med* 2012;359:704-12. doi:10.1001/archinternmed.2012.777 pmid:22782199.
- Murray BE, Rensimer ER, DuPont HL. Emergence of high-level trimethoprim resistance in fecal *Escherichia coli* during oral administration of trimethoprim or trimethoprim-sulfamethoxazole. *N Engl J Med* 1982;359:130-5. doi:10.1056/NEJM198201213060302 pmid:7033781.
- O'Kane DB, Dave SK, Gore N, et al. Urinary alkalisation for symptomatic uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev* 2016;359:CD010745.pmid:27090883.
- Schwenger EM, Tejani AM, Loewen PS. Probiotics for preventing urinary tract infections in adults and children. *Cochrane Database Syst Rev* 2015;359:CD008772.pmid:26695595.
- Flower A, Wang LQ, Lewith G, Liu JP, Li Q. Chinese herbal medicine for treating recurrent urinary tract infections in women. *Cochrane Database Syst Rev* 2015;359:CD010446.pmid:26040964.
- Lee BSB, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev* 2012;359:CD003265.pmid:23076896.
- Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev* 2012;359:CD001321.pmid:23076891.
- Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev* 2008;359:CD005131.pmid:18425910.
- Kranjčec B, Papeš D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol* 2014;359:79-84. doi:10.1007/s00345-013-1091-6 pmid:23633128.
- Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev* 2008;359:CD001321.pmid:18253990.
- Naber KG, Cho YH, Matsumoto T, Schaeffer AJ. Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. *Int J Antimicrob Agents* 2009;359:111-9. doi:10.1016/j.ijantimicag.2008.08.011 pmid:18963856.
- Wagenlehner FME, Ballarín S, Pilatz A, Weidner W, Lehr L, Naber KG. A randomized, double-blind, parallel-group, multicenter clinical study of *Escherichia coli*-lyophilized lysate for the prophylaxis of recurrent uncomplicated urinary tract infections. *Urol Int* 2015;359:167-76. doi:10.1159/000371894 pmid:25721866.
- National Institute for Health Research. ALternative to prophylacticaAntibiotics for the treatment of recurrent urinary tract infections in women (ALTAR study) 2016. In progress. www.nets.nihr.ac.uk/projects/hta/138821
- De Vita D, Antell H, Giordano S. Effectiveness of intravesical hyaluronic acid with or without chondroitin sulfate for recurrent bacterial cystitis in adult women: a meta-analysis. *Int Urogynecol J* 2013;359:545-52. doi:10.1007/s00192-012-1957-y pmid:23129247.
- Lorenzo-Gómez MF, Padilla-Fernández B, García-Criado FJ, et al. Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics. *Int Urogynecol J* 2013;359:127-34. doi:10.1007/s00192-012-1853-5 pmid:22806485.
- Beerepoot MA, Geerlings SE, van Haarlem EP, van Charante NM, ter Riet G. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. *J Urol* 2013;359:1981-9. doi:10.1016/j.juro.2013.04.142 pmid:23867306.

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Table

Table 1 | Summary of meta-analyses of preventive treatments for women with recurrent UTIs

Study	Study details	Population	Comparison	Outcome/results	Interpretation and uncertainty	GRADE
Urinary alkalisation ⁸	No RCTs available	NA	172 studies found—none fulfilled inclusion criteria owing to: wrong intervention (126), duplication (29), wrong population (9), wrong comparator (5) and not RCT (3)	NA	Insufficient sample size/evidence. Unable to give recommendation. Larger, well designed RCTs are necessary and should include symptomatic rUTI as primary outcome	Very low
Probiotics ⁹	8 RCTs, 615 patients. (1 RCT in children was excluded)	Women only, both pre and post menopause. 7/8 RCTs looked at rUTI, 1 in “healthy” women	7 studies—v placebo or no comparator	RR 0.82, 95% CI 0.6 to 1.12. No reduction in risk of rUTI	Insufficient sample size/evidence. Unable to give recommendation. No significant reduction in risk of symptomatic bacterial rUTI shown in limited data	Low
			1 study—v antibiotic	RR 1.12, 95% CI 0.95 to 1.33. No reduction in risk of rUTI		Low
Chinese herbal medicine (CHM) ¹⁰	7 RCTs, 542 patients	All 3 studies in women post menopause looked at rUTI following initial presentation with acute UTI	3 studies v antibiotics	RR 0.28, 95% CI 0.09 to 0.82. Reduction in risk of rUTI	Some benefit shown in women post menopause women. Recommendations taken with caution owing to small study sizes, high risk of bias, and the results might not be transferrable to the premenopausal population	Very low
		1 study in pre- and 1 study in women post menopause looking at rUTI after initial presentation with acute UTI.	2 studies CHM+antibiotics v antibiotics alone	RR 0.53, 95% CI 0.35 to 0.80. Reduction in risk of rUTI		Very low
		1 study in pre and 1 study in women post menopause looked at rUTI after initial presentation with acute UTI	2 studies v another CHM	RR 1.28, 95% CI 1.03 to 1.57. Reduction in risk of rUTI		Very low
Methenamine hippurate ¹¹	13 RCTs, 2032 patients	5 studies included men. Studies including/only assessing women included women both pre and post menopause. One study looked at pregnant women with bacteriuria. Only 1 RCT looked specifically at rUTI	6 studies looked at preventing acute symptomatic UTI as primary outcome	RR 0.53, 95% CI 0.24 to 1.18. High heterogeneity	Poor studies: high risk of bias. Six studies had <1 month follow-up. High heterogeneity of cohorts in all studies makes direct comparison impossible. Might be effective in reducing risk of symptomatic UTI in patients with no abnormalities of their urinary tract via subgroup analysis	Low
			12 Studies looked at presence of bacteriuria as primary or secondary outcome	RR 0.67, 95% CI 0.45 to 0.99. High heterogeneity		Low
			1 study looked at rUTI in mixed population (92% women)	Methenamine showed reduction in risk of rUTI compared with placebo (RR 0.46)		
Cranberries ¹²	24 RCTs, 2463 patients	Mixed sex (9), children (5), women only (8), pregnant women (2). Subgroup of 4 RCTs looked at rUTI: 594 patients. Women pre menopause (2), Women ≥45 years (1), women 21-72 years (1)	Subgroup analysis of the 4 rUTI studies: 2 studies cranberry v placebo and 2 studies cranberry v antibiotics	Subgroup analysis: RR 0.74, 95% CI 0.42 to 1.31. Non-statistically significant result	High heterogeneity of study cohorts.	Moderate
Oestrogens ¹³	9 RCTs, 3345 patients	Women post menopause	4 studies oral oestrogens v placebo	RR 1.08, 95% CI 0.88 to 1.33. No reduction in risk of rUTI	Benefit in topical oestrogen therapy in reducing risk of rUTI. Topical oestrogen associated with increased local side effects. Only applicable in women post menopause	Moderate
			3 studies vaginal oestrogens v placebo	RR 0.25, 95% CI 0.13 to 0.50. Small reduction in risk of rUTI		Moderate
			2 studies vaginal oestrogens v antibiotics	Evidence from these two small studies shows that in women post menopause with rUTI, vaginal oestrogens reduce the number of UTIs, but owing to significant heterogeneity results not appropriate to be pooled		Low

RCT, randomised controlled trial

rUTI, recurrent urinary tract infection

RR, relative risk

Table 1 (continued)

Study	Study details	Population	Comparison	Outcome/results	Interpretation and uncertainty	GRADE
CI, confidence interval						

Figure

Fig 1 Non-antibiotic treatment options for UTIs in women