Urinary alkalisation for symptomatic uncomplicated urinary tract infection in women

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TABLE OF CONTENTS

[Intervention Review]

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ABSTRACT

Background

Uncomplicated urinary tract infection (UTI) is the most common bacterial infection in women, characterised by dysuria and urinary frequency. Urinary alkalisers are widely used in some countries for the symptomatic treatment of uncomplicated UTI, and they are recommended in some national formularies. However, there is a lack of empirical evidence to support their use for UTI and some healthcare guidelines advise against their use.

Objectives

We aimed to look at the benefits and harms of the use of urinary alkalisers for the treatment of uncomplicated UTIs in adult women.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 19 January 2016 through contact with the Trials Search Co-ordinator using search terms relevant to this review.

Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs on the use of (any) urinary alkalisers (either exclusively or non-exclusively) for the symptomatic treatment of uncomplicated UTI amongst women aged 16 and over, were included. Studies were eligible if they included patients whose diagnosis of UTI was decided by symptoms alone, or positive urine dipstick test or urine culture; and patients with recurrent UTI, provided patients had no symptoms of UTI in the two weeks prior to the onset of symptoms that lead them to seek medical advice. Studies were ineligible if they studied patients with complicated UTIs; immune-compromising conditions; acute pyelonephritis; or chronic conditions such as interstitial cystitis.

Data collection and analysis

Three authors independently assessed and screened papers, and this was repeated by two separate authors (independently). An additional investigator acted as arbitrator, where necessary. There were no papers which fulfilled the inclusion criteria for this review, and therefore no data extraction was performed.

Main results

Our search identified 172 potential studies for inclusion. However, following assessment none fulfilled the inclusion criteria for this review.

Authors' conclusions

Until relevant evidence is generated from randomised trials, the safety and efficacy of urinary alkalisers for the symptomatic treatment of uncomplicated UTI remains unknown.

PLAIN LANGUAGE SUMMARY

Urinary alkalisation for uncomplicated urinary tract infections

Urinary tract infection (UTI) is the most common form of bacterial infection among women and can cause pain and frequent urination.

Urinary alkalisers are medications that reduce the acidity of urine; these are commonly purchased over the counter, or prescribed by doctors to treat the symptoms of UTI.

We aimed to investigate the benefits and harms of urinary alkalisers for the treatment of UTI. We searched the literature to 19 January 2016 but found no randomised controlled trials (RCTs) undertaken to investigate these agents that met our study inclusion criteria. We were unable to judge the benefits or harms of the use urinary alkalisers in the context of UTI.

It is important that further research in the form of RCTs be carried out to determine the benefits or harms of urinary alkalisers.

BACKGROUND

Description of the condition

Urinary tract infections (UTIs) are the most common bacterial infections in women, most of which are uncomplicated (Foxman 2003). UTIs are considered uncomplicated in the absence of urinary tract abnormalities, obstruction or resistant pathogens, pregnancy, immunocompromised state, or involvement of the upper renal tract. The term 'uncomplicated' generally does not apply to UTIs in men.

Standard conventional management of suspected UTI is to treat empirically with antibiotics, although studies have challenged this approach (Bleidorn 2010; Richards 2005). UTI can then be confirmed with urine microscopy and culture, from a urine sample taken prior to the commencement of antibiotics. Whatever the role of antibiotics, women often seek relief from the symptoms of UTI until either the infection is cleared with antibiotics or resolves spontaneously. Uncomplicated UTIs often remit spontaneously without antibiotics: a recent pilot RCT found that symptomatic treatment of uncomplicated UTI with nonsteroidal anti-inflammatory drugs (NSAIDs) was non-inferior to antimicrobial therapy with ciprofloxacin (Bleidorn 2010). Nonetheless, an earlier study also found that women with symptoms of UTI who are culture-negative respond to antibiotics (Richards 2005).

Description of the intervention

Several clinical guidelines for UTI treatment advise first-line use of antibiotics (ACOG 2008; Grabe 2010; IDSA/ESMI 2011). However, until infection has cleared (due to either antimicrobial therapy or spontaneous remission), symptoms may be troublesome. The use of urinary alkalisers for the symptomatic treatment of uncomplicated UTI is very common in some countries. For example, more than one million units of urinary alkalisers are sold in Australia annually; many of these are used specifically for UTIs and acute culture-negative cystitis. Use of urinary alkalisers for the symptomatic treatment of UTI and cystitis appear in MIMS Australia and other national formularies (eMC 2016; MIMS 2016). Use is also widely promoted by primary healthcare practitioners (Murtagh 2015; Phelps 2011). Literature supporting benefits from use of these agents is sparse; some guidelines specifically state that they are not recommended (NICE 2009). The most commonly available urinary alkalisers are potassium citrate, sodium citrate, and sodium bicarbonate.

How the intervention might work

Urinary alkalisers primarily work to raise urine pH, which in theory, aids in the symptomatic relief of dysuria. Dysuria and urinary frequency are the most common and bothersome symptoms of UTI and acute culture-negative cystitis (Munday 1990; Spooner 1984).

Urinary pathogens, such as *Proteus mirabilis* can also increase urinary pH and are associated with symptoms of dysuria and urinary frequency (Franz 1999); however, it has been suggested elsewhere that there is no correlation between the urine pH and the sensation of dysuria (Brumfitt 1990).

Why it is important to do this review

Uncomplicated UTI is very common, and imposes significant financial burden. In the USA, UTI is responsible for over seven million physician visits annually, and account for the use of approximately 15% of all community-prescribed antibiotics. The total annual estimated cost of antibiotics for UTI in the USA exceeds one billion dollars (Foxman 2002; Mazzulli 2002). The advent of increasing numbers of drug resistant organisms means that avoidance of unnecessary antibiotics is important.

Urinary alkalisers are widely used in certain parts of the world, particularly Australia, for symptomatic relief of UTI and acute culture-negative cystitis. There is however a paucity of good evidence to support their use. There is also conflicting evidence surrounding urinary alkalisation for antimicrobial eradication in UTI. Some studies show benefit of concomitant urinary alkalisers and antibiotic use, with reduced antibiotic minimum inhibitory concentration when urine is at alkaline pH. Other studies show that urine pH within the acidic range is favourable, as it can have a bactericidal effect (Burian 2012; Carlsson 2003; Zhanel 1991). Although we aimed to focus on symptom relief in UTI, antimicrobial eradication may also be important, as prolonged positive urine culture may lead to a prolongation of symptoms.

OBJECTIVES

We aimed to look at the benefits and harms of the use of urinary alkalisers for the treatment of uncomplicated UTIs in adult women.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the use of urinary alkalisers (of any type) for the symptomatic relief of UTI were eligible for inclusion.

Types of participants

Inclusion criteria

We included women aged 16 years or over with symptoms of uncomplicated UTI or cystitis; including urinary frequency, urgency and dysuria. Participants were to be included regardless of whether diagnoses were made based on positive urine dipstick test results, positive urine culture, or symptoms alone. Women with recurrent UTI were to be included if they had no symptoms of UTI in the two weeks prior to the onset of the symptoms that lead to their presentation to the general practitioner/health clinic.

Exclusion criteria

- Complicated UTIs, such as those requiring hospital admission, infections associated with fevers or rigours, those involving multidrug resistant pathogens, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* urethritis, urinary tract abnormalities, urinary tract calculi or urinary tract obstruction
- Immunocompromising conditions
- Acute pyelonephritis
- UTI symptoms in the two weeks prior to the onset of symptoms that lead to presentation
- Chronic conditions such as interstitial cystitis, painful bladder syndrome, chronic pelvic pain syndrome.

Types of interventions

Any urinary alkalisers used exclusively or non-exclusively for the treatment of symptoms of UTI were included. We aimed to compare:

- Urinary alkalisers versus placebo/no treatment
- Urinary alkalisers versus antibiotics
- Urinary alkalisers + antibiotics versus antibiotics alone
- Urinary alkalisers versus NSAIDs.

Types of outcome measures

Primary outcomes

- Early and late symptoms (at days 1 to 4 and days 5 to 10): dysuria, urinary frequency, and abdominal pain

- Any adverse events: worsening of UTI, progression to complicated UTI, need for hospitalisation or intravenous antibiotics.

Secondary outcomes

- Duration of symptoms
- Severity of symptoms (negligible, mild, moderate, severe) as measured on days 1 to 4 and days 5 to 10
- Number of return visits to the GP
- Days absent from work
- Bacterial eradication.

Search methods for identification of studies

Electronic searches

We searched Cochrane Kidney and Transplant's Specialised Register to 19 January 2016 through contact with the Trials Search Co-ordinator using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

Searching other resources

1. Reference lists of clinical practice guidelines, review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies which were relevant to the review. Titles and abstracts were screened independently by three authors, who discarded studies that were not applicable based on title and abstract alone. Where relevance to the review was unclear based on the title and abstract, these studies were retained, and the full papers obtained. In the case where the full paper was not published in English, the paper was translated to English. Four authors independently assessed the full manuscripts of the retained papers to determine whether the inclusion criteria were satisfied, and papers were included or excluded based on this assessment. Where consensus was not reached, an additional investigator acted as arbiter. The screening process was repeated by two separate investigators independently, and the same outcome was reached.

Data extraction and management

Data extraction was to be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were to be translated before assessment. Where more than one publication of one study existed, reports were to be grouped together and the publication with the most complete data was to be used in the analyses. Where relevant outcomes were only published in earlier versions these data were to be used. Any discrepancies between published versions were to be highlighted.

Assessment of risk of bias in included studies

We planned to assess risk of bias using the Cochrane risk of bias assessment tool (Higgins 2011) (Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
    - Participants and personnel (performance bias)
    - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes such as resolution of symptoms by day three and day seven (dysuria, urinary frequency, abdominal pain) and progression to complicated UTI, we planned to express results as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects

of treatment, such as duration of symptoms, severity of symptoms (negligible, mild, moderate, severe; 0 to 3), the mean difference (MD) was to be used, or the standardised mean difference (SMD) if different scales had been used.

Unit of analysis issues

In relation to cluster-RCTs, only studies where analyses were made at the same level as allocation (and using summary measurements for each cluster) were to be included. Cluster-RCTs could have been included if statistical methods were employed to deal with analysis at the individual level, which could account for data clustering, and that statistical methods were clearly outlined in the methods, and were sound.

Data from cross-over RCTs could also be assessed, but only the first randomisation period was included. Complete cross-over data were inappropriate for the intervention under review.

Urinary alkalisers could be investigated alone or in combination with another agent(s) where the only difference between groups was addition of a urinary alkaliser. Where possible we aimed to combine groups with the same intervention and create a single pair-wise comparison.

Dealing with missing data

Any further information required from original authors was to be requested by written correspondence (e.g. emailing or writing to corresponding author) and any relevant information obtained in this manner was to be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population was to be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were to be investigated. Issues of missing data and imputation methods (e.g. last-observation-carried-forward) were to be critically appraised (Higgins 2011).

Assessment of heterogeneity

We planned to analyse heterogeneity using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance, and the I² statistic (Higgins 2003).

Assessment of reporting biases

Funnel plots were to be used to assess for the potential existence of small study bias (Higgins 2011). Because no studies met our inclusion criteria, this could not be performed.

Data synthesis

Data were to be pooled using the random-effects model but the fixed-effect model was also to be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was to be used to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could be related to age, urinary pathogen (including urinary bacterial cell counts), chronicity of symptoms before seeking medical advice, and history of urinary symptoms (including recurrent UTIs). If data were available we planned subgroup analysis comparing the use of urinary alkalisers in sporadic and recurrent UTIs. Heterogeneity in treatments could be related to prior or concomitant (or both) agent(s) used and the agent, dose and duration of therapy. These could include antibiotics, analgesics and anti-inflammatory medications. We also planned subgroup analysis comparing doses and duration of urinary alkaliser therapy. Adverse effects were to be tabulated and assessed using descriptive techniques because they were likely to be different for the various agents used. Where possible, the risk difference with 95% CI was to be calculated for each adverse effect, either compared with no treatment or another agent.

Sensitivity analysis

We planned sensitivity analyses to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

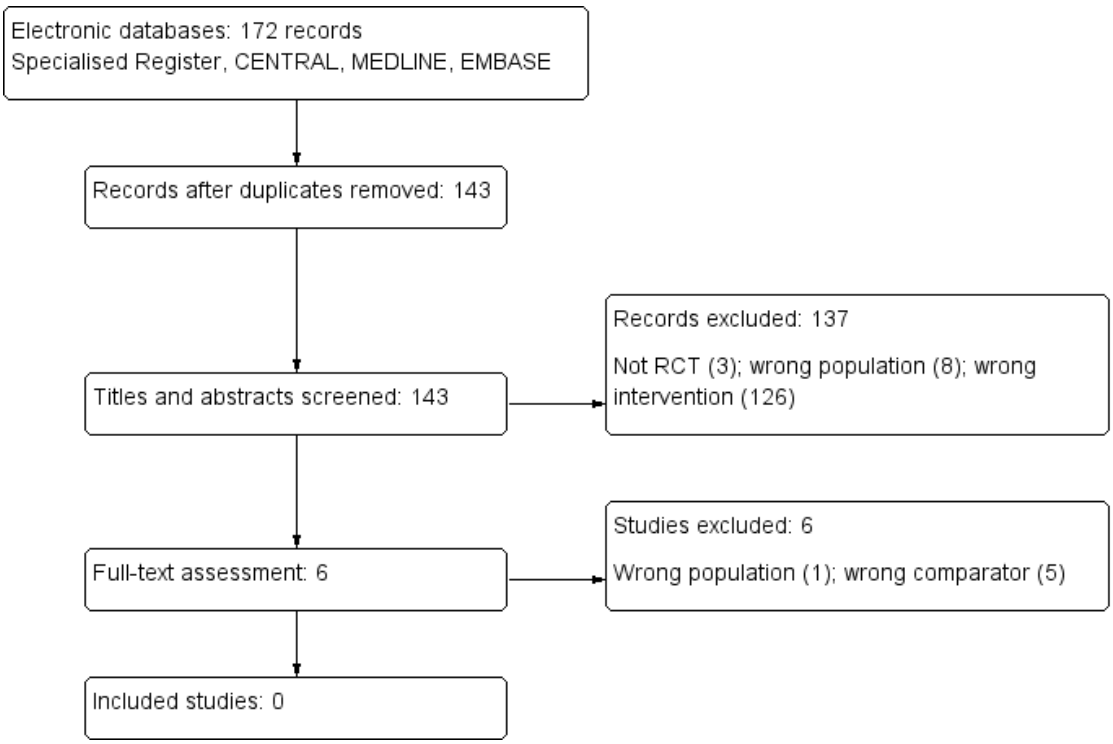
RESULTS

Description of studies

Results of the search

Searches yielded 172 records, of which 29 were duplicates. We assessed 143 records based on title and abstract and excluded 137 records that did not fulfil our inclusion criteria (Figure 1). We identified six records for possible inclusion and full-text assessment (Brumfitt 1990; Butler 1983; Carter 1991; Darioli 1983; Klastersky 1971; Reeves 1984). Reasons for exclusion were inappropriate intervention used (Klastersky 1971; Butler 1983; Darioli 1983; Reeves 1984), no urinary alkaliser used (Brumfitt 1990), and symptoms in the context of urethral instrumentation (Carter 1991). See Characteristics of excluded studies.

Figure 1. Flow chart



Thus, no studies could be included in this review.

Risk of bias in included studies

Risk of bias assessment could not be conducted.

Effects of interventions

No studies met our inclusion criteria.

DISCUSSION

Summary of main results

We were surprised to find no RCTs investigating the use of urinary alkalisers for uncomplicated UTIs, given the widespread use of these agents in some parts of the world. Due to the lack of adequate research into the use of urinary alkalisers for this indication, we were unable to offer conclusions about their efficacy.

Research supporting the use of urinary alkalisers to date have been single arm studies (Munday 1990; Spooner 1984). The lack of a comparison group in these studies precludes any conclusion of efficacy. The only studies to randomise groups to different intervention arms with urinary alkalisers confounded the comparisons by using different antibiotics in combination (Butler 1983; Reeves 1984).

The mechanism of action suggested for urinary alkalisers in UTI is that raising urine pH directly, by local action, reduces symptom severity on bladder and urethral mucosa. However an observational study of 128 women with uncomplicated UTIs found no correlation between reported symptoms of UTI (or infection) and urine pH (Brumfitt 1990).

Overall completeness and applicability of evidence

There is a lack of evidence for the use of urinary alkalisation in the treatment of lower urinary tract symptoms, particularly in the setting of uncomplicated UTIs. There have been a number of papers published wherein the researchers investigate the use of urinary alkalisers for symptomatic relief following or prophylactically for different urological procedures and investigations, such as flexible cystoscopy and urodynamics studies (Nguan 2005; Wong 2010). These papers failed to show any benefit of the use of urinary alkalisers. The relevance of these studies to our review question is not clear however.

There have been no RCTs particularly looking at the use of urinary alkalisers for uncomplicated UTI in the cohort of patients that we wished to study.

Quality of the evidence

Research on urinary alkalisation for lower urinary tract symptoms has not been robust. In the studies we identified, subject numbers were small. Groups have been quasi-randomised or not randomised at all and intervention arms are inappropriate to show effect.

Potential biases in the review process

There were no published RCTs.

Agreements and disagreements with other studies or reviews

Despite extensive literature searches we were unable to find any other studies or reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

Currently there is insufficient evidence to support the use of urinary alkalisers for symptoms in acute uncomplicated UTI.

Implications for research

Research is needed to investigate urinary alkalisers for uncomplicated UTIs with well-constructed RCTs.

ACKNOWLEDGEMENTS

We would like to thank the referees for their assistance, comments and feedback.

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Butler 1983 *{published data only}*
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Carter 1991 *{published data only}*
Carter P, Lewis P, Abrams P. Urodynamic morbidity and dysuria prophylaxis. *British Journal of Urology* 1991;**67**(1): 40–1. MEDLINE: 1847088

Darioli 1983 *{published data only}*
Darioli R, Chappuis P, Dubi J. Evaluation of the treatment of symptomatic urinary tract infection with a single dose of antibiotics or bicarbonate [Evaluation du traitement de l'infection urinaire symptomatique par dose unique d'antibiotiques ou par bicarbonate]. *Schweizerische Medizinische Wochenschrift* 1983;**113**(1):14–6. MEDLINE: 6298934

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Reeves 1984 *{published data only}*
Reeves DS, Lacey RW, Mummery RV, Mahendra M, Bint AJ, Newsom SW. Treatment of acute urinary infection by norfloxacin or nalidixic acid/citrate: a multi-centre comparative study. *Journal of Antimicrobial Chemotherapy* 1984;**13 Suppl B**:99–105. MEDLINE: 6234282

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Murtagh 2015
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O'Kane 2013

O'Kane DB, Dave SK, Gore N, Patel F, Hoffmann T, Del Mar CB. Urinary alkalisation for uncomplicated urinary tract infection. *Cochrane Database of Systematic Reviews* 2013, Issue 10. [DOI: 10.1002/14651858.CD010745]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by year of study]*

Study	Reason for exclusion
Klastersky 1971	This paper compared an antibiotic (erythromycin) in alkaline conditions with a different antibiotic (nitrofurantoin) . Although this paper included a urinary alkaliser, the fact that it was coupled with a different antibiotic to the other study arm means that no conclusions on the efficacy of the alkaliser can be made by comparison of these two groups. Furthermore most of the patients in this study had advanced pelvic cancers, some had urological issues, and some had indwelling urinary catheters meaning that they did not meet inclusion criteria for this review
Darioli 1983	This study compared a single dose of urinary alkaliser with a single dose of an antibiotic. A single dose of an antibiotic is not an accepted treatment for UTI, and therefore is not an appropriate comparison. The aim of this study was actually to investigate the use of a single dose of antibiotic, and the alkaliser arm was acting as a placebo arm. Furthermore a single dose of urinary alkaliser is not an appropriate dose to change urinary pH
Butler 1983	This paper compared an antibiotic (nalidixic acid) coupled with a urinary alkaliser (citrate) with a different antibiotic (cotrimoxazole). As in the Klastersky 1971 paper above, no conclusions on the efficacy of the urinary alkaliser can be made from comparison of the two arms in this study
Reeves 1984	Similar to Klastersky 1971 and Butler 1983, this paper compared an antibiotic (nalidixic acid) coupled with a urinary alkaliser (citrate) with a different antibiotic norfloxacin. No conclusions on the efficacy of the urinary alkaliser can be drawn from this comparison
Brumfitt 1990	This paper reported on the different urinary pHs seen in patients with 'cystitis'. However, there was no intervention, no urinary alkaliser used
Carter 1991	This study reported on the use of urinary alkalisers for prophylaxis against dysuria following urological intervention. Because there was instrumentation of the urethra/bladder in this study the patients were not eligible for inclusion into this review

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. urinary next tract next infection*:ti,ab,kw 2. bacteriuri*:ti,ab,kw 3. cystitis:ti,ab,kw 4. pyelonephritis:ti,ab,kw 5. (uti or utis):ti,ab,kw 6. {or #1-#5} 7. dysuria:ti,ab,kw 8. stranguria:ti,ab,kw 9. ((pain* or frequen* or urgency) near/25 (micturation or urin*)):ti,ab,kw 10. {or #7-#9} 11. #6 or #10 12. sodium next bicarbonate:ti,ab,kw 13. citrate*:ti,ab,kw 14. "citric acid":ti,ab,kw 15. alkali*:ti,ab,kw 16. {or #12-#15} 17. #11 and #16
MEDLINE	1. urinary tract infections/ 2. bacteriuria/ 3. cystitis/ 4. Pyelonephritis/ 5. urinary tract infection*.tw. 6. (uti or utis).tw. 7. bacteriuri*.tw. 8. cystitis.tw. 9. pyelonephritis.tw. 10. or/1-9 11. Dysuria/ 12. stranguria.tw. 13. dysuria.tw. 14. ((pain* or frequen* or urgency) adj25 (micturation or urin*)).tw. 15. or/11-14 16. or/10,15 17. Sodium Bicarbonate/ 18. exp Citrates/

(*Continued*)

	19. sodium bicarbonate.tw,nm. 20. citrate.tw,nm. 21. alkali*.tw. 22. or/17-21 23. and/16,22
EMBASE	1. Urinary Tract Infection/ 2. Bacteriuria/ 3. Asymptomatic Bacteriuria/ 4. Cystitis/ 5. exp Pyelonephritis/ 6. urinary tract infection*.tw. 7. (uti or utis).tw. 8. bacteriuri*.tw. 9. cystitis.tw. 10. pyelonephritis.tw. 11. or/1-10 12. Dysuria/ 13. Urinary Urgency/ 14. Urinary Frequency/ 15. stranguria.tw. 16. dysuria.tw. 17. ((pain* or frequen* or urgency) adj25 (micturation or urin*)).tw. 18. or/12-17 19. or/11,18 20. Alkalinization/ 21. Bicarbonate/ 22. Citric Acid/ 23. Citrate Sodium/ 24. Citrate Potassium Sodium/ 25. Citrate Potassium/ 26. sodium bicarbonate.tw. 27. citrate*.tw,rn. 28. alkali*.tw. 29. or/20-28 30. and/19,29

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)

(*Continued*)

	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding

(*Continued*)

	could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome

(*Continued*)

	that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: DOK, SD, NG, FP, CDM
2. Study selection: DOK, SD, NG, FP, CDM, JT
3. Carry out the analysis: DOK, CDM, TH, SD, NG, FP, JT
4. Interpret the analysis: DOK, CDM, TH, SD, NG, FP, JT
5. Draft the final review: DOK, JT
6. Disagreement resolution: DOK, CDM, TH
7. Update the review: DOK, CDM, TH, SD, NG, FP, JT

DECLARATIONS OF INTEREST

- Dermot B O'Kane: none known
- Sameer K Dave: none known
- Neel Gore: none known
- Farhaan Patel: none known
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INDEX TERMS

Medical Subject Headings (MeSH)

Antacids [*urine]; Anti-Infective Agents, Urinary [therapeutic use]; Hydrogen-Ion Concentration [drug effects]; Urinary Tract Infections [*drug therapy; urine]; Urine [chemistry]

MeSH check words

Adult; Female; Humans