Cochrane Library

Cochrane Database of Systematic Reviews

Methenamine hippurate for preventing urinary tract infections (Review)

Lee BSB, Bhuta T, Simpson JM, Craig JC

Lee BSB, Bhuta T, Simpson JM, Craig JC.
Methenamine hippurate for preventing urinary tract infections.
Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD003265.
DOI: 10.1002/14651858.CD003265.pub3.

www.cochranelibrary.com

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Methenamine hippurate for preventing urinary tract infections

Bon San B Lee[1], Tushar Bhuta[2], Judy M Simpson[3], Jonathan C Craig[3,4]

[1]Spinal Medicine Department, Prince of Wales Hospital, Randwick, Australia. [2]Department of Neonatal Medicine, Royal North Shore Hospital, Sydney, Australia. [3]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [4]Cochrane Renal Group, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia

Contact address: Bon San B Lee, Spinal Medicine Department, Prince of Wales Hospital, Level 2, High St Entrance, Randwick, NSW, 2031, Australia. guslogie@gmail.com, blee@medicalinformatics.net.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 11, 2012.

Citation: Lee BSB, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database of Systematic Reviews* 2012, Issue 10. Art. No.: CD003265. DOI: 10.1002/14651858.CD003265.pub3.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Methenamine salts are often used as an alternative to antibiotics for the prevention of urinary tract infection (UTI). This review was first published in Issue 1, 2002 and updated in Issue 4, 2007.

Objectives

To assess the benefits and harms of methenamine hippurate in preventing UTI.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library)*, MEDLINE (from 1950), EMBASE (from 1980), reference lists of articles and abstracts from conference proceedings without language restriction. Manufacturers' of methenamine salts were contacted for unpublished studies and contact was made with known investigators.

Date of last search: June 2012

Selection criteria

Randomised controlled trials (RCT) and quasi-RCTs of methenamine hippurate used for the prevention of UTIs in all population groups were eligible. A comparison with a control/no treatment group was a prerequisite for selection.

Data collection and analysis

Two authors independently assessed study quality and extracted data. Statistical analyses were performed using the random effects model and the results expressed as risk ratio (RR) for dichotomous outcomes with 95% confidence intervals (CI). An exploration of heterogeneity and a detailed description of results, grouped by population, was undertaken.

Main results

Thirteen studies (2032 participants) were included. Six studies (654 patients) reported symptomatic UTI and eight studies (796 patients) reported bacteriuria. Overall, study quality was mixed. The overall pooled estimates for the major outcome measures were not interpretable because of underlying heterogeneity. Subgroup analyses suggested that methenamine hippurate may have some benefit in patients without renal tract abnormalities (symptomatic UTI: RR 0.24, 95% CI 0.07 to 0.89; bacteriuria: RR 0.56, 95% CI 0.37 to 0.83), but not in patients with known renal tract abnormalities (symptomatic UTI: RR 1.54, 95% CI 0.38 to 6.20; bacteriuria: RR 1.29, 95% CI 0.54 to 3.07). For short-term treatment duration (1 week or less) there was a significant reduction in symptomatic UTI in those without renal tract abnormalities (RR 0.14, 95% CI 0.05 to 0.38). The rate of adverse events was low.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Authors' conclusions

Methenamine hippurate may be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short-term prophylaxis. It does not appear to work in patients with neuropathic bladder or in patients who have renal tract abnormalities. The rate of adverse events was low, but poorly described.

There is a need for further large well-conducted RCTs to clarify this question, particularly for longer term use for people without neuropathic bladder.

PLAIN LANGUAGE SUMMARY

Methenamine hippurate for preventing urinary tract infections

Bladder and kidney infections (urinary tract infections - UTI) can cause vomiting, pain, dysuria, septicaemia, fever and tiredness, and occasionally kidney damage. Some people are at high risk of repeated UTIs, and they are also more likely to have serious complications (including people with kidney problems, or people who have catheters to release urine). Long-term use of antibiotics can lead to resistance, so methenamine salts (methenamine or hexamine hippurate) are often used. This review identified 13 studies (2032 participants). Methenamine hippurate may be effective in preventing UTI in patients without renal tract abnormalities particularly when used for short term prophylaxis. It does not appear to be effective for long term prophylaxis in patients who have neuropathic bladder. There were few adverse effects.Additional well controlled randomised controlled trials are necessary in particular to clarify effectiveness for longer term prophylaxis in those without neuropathic bladder.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Description of the condition

Patients at greater risk of UTI include women, those undergoing genito-urinary procedures, those with abnormal renal tract anatomy or physiology, those with foreign bodies (such as catheters), the immunocompromised, or those with a neuropathic bladder (Macfarlane 1985). One such high risk group is the spinal injured population (with associated neuropathic bladder), where the incidence is estimated at 1.82 UTI episodes/patient/year (Waites 1993). In these high-risk patients, problems can result from antibiotic resistance and other complications such as autonomic dysreflexia, vesicoureteric reflux, related pyelonephritis, septicaemia, the need for a change in the method of bladder management, or recatheterisation. The end result is that highly susceptible populations often require hospitalisation for what in the general community would be an easily treated condition.

Description of the intervention

Methenamine salts are often used in the prevention of urinary tract infection (UTI). They are frequently used for prolonged periods because, unlike conventional antibiotics, acquired resistance does not appear to develop (Parfitt 1999). Given the problems of increasing antibiotic resistance, methenamine salts may be especially useful in populations susceptible to recurrent UTI.

How the intervention might work

Methenamine salts act via the production of formaldehyde from hexamine, which in turn acts as a bacteriostatic agent (Mayrer 1982). It is uncertain whether urinary acidification and the direct bacteriostatic effect of hippuric acid contribute significantly to its action (Nahata 1982; Wall 1990). Methenamine salts are well tolerated and adverse effects, including minor gastrointestinal upsets, dysuria, abdominal cramps, anorexia, rash and stomatitis (3M 2000; McEvoy 1999), are generally mild (Mayrer 1982).

Why it is important to do this review

It remains highly controversial whether methenamine salts are effective in preventing UTI (Saint 1999). In vitro studies suggest that a urinary pH below 5.5 is needed for bacteriostatic concentrations of free formaldehyde to be generated from methenamine hippurate (Greenwood 1981). There are suggestions that it may be difficult to maintain urinary pH below this level with conventional techniques (typically ascorbic acid) long-term (Hetey 1990; Wall 1990). It is also suggested that in catheterised patients, the amount of time that any formaldehyde produced remains in the bladder may be insufficient to be clinically effective (Devenport 1984; Saint 1999).

There are two salts of methenamine described in clinical use. It is uncertain whether methenamine hippurate* and methenamine mandelate** are equivalent in effectiveness (Gow 1974; Greenwood 1981; Kasanen 1974). The mandelate salt is not widely available. This review will only consider the effectiveness of methenamine hippurate in preventing UTIs.

Common alternatives to methenamine hippurate in oral urinary prophylaxis include antibiotic therapy (Albert 2004; Niel-Weise 2005) and cranberry juice or capsules (Jepson 2004).

** Methenamine hippurate is the US adopted name (USAN) and recommended international non-proprietary name modified (rINNM). Other synonyms are: hexamine hippurate - British approved name (BAN) and hexamethylenetramine hippurate.*
*** Methenamine mandelate is the recommended international non-proprietary name modified (rINNM). Other synonyms are: hexamine mandelate, hexamine amygdalate, mandelato de metenamina, and hexamethylenetramine mandelate.*

OBJECTIVES

- To determine the benefits and harms of methenamine hippurate is in the prevention of UTI.
- To determine whether the following may cause variability in observed treatment effects:
  - The method of bladder management type.
  - The use of intercurrent urinary acidification in the treatment group.
  - The effect of short or longer term duration of treatment.
  - Study quality.
  - Abnormalities of renal tract function and/or structure.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCT) (including randomised cross-over trials or quasi-RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) of methenamine hippurate used for the prophylaxis of UTIs were considered. Trials evaluating curative treatment were excluded.

Types of participants

At-risk populations for UTI, including all bladder management types, sex, age and underlying conditions were eligible for this review.

Types of interventions

Methenamine hippurate versus placebo/no treatment. There were no restrictions based on the dose of drug administered. The treatment group was compared either with a placebo control group or a "no-treatment" control group. There was no restriction on duration of therapy.

Types of outcome measures

Symptomatic UTI

The primary outcome measure was the proportion of patients with symptomatic UTI according to defined clinical criteria, along with a positive urine culture. This is the most clinically significant outcome measure for populations at long-term risk of recurrent UTIs. Symptoms of UTI in the general population include: fever, dysuria, frequency, urgency, voiding of small volumes, abrupt onset, suprapubic pain, and loin pain (Stamm 1988). In spinal injured patients, relevant symptoms should be unexplained by other inter-current pathology and include: fever, autonomic dysreflexia, increased frequency of muscle spasms or spasticity, failure of usual control of urinary incontinence and new abdominal discomfort (NIDRRS 1992).

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Quantitative urine culture (irrespective of the presence of symptoms suggestive of UTI)

The number of UTI confirmed by appropriate microbiological criteria. Bacteriuria on quantitative urine analysis of more than 100,000 organisms of a single species per mL is the accepted standard - however, the colony count may vary from 100 to 100,000 depending on the clinical setting (Stamm 1988). Therefore in some situations, (such as a clean suprapubic tap) a colony count of less than 100,000 is acceptable.

Adverse reactions in patients with or without symptoms suggestive of UTI

- The proportion of people who reported side effects, and a description of these side effects.
- The numbers of people withdrawing from the trials due to side effects, and a description of these side effects.

Search methods for identification of studies

Initial search

Relevant studies were identified by searching electronic databases (Appendix 1 - *Electronic search strategies)* and other resources:

1. Cochrane Central Register of Controlled Trials CENTRAL (in *The Cochrane Library).*
2. MEDLINE (from 1966): the search strategy incorporated the Cochrane highly sensitive search strategy for identifying RCTs in MEDLINE (Dickersin 1994).
3. EMBASE (from 1980): the search strategy incorporated a sensitive strategy for identifying RCTs in EMBASE (Lefebvre 1996).
4. Reference lists of identified studies and major reviews.
5. Contact with researchers active in the field and primary authors of identified relevant studies for details of unpublished studies.
6. Contact with manufacturers' of methenamine salts (3M and Parke Davis) were contacted for unpublished studies.

No language restrictions were applied. Formal translation of selected articles was undertaken through the support of the Royal North Shore Hospital Spinal Unit Research Trust. Letters, abstracts, and unpublished studies were accepted to reduce publication bias. If duplicate publication was suspected, authors were contacted for clarification, and if confirmed, the publication with the most and/or the longest follow-up data was used for the review.

Review update

For this update the Cochrane Renal Group's Specialised Register and CENTRAL was searched. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective. Please refer to The Cochrane Renal Group's Module in *The Cochrane Library* for the complete list of nephrology conference proceedings searched.

An update search was carried out in the Cochrane Renal Group's Specialised Register on 16th January 2012.

Data collection and analysis

Selection of studies

Two independent search strategies were conducted by BL and TB. The titles and abstracts were screened by BL. Eligibility of studies for inclusion in this review was determined by BL and TB. A third author JS or JC was consulted to review discrepancies in study inclusion.

Data extraction and management

Data extraction from eligible studies was performed independently by BL and TB. A third author JS or JC was consulted to review discrepancies in data extraction. Decisions of a content or methodological nature were arbitrated by JC and decisions of a statistical nature (such as the episodes to participants discrepancy) were arbitrated by JS.

Assessment of risk of bias in included studies

Allocation concealment

Studies were divided into three groups:

- Adequate (A): Central randomisation; randomisation by a pharmacy; use of numbered or coded containers; or sequentially numbered, opaque sealed envelopes.
- Inadequate (B): Alternation, reference to case record number or date of birth.
- Unclear (C): No allocation concealment was reported at all, or an approach which did not fall into the two previous groups was used.

Generation of randomisation sequence

Studies were divided into three groups:

- Adequate: Computer, random number table, shuffled cards, tossed coins or minimisation.
- Inadequate: All other methods of sequence generation.
- Undefined.

Inclusion in the analysis of all randomised participants

Studies were divided into two groups:

- Studies that reported or gave the impression that no subjects had been excluded from the analysis.
- Studies that reported having made exclusions.

The reasons for exclusions were documented (e.g. protocol deviations, withdrawals, dropouts and losses to follow-up).

Intention-to-treat analysis

Studies were divided into three groups:

- Intention-to-treat analysis: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment, or not stated but confirmed on study assessment.
- Not intention-to-treat analysis: Not reported and lack of intention-to-treat analysis confirmed on study assessment (patients who were randomised were not included in the analysis because they did not receive the study intervention,

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

they withdrew from the study or were not included because of protocol violation); or stated but not confirmed upon study assessment.
- Unclear.

Blinding

- Blinding of investigators: yes, no.
- Blinding of participants: yes, no.
- Blinding of outcome assessors: yes, no.

Measures of treatment effect

Where appropriate, pooled analysis was conducted. A random effects model was used for the pooled analysis. This model considers both between and within study variation, and tends to be more conservative than fixed effect modelling (Lau 1998). For dichotomous outcomes, risk ratio (RR) was used as the measure of effect (with 95% confidence interval).

Assessment of heterogeneity

A Cochran "Q" test for heterogeneity and, for the review update, the I^2 test (Higgins 2003) was performed on all pooled analyses. I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Study assessment was based on the evaluation criteria of Schulz 1995.

Data synthesis

A pooled analysis was attempted for the outcomes symptomatic bacteriuria and bacteriuria using a random-effects model.

Subgroup analysis and investigation of heterogeneity

Issues of heterogeneity were initially explored by between-study comparisons. Pre-specified possible explanations for variations in treatment effect were explored based on interventions, study quality and population. Subgroup analyses were attempted as defined in the objectives. Where studies involved multiple arms, only the methenamine hippurate and control arms were included. A test of interaction was considered to further analyse the subgroups. This approach was not taken due to within strata heterogeneity and sparse data.

RESULTS

Description of studies

Included studies

Thirteen studies (2032 participants) were identified (see - Characteristics of included studies). A variety of methenamine hippurate doses were used (from 1 g to 4 g as the total daily dose). Only two of the studies combined methenamine hippurate with acidification agents (Sander 1976; Thomlinson 1968). The studies involved heterogeneous population groups including; renal tract calculi (Pettersson 1989), women following gynaecological operations (Knoff 1985; Ladehoff 1984; Thomlinson 1968; Tyreman 1986; Schiotz 2002), men undergoing prostate operations (Sander 1976), pregnant women (Furness 1975), patients (predominantly women) with recurrent UTI (Gundersen 1986) post-menopausal women (Hoivik 1984); pre-menopausal women (Kasanen 1982) and spinally injured patients (Kuhlemeier 1985; Lee 2007). Six studies involved follow-up of one month or less (Knoff 1985; Ladehoff 1984; Pettersson 1989; Sander 1976; Thomlinson 1968; Tyreman 1986) and seven studies had follow-up periods longer than one month (Furness 1975; Gundersen 1986; Hoivik 1984; Kasanen 1982; Kuhlemeier 1985; Lee 2007; Schiotz 2002).

Outcome measures

Symptomatic UTI was measured in eight studies (Furness 1975; Gundersen 1986; Hoivik 1984; Knoff 1985; Lee 2007; Pettersson 1989; Schiotz 2002; Tyreman 1986). None of the studies that included symptomatic UTI used the same criteria. Often the criteria were not adequately described (Knoff 1985; Pettersson 1989), or not described at all (Gundersen 1986; Hoivik 1984; Tyreman 1986). Bacteriological criteria was described by 13 studies and was used as an outcome measure in 12. Most studies used > 100,000 bacteria/mL as the threshold level for significant bacteriuria (Furness 1975; Gundersen 1986; Hoivik 1984; Knoff 1985; Ladehoff 1984; Lee 2007; Thomlinson 1968; Tyreman 1986). Of the other studies, Sander 1976 chose 10,000 bacteria/mL and Kuhlemeier 1985 used 1000 bacteria/mL for catheter specimens and 100,000 bacteria/mL for clean catch samples. Schiotz 2002 used 10,000 bacteria/mL for catheter specimens and 100,000 bacteria/mL for mid-stream urinary (MSU) samples. Pettersson 1989 did not provide a description of quantitative bacteriological criteria. Unpublished data from two studies (Lee 2007; Schiotz 2002) was used.

Adverse events were poorly described by the majority of studies. The only study to provide a specific methodological design for the collection of adverse events was Furness 1975, who reported birth weight, maturity at delivery and foetal mortality and abnormalities in a study on pregnant women. Five studies collected data at each follow-up stage (Gundersen 1986; Hoivik 1984; Kasanen 1982; Knoff 1985; Sander 1976). The methodology was not well described and there was no mention of these questions being standardised.

Excluded studies

A total of 32 studies were excluded, usually due to a lack of an untreated control group (see - Characteristics of excluded studies).

Risk of bias in included studies

The overall quality of the studies was poor. Two of the more recent studies demonstrated adequate allocation concealment and blinding (Lee 2007; Schiotz 2002). Those studies with short follow-up periods were better described. Most studies provided only limited descriptions of comparative baseline characteristics. The baseline characteristics were not described at all in Furness 1975 and Kuhlemeier 1985, and in Gundersen 1986, only age was described. Sander 1976 mentioned a balanced age distribution, but did not provide specific details.

These was a particular problem in four studies (Hoivik 1984; Kuhlemeier 1985; Ladehoff 1984; Thomlinson 1968) where the post-randomisation exclusions were over 20% (see - Characteristics of included studies). Schiotz 2002, provided unpublished data to address post randomisation exclusions in five participants (from a total of 150).

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Effects of interventions

Four studies (Gundersen 1986; Hoivik 1984; Kasanen 1982; Kuhlemeier 1985), counted recurrent events, so that a participant could potentially make multiple contributions to the numerator (see below - episode to participant discrepancy). These studies were not included in the pooled analysis (see below - unpooled studies). Lee 2007 had missing bacteruria data at follow-up for 34/305 participants. For the numerator in the symptomatic bacteruria analysis, those people with symptoms of UTI and positive bacteriological count were included. As this potentially has an inherent bias towards the null, a sensitivity analysis was performed by repeating the analysis including subjects unconfirmed by positive urine tests (for Lee 2007) (Analysis 1.3).

Symptomatic bacteriuria

This analysis involved six studies (Furness 1975; Knoff 1985; Lee 2007; Pettersson 1989; Schiotz 2002; Tyreman 1986) (Analysis 1.1 (6 studies, 853 participants): RR 0.53, 95% CI 0.24 to 1.18). The tests of heterogeneity was significant (Chi^2 = 17.74, df = 5, P = 0.003; I^2 = 71.8%). The sensitivity analysis did not reveal any difference in overall effect when missing urine tests were assumed to be positive (Analysis 1.3 (6 studies, 853 participants): RR 0.53, 95% CI 0.24 to 1.17; I^2 = 72.4%).

Bacteriuria

This analysis involved eight studies (Knoff 1985; Ladehoff 1984; Lee 2007; Pettersson 1989; Sander 1976; Schiotz 2002; Thomlinson 1968; Tyreman 1986) (Analysis 2.1(8 studies, 1114 participants): RR 0.67, 95% CI 0.45 to 0.99). The "Q" test was significant using a random effects model (Chi^2 = 28.55, df = 7, P = 0.0002; I^2 = 75.5%), indicating heterogeneity.

Exploration of heterogeneity

Symptomatic bacteriuria

Scrutiny of the forest plot suggests that the study which contributes most to the heterogeneity was Pettersson 1989 which was the only study that did not provide a quantitative threshold value for the confirmatory urinalysis. In addition this study, along with Lee 2007, were the only studies in this group that had a patient population with known renal tract abnormalities. Lee 2007 differed significantly in the underlying population studied (spinal cord injured patients with neuropathic bladder). Furness 1975 had a longer (but ill defined) treatment duration, and used bacteriuria as an inclusion criterion (as opposed to an exclusion criterion in the other studies).

No study included a treatment group with urinary acidification which we could use for subgroup comparison. Four studies used short-term catheterisation (Knoff 1985; Pettersson 1989; Schiotz 2002; Tyreman 1986), while Furness 1975 did not. Lee 2007 included a mix of bladder management techniques including long term permanent catheterisation. There did not appear to be a trend based on this bladder management subgroup due to the strong influence of Pettersson 1989.

Three studies used higher doses of methenamine hippurate. Pettersson 1989 and Tyreman 1986 used 1 g thrice daily, while Knoff 1985 used 2 g twice daily. The remaining studies (Furness 1975; Lee 2007; Schiotz 2002) used 1 g twice daily. There did not appear to be a consistent effect of methenamine hippurate dose.

Subgroup analysis

A subgroup analysis of studies involving people with and without known renal tract abnormalities was performed (Analysis 1.2). Subgroup analysis suggested that methenamine hippurate may have some efficacy in patients without renal tract abnormalities (Analysis 1.2.1: RR 0.24, 95% CI 0.07 to 0.89; I^2 = 69.8%) but not with (Analysis 1.2.2: RR 1.54, 95% CI 0.38 to 6.20; I^2 = 53.4%). The study by Pettersson 1989 included patients with upper renal tract abnormalities, while Lee 2007 also included patients with renal tract abnormalities (15 patients had renal or bladder stones and all participants had neuropathic bladder) and had the longest potential duration of treatment (patients studied up to six months or until they had a UTI). Methenamine hippurate may be ineffective when used in renal tract abnormalities and/or neuropathic bladders (where the outcome is symptomatic UTI).

Four studies had shorter durations of treatment (≤ 7 days) (Knoff 1985; Pettersson 1989; Schiotz 2002; Tyreman 1986) (Analysis 1.4.1: RR 0.30, 95% CI 0.06 to 1.56; I^2 = 68.0%). Heterogeneity for this subgroup could be attributed to Pettersson 1989, which included patients with upper renal tract abnormalities. When Pettersson 1989 was removed (Analysis 1.5.1: RR 0.14, 95% CI 0.05 to 0.38; I^2 = 0%), heterogeneity became not significant. Methenamine hippurate appears to be effective for short duration treatment in those individuals without renal tract abnormalities (where the outcome is symptomatic UTI).

Two studies had longer durations of treatment (≥ 7 days); Furness 1975 (possibly several months) and Lee 2007 (up to six months) (Analysis 1.4.2: RR 0.95, 95% CI 0.72 to 1.25; I^2 = 0%). The test for heterogeneity was not significant. Methenamine hippurate may be ineffective when used for longer durations.

Bacteriuria

Review of the forest plot (Analysis 2.1) suggests that the study with the largest effect on the heterogeneity was Pettersson 1989. This study (as previously discussed), has a non quantitatively defined outcome measure, and a population group with upper renal tract abnormalities. Lee 2007 and Pettersson 1989 both studied populations which included known renal tract problems. Sander 1976 and Thomlinson 1968 used urinary acidification, but there was no evidence of effect. All studies, with the exception of Lee 2007, used relatively short-term catheterisation, although this was not specifically defined by Thomlinson 1968. Duration of catheterisation was variable: one day (Pettersson 1989), one to 2.5 days (Schiotz 2002), one to three days (Knoff 1985), usually three days (Tyreman 1986), three to six days (Sander 1976), five to 10 days (Ladehoff 1984) and a mix of bladder management types including permanent catheterisation for up to six months (Lee 2007). Again no consistent effect of bladder management type was found. All studies, with the exception of Lee 2007 and possibly Sander 1976, used short durations of treatment in the study arm. Three of the studies used higher doses of methenamine hippurate (Knoff 1985; Pettersson 1989; Tyreman 1986). No consistent effect with regard to dose was seen.

Subgroup analyses

A subgroup analysis was performed by renal tract abnormality (Analysis 2.2). Subgroup analysis suggested that methenamine hippurate may have some efficacy in patients without renal tract abnormalities (Analysis 2.2.1: RR 0.56, 95% CI 0.37 to 0.83; I^2 =

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

56.3%) but not with (Analysis 2.2.2: RR 1.29, 95% CI 0.54 to 3.07; I^2 = 43.8%).

Five studies had shorter durations of treatment (≤ 7 days) (Knoff 1985; Pettersson 1989; Schiotz 2002; Thomlinson 1968; Tyreman 1986) (Analysis 2.3.1: RR 0.59, 95% CI 0.29 to 1.22; I^2 = 71.9%). There was significant heterogeneity for this subgroup however when Pettersson 1989 was removed (Analysis 2.4.1: RR 0.48, 95% CI 0.23 to 0.99; I^2 = 72.7%), the test for heterogeneity remained significant.

Two studies had longer durations of treatment (≥ 7 days) Ladehoff 1984 (8 to 13 days); Lee 2007 (up to 6 months) (Analysis 2.3.2: RR 0.85, 95% CI 0.55 to 1.31; I^2 = 81.3%). The test for heterogeneity was significant.

Lee 2007 was the only pooled study which included (spinal cord injured) patients with neuropathic bladder. The results showed a null result with tight confidence intervals.

Unpooled studies

Four studies were excluded from the pooled analysis. The study populations were: recurrent UTI (Kasanen 1982), male spinal cord injury (Kuhlemeier 1985), post-menopausal (Gundersen 1986) and pre-menopausal (Hoivik 1984) women. All of these studies used a design where a participant could potentially make multiple contributions to the total number of positive tests (the numerator), and possibly the total number of tests carried out (the denominator). We have called this an "episode to participant discrepancy" (described below) and excluded these studies from the pooled analysis because of the lack of independence of repeated observations in the same individual. In addition, there were excessive post-allocation losses in Kuhlemeier 1985 (38%). The overall direction of three of these studies (Gundersen 1986; Hoivik 1984; Kasanen 1982) was towards a treatment effect from methenamine hippurate. The results of Kuhlemeier 1985 were difficult to interpret in view of the high post-allocation losses. Given the methodological problems with these studies, it is possible that any estimate of effect size may be exaggerated by these studies.

Adverse events

All the studies that reported adverse events showed low rates, although the methodology for most of these studies was poor with regard to this outcome measure (Table 1 - *Population and adverse events*). Nausea was the most common symptom and was noted in 12 patients from a total of six studies (Gundersen 1986; Kasanen 1982; Kuhlemeier 1985; Ladehoff 1984; Lee 2007; Schiotz 2002). In pregnancy, no obvious differences in birth weight, maturity at delivery, foetal abnormality or abortion were noted between treated and untreated patients (Furness 1975). Constipation was described once by Gundersen 1986 and twice by Lee 2007. Rash was described in single instances by Kasanen 1982 and Schiotz 2002 and twice by Lee 2007. Diarrhoea (Lee 2007), sore throat (Knoff 1985) and stinging in the bladder (Hoivik 1984) were all described in single instances.

Episodes to participant discrepancy

Four studies (Gundersen 1986; Hoivik 1984; Kasanen 1982; Kuhlemeier 1985) used a design where a participant could potentially make multiple contributions to the total number of positive tests (the numerator), and possibly the total number of tests carried out (the denominator).

- Gundersen 1986: Six patients in the experimental group reported seven times with symptoms of UTI, while ten patients in the control reported 29 times. Follow-up was every month for six months.
- Hoivik 1984: Nineteen symptomatic recurrences were documented in the 28 patients in the full dose experimental group, four recurrences were documented in the 12 patients in the half dose experimental group and 26 recurrences were documented in the 12 patients in the placebo group. Follow-up took place at seven specified intervals over one year.
- Kasanen 1982: Eighteen (bacteriuria) recurrences were documented in the 72 patients in the experimental group, 43 recurrences were documented in the 68 patients in the placebo group. Urine investigations were performed at two-month intervals, up to one year.
- Kuhlemeier 1985: Two hundred and two studies were performed in 161 patients.

Three studies (Gundersen 1986; Hoivik 1984; Kasanen 1982) used repeated measures (regular urine tests), which led to individuals potentially contributing several times to the number of positive tests. It may be possible, after access to primary study data, for some of these studies to be included in the pooled analysis. Kuhlemeier 1985 allowed patients to pass through the study process more than once, hence allowing them to contribute multiply to both the total number of positive tests, and disproportionately to the number of tests carried out. This was one of a number of serious methodological problems found in this study (see - Characteristics of included studies).

The standard significance tests used in this meta-analysis assume that a series of observations are selected randomly from the population (Armitage 1994). The result of an "episode to participant discrepancy" is that these tests may not be valid, as they do not take into account the possible dependence among repeated observations in the same individual.

In order to address this issue, clarification has been sought from each of the primary authors involved. Until the discrepancy is resolved with primary study data, these studies will not be included in the pooled analysis. It is possible that any estimate of effect size may be exaggerated by these studies.

DISCUSSION

Summary of main results

Symptomatic UTIs

The outcome measure of most clinical significance is symptomatic UTI. Unfortunately, there was no consistency in definition and most were poorly defined. Eight studies addressed this outcome, from six different populations. Although six of the eight studies suggested a study direction in favour of treatment with methenamine hippurate, the significant methodological problems discussed above suggest that this should be treated cautiously. Two studies that dealt with longer term use of methenamine hippurate unfortunately had to be excluded because they treated recurrent events as independent. Exploration of heterogeneity among the six studies included in the pooled analysis provided a further look at

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

between-study differences. The subgroup analysis by renal tract abnormality revealed continued heterogeneity between the four studies of patients without renal tract abnormality (Furness 1975; Knoff 1985; Schiotz 2002; Tyreman 1986).

A subgroup analysis of four studies that used short duration (≤ 7 days) treatment with methenamine hippurate also showed heterogeneity. When Pettersson 1989 was removed (*analysis 01.05.01*), the heterogeneity became non-significant. It may be that methenamine hippurate is more effective for short duration treatment in those individuals without renal tract abnormalities (where the outcome is symptomatic UTI). Combining the two studies with longer duration treatment (Furness 1975; Lee 2007) suggested that methenamine hippurate may be ineffective when used for longer durations, although this tentative conclusion should be treated with extreme caution as it is based on one of several subgroup analyses and a subgroup containing only two very different studies. Lee 2007 was the largest clinical study with the tightest confidence intervals and for the spinal cord injured group with neuropathic bladder showed no treatment effect when used (predominantly) for community prophylaxis. A test for modification of the treatment effect by urinary acidification, bladder management type or dose through formal subgroup analysis was not possible due to insufficient studies.

Bacteriuria

Bacteriuria as an outcome measure was much better defined. Unfortunately it is also of less clinical significance in population groups who experience chronic infections (NIDRRS 1992). Twelve studies addressed this outcome measure. Again, the majority reported results in favour of treatment. Unfortunately, counting of recurrent events was again a problem. Excluding these studies and conducting a pooled analysis of eight studies revealed an overall direction in favour of treatment but in the presence of significant heterogeneity. The study that showed a treatment effect in the opposite direction was Pettersson 1989. Heterogeneity was explored by looking at differences among the eight studies in the pooled analysis. A subgroup analysis of six studies of patients without underlying renal tract abnormality still showed heterogeneity. The direction of the pooled estimate for this subgroup favoured treatment with methenamine hippurate. It is possible that methenamine hippurate is more effective in patients without underlying renal tract abnormality, although this information would need to be treated cautiously, given the persisting heterogeneity. A subgroup analysis of five studies with short treatment duration also demonstrated heterogeneity. Exclusion of the Pettersson 1989 outlier explained much but not all of the underlying heterogeneity. It is possible that short duration treatment is more effective in people without underlying renal tract abnormality, but again this possibility would need to be treated very cautiously.

Adverse events

Adverse events were poorly described, with data of insufficient quality to perform formal statistical evaluation. Overall, the frequency of reported side-effects was low compared to control.

Alternative oral prophylactic agents

This meta-analysis provides the suggestion that methenamine hippurate may be more effective for short duration treatment in those individuals without renal tract abnormalities (where the outcome is symptomatic UTI). Caution needs to be taken when interpreting this result due to underlying heterogeneity, the small sample and the subgroup analysis involved. Participants likely to benefit in this short-duration treatment group are likely to have access to treatment alternatives which are potentially more effective, in particular oral antibiotics, where a recent Cochrane review has demonstrated (weak) evidence that prophylactic antibiotic use reduces symptomatic UTI rates in females undergoing abdominal surgery and short-term bladder catheterisation (Niel-Weise 2005). Another Cochrane review demonstrates that cranberry juice may reduce UTI over a 12 month period in women without abnormal renal tracts (Jepson 2004). Unfortunately, such alternative treatments are less demonstrable for those with abnormal renal tracts (including neuropathic bladder) who have high rates of antibiotic resistance (Thom 1999; Waites 2000) and are arguably most in need of non-antibiotic prophylaxis.

Quality of the evidence

Overall, the studies were of poor quality, although more recent studies were better. The two most recent studies (Lee 2007; Schiotz 2002) demonstrated adequate allocation concealment while the others did not. The majority of the other studies were unblinded. These study characteristics are associated with exaggerated treatment effects (Schulz 1995). Publication bias cannot be completely excluded, as the number of studies available for the pooled analysis was too small to be interpreted using methods such as "funnel plots" (NHMRC 1999). "Episodes to participant discrepancy" problems in four studies (Gundersen 1986; Hoivik 1984; Kasanen 1982; Kuhlemeier 1985) reduced the number of studies available for the pooled analysis.

AUTHORS' CONCLUSIONS

Implications for practice

An exploration of heterogeneity raises the (hypothesis generating) possibility that methenamine hippurate may have some efficacy in patients without (but not in patients with) known renal tract abnormality. Short duration therapy (≤ 7 days) in people without renal tract abnormalities may be effective, but this group also have effective clinical alternatives such as oral antibiotic therapy available. Methenamine hippurate appears to be ineffective when used in spinal cord injured patients with neuropathic bladder. The rate of adverse events reported by the studies was low, which suggests that current usage is unlikely to be causing significant harm. There is a need for further large RCTs in particular to explore long duration therapy for patients without neuropathic bladder.

Implications for research

Additional well controlled RCTs are necessary, in particular to further clarify longer term prophylaxis in those without neuropathic bladder. There needs to be better definition of symptomatic bacteruria outcomes in these clinical studies.

ACKNOWLEDGEMENTS

- Dr Michelle Chew assisted in screening and translating the Danish and Norwegian articles
- Dr Lianne Hunt assisted in translating the French and Belgian articles

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

- Dr Gerrit Fialla and Ms Gudrun Hofmann assisted in translating the German articles
- The Royal North Shore Hospital Spinal Unit funded the formal translation of the Norwegian and Danish Articles (Trine).
- The referees for their comments and feedback during the preparation and updating of this review.

Thanks to all.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

REFERENCES

References to studies included in this review

Furness 1975 *{published data only}*

Furness ET, McDonald PJ, Beasley NV. Urinary antiseptics in asymptomatic bacteriuria of pregnancy. *New Zealand Medical Journal* 1975;**81**(539):417-9. [MEDLINE: 1099490]

Gundersen 1986 *{published data only}*

Gundersen R, Hoivik HO, Osmundsen K. Frequent cystitis in elderly women. A double-blind comparison of hiprex and placebo in general practice [Hyppig forekommende cystitter hos eldre kvinner]. *Tidsskrift for Den Norske Laegeforening* 1986;**106**(25):2048-9. [MEDLINE: 3535165]

Hoivik 1984 *{published data only}*

Hoivik H. O, Gundersen R, Osmundsen K, Halvorsen P, Hjortdahl P, Stokke JG. Prevention of recurrent cystitis in fertile women. A double-blind comparison of hiprex and placebo in general practice. *Tidsskrift for Den Norske Laegeforening* 1984;**104**(16):1150-2. [MEDLINE: 6377577]

Kasanen 1982 *{published data only}*

Kasanen A, Junnila SY, Kaarsalo E, Hajba A, Sundquist H. Secondary prevention of recurrent urinary tract infections. Comparison of the effect of placebo, methenamine hippurate, nitrofurantoin and trimethoprim alone. *Scandinavian Journal of Infectious Diseases* 1982;**14**(4):293-6. [MEDLINE: 6761854]

Knoff 1985 *{published data only}*

Knoff T. Methenamine hippurate. Short-term catheterization in gynecologic surgery. A double-blind comparison of hiprex and placebo. *Tidsskrift for Den Norske Laegeforening* 1985;**105**(7):498-9. [MEDLINE: 3887639]

Kuhlemeier 1985 *{published data only}*

Kuhlemeier KV, Stover SL, Lloyd LK. Prophylactic antibacterial therapy for preventing urinary tract infections in spinal cord injury patients. *Journal of Urology* 1985;**134**(3):514-7. [MEDLINE: 3897577]

Ladehoff 1984 *{published data only}*

Ladehoff P, Jacobsen JC, Olsen H, Pedersen GT, Sorensen T. The preventive effect of methenamine hippurate (haiprex) on urinary infections after short-term catheterization. A clinical study [Metenaminhippurats (Haiprex) profylaktiske virkning over for urinvejsinfektion ved korttidskateterisation]. *Ugeskrift for Laeger* 1984;**146**(19):1433-4. [MEDLINE: 6515752]

Lee 2007 *{published and unpublished data}*

Lee BB, Haran MJ, Hunt LM, Simpson JM, Marial O, Rutkowski SB, et al. Spinal-injured neuropathic bladder antisepsis (SINBA) trial. *Spinal Cord* 2007;**45**(8):542-50. [MEDLINE: 17043681]

Pettersson 1989 *{published data only}*

Pettersson B, Tiselius HG. Are prophylactic antibiotics necessary during extracorporeal shockwave lithotripsy?. *British Journal of Urology* 1989;**63**(5):449-52. [MEDLINE: 2659132]

Sander 1976 *{published data only}*

Sander S, Jakobsen A Jr. Preventive hiprex in urinary tract operations. *Tidsskrift for Den Norske Laegeforening* 1976;**96**(3):167-9. [MEDLINE: 766295]

Schiotz 2002 *{published data only}*

Schiotz HA. Personal communication 15 October 2006.

* Schiotz HA, Guttu K. Value of urinary prophylaxis with methenamine in gynecologic surgery. *Acta Obstetricia et Gynecologica Scandinavica* 2002;**81**(8):743-6. [MEDLINE: 22163917]

Thomlinson 1968 *{published data only}*

Thomlinson J, Williams JD, Cope E. Persistence of bacteriuria following gynaecological surgery: A trial of methenamine hippurate. *British Journal of Urology* 1968;**40**(4):479-82. [MEDLINE: 4878126]

Tyreman 1986 *{published data only}*

Tyreman NO, Andersson PO, Kroon L, Orstam S. Urinary tract infection after vaginal surgery. Effect of prophylactic treatment with methenamine hippurate. *Acta Obstetricia et Gynecologica Scandinavica* 1986;**65**(7):731-3. [MEDLINE: 3544661]

References to studies excluded from this review

Banovac 1991 *{published data only}*

Banovac K, Wade N, Gonzalez F, Walsh B, Rhamy RK. Decreased incidence of urinary tract infections in patients with spinal cord injury: effect of methenamine. *Journal of the American Paraplegia Society* 1991;**14**(2):52-4. [MEDLINE: 2051157]

Brumfitt 1981 *{published data only}*

Brumfitt W, Cooper J, Hamilton-Miller JM. Prevention of recurrent urinary infections in women: a comparative trial between nitrofurantoin and methenamine hippurate. *Journal of Urology* 1981;**126**(1):71-4. [MEDLINE: 7019458]

Brumfitt 1983 *{published data only}*

Brumfitt W, Hamilton-Miller JM, Gargan RA, Cooper J, Smith GW. Long-term prophylaxis of urinary infections in women: comparative trial of trimethoprim, methenamine hippurate and topical povidone-iodine. *Journal of Urology* 1983;**130**(6):1110-4. [MEDLINE: 6227756]

Casselman 1966 *{published data only}*

Casselman J. Hexamethylene-tetramine hippurate in the treatment of urinary infections. *Acta Urologica Belgica* 1966;**34**(3):354-8. [MEDLINE: 5915552]

Chrapowicki 1975 *{published data only}*

Chrapowicki T, Krzyzanowska-Rogozinska T, Kurowska D. Treatment of acute and chronic urinary tract infections in children with an urinary chemotherapeutic agent. *Zeitschrift fur Allgemeinmedizin* 1975;**51**(27):1215-9. [MEDLINE: 1105992]

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Christopher 1969 *{published data only}*

Christopher LJ, Thompson GR. A trial of hippramine in the treatment of bacteriuria of pregnancy. *Irish Journal of Medical Science* 1969;**8**(7):331-7. [MEDLINE: 5806178]

Cronberg 1987 *{published data only}*

Cronberg S, Welin CO, Henriksson L, Hellsten S, Persson KM, Stenberg P. Prevention of recurrent acute cystitis by methenamine hippurate: double blind controlled crossover long term study. *British Medical Journal Clinical Research Ed* 1987;**294**(6586):1507-8. [MEDLINE: 3111615]

Elo 1978 *{published data only}*

Elo J, Sarna S, Ahava K, Lepo A. Methenamine hippurate in urinary tract infections in children: prophylaxis, treatment and side effects. *Journal of Antimicrobial Chemotherapy* 1978;**4**(4):355-65. [MEDLINE: 690036]

Genster 1970 *{published data only}*

Genster HG, Madsen PO. Urinary tract infections following transurethral prostatectomy: with special reference to the use of antimicrobials. *Journal of Urology* 1970;**104**(1):163-8. [MEDLINE: 4193409]

Gerstein 1968 *{published data only}*

Gerstein AR, Okun R, Gonick HC, Wilner HI, Kleeman CR, Maxwell MH. The prolonged use of methenamine hippurate in the treatment of chronic urinary tract infection. *Journal of Urology* 1968;**100**(6):767-71. [MEDLINE: 5696669]

Gow 1974 *{published data only}*

Gow JG. A comparative trial of hexamine hippurate and hexamine mandelate in prevention of recurrent infection of the urinary tract. *Practitioner* 1974;**213**(1273):97-101. [MEDLINE: 4280569]

Horcickova 1986 *{published data only}*

Horcickova M, Prat V, Hatala M, Nezadalova E, Milotova Z. Methenamine hippurate VUFB and mandelamine VUFB in the prevention of recurrent dysuria in women. *Casopis Lekaru Ceskych* 1986;**125**(27):849-53. [MEDLINE: 3731221]

Kasanen 1974a *{published data only}*

Kasanen A, Kaarsalo E, Hiltunen R, Soini V. Comparison of long-term, low-dosage nitrofurantoin, methenamine hippurate, trimethoprim and trimethoprim-sulphamethoxazole on the control of recurrent urinary tract infection. *Annals of Clinical Research* 1974;**6**(5):285-9. [MEDLINE: 4475571]

Kasanen 1974b *{published data only}*

Kasanen A, Mustakallio E, Koskinen EH, Soini V. Methenamine hippurate in the treatment of urinary tract infections. *Annals of Clinical Research* 1974;**6**(5):279-84. [MEDLINE: 4614694]

Klein 1976 *{published data only}*

Klein D, Puchegger R. Methenamine hippurate in urinary tract infections. *Zfa - Zeitschrift Fur Allgemeinmedizin* 1976;**52**(21):1110-4. [MEDLINE: 785852]

Kostiala 1982 *{published data only}*

Kostiala AA, Nyren P, Runeberg L. Effect of nitrofurantoin and methenamine hippurate prophylaxis on bacteria and yeasts in the urine of patients with an indwelling catheter. *Journal of Hospital Infection* 1982;**3**(4):357-64. [MEDLINE: 6190868]

Krechnakova 1979 *{published data only}*

Krechnakova A, Dzurik R. Prevention of chronic pyelonephritis relapses using metenamine hipuran (author's transl). *Casopis Lekaru Ceskych* 1979;**118**(13):402-4. [MEDLINE: 455351]

LeBlanc 1964 *{published data only}*

LeBlanc AQL, McGanity WJ. The impact of bacteriuria in pregnancy - a survey of 1300 pregnant patients. *Texas Reports on Biology & Medicine* 1964;**22**:336-47. [MEDLINE: 14157822]

Murray 1977 *{published data only}*

Murray CP, Feeney J. A comparison of hexamine hippurate and sulphamethizolein patients with indwelling catheters following pelvic-floor surgery. *Irish Medical Journal* 1977;**69**(4):97-8. [MEDLINE: 852964]

Nilsson 1975 *{published data only}*

Nilsson S. Long-term treatment with methenamine hippurate in recurrent urinary tract infection. *Acta Medica Scandinavica* 1975;**198**(1-2):81-5. [MEDLINE: 1166827]

Norberg-A 1980 *{published data only}*

Norberg A, Norberg B, Parkhede U, Gippert H, Lundbeck K. Randomized double-blind study of prophylactic methenamine hippurate treatment of patients with indwelling catheters. *European Journal of Clinical Pharmacology* 1980;**18**(6):497-500. [MEDLINE: 7007058]

Norberg-B 1979a *{published data only}*

Norberg B, Norberg A, Parkhede U, Gippert H. Effect of short-term high-dose treatment with methenamine hippurate on urinary infection in geriatric patients with an indwelling catheter. IV. Clinical evaluation. *European Journal of Clinical Pharmacology* 1979;**15**(5):357-61. [MEDLINE: 37095]

Norberg-B 1979b *{published data only}*

Norberg B, Norberg A, Parkhede U, Gippert H, Akerman M. The effect of short-term high-dose treatment with methenamine hippurate of urinary infection in geriatric patients with indwelling catheters. I. The preparation and morphology of a quantified urine sediment. *Upsala Journal of Medical Sciences* 1979;**84**(1):67-74. [MEDLINE: 87049]

Nyren 1981 *{published data only}*

Nyren P, Runeberg L, Kostiala AI, Renkonen OV, Roine R. Prophylactic methenamine hippurate or nitrofurantoin in patients with an indwelling urinary catheter. *Annals of Clinical Research* 1981;**13**(1):16-21. [MEDLINE: 7247321]

Olsen 1983 *{published data only}*

Olsen JH, Friis-Moller A, Jensen SK, Korner B, Hvidt V. Cefotaxime for prevention of infectious complications in bacteriuric men undergoing transurethral prostatic resection. A controlled comparison with methenamine. *Scandinavian*

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Journal of Urology & Nephrology 1983;**17**(3):299-301. [MEDLINE: 6196841]

Parkhede 1982 *{published data only}*

Parkhede U, Norberg B, Norberg A, Eriksson S. The effect of treatment with methenamine hippurate of urinary tract infection in long-stay geriatric in-patients with indwelling catheters: III. Evaluation by urine viscosimetry. *Journal of Clinical & Experimental Gerontology* 1982;**4**(1):71-81. [EMBASE: 1982226624]

Parvio 1976 *{published data only}*

Parvio S. Methenamine hippurate ('hiprex') in the treatment of chronic urinary tract infections: a trial in a geriatric hospital. *Journal of International Medical Research* 1976;**4**(2):111-4. [MEDLINE: 1026539]

Pedersen 1977 *{published data only}*

Pedersen FB, Korner B. Urinary tract infection after prostate surgery. A controlled, clinical-bacteriological comparison between methenamine hippurate (haiprex) and phenylsalicylate methenamine preparations. *Ugeskrift for Laeger* 1977;**139**(23):1350-2. [MEDLINE: 327643]

Scetbon 1973 *{published data only}*

Scetbon V, Peycelon-de la Selle MF. Value of mandelamine in the prolonged treatment of urinary infections caused by escherichia coli. *Therapeutique* 1973;**49**(4):283-6. [MEDLINE: 4204467]

Stover 1980 *{published data only}*

Stover SL, Fleming WC. Recurrent bacteriuria in complete spinal cord injury patients on external condom drainage. *Archives of Physical Medicine & Rehabilitation* 1980;**61**(4):178-82. [MEDLINE: 7369858]

Vainrub 1977 *{published data only}*

Vainrub B, Musher DM. Lack of effect of methenamine in suppression of, or prophylaxis against, chronic urinary infection. *Antimicrobial Agents & Chemotherapy* 1977;**12**(5):625-9. [MEDLINE: 921259]

Wibell 1980 *{published data only}*

Wibell L, Scheynius A, Norrman K. Methenamine-hippurate and bacteriuria in the geriatric patient with a catheter. *Acta Medica Scandinavica* 1980;**207**(6):469-73. [MEDLINE: 7424566]

Additional references

3M 2000

3M Pharmaceuticals Pty Ltd. MIMS Full prescribing information for hiprex. In: Caswell A editor(s). Mims online version 1.1. Vol. **refer: MIMS OTC 1999 p. 249**, MIMS Australia, Jan - Mar 2000.

Albert 2004

Albert X, Huertas I, Pereiro I, Sanfelix J, Gosalbes V, Perrota C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD001209.pub2]

Armitage 1994

Armitage G, Berry G. Statistical inference. Statistical methods in medical research. 3rd Edition. Oxford: Blackwell Scientific Publications, 1994:93-5.

Devenport 1984

Devenport JK, Swenson JR, Dukes GE Jr, Sonsalla PK. Formaldehyde generation from methenamine salts in spinal cord injury. *Archives of Physical Medicine & Rehabilitation* 1984;**65**(5):257-9. [MEDLINE: 6712452]

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**(6964):1286-91. [MEDLINE: 7718048]

Greenwood 1981

Greenwood D, Slack RC. The antibacterial activity of hexamine (methenamine), hexamine hippurate and hexamine mandelate. *Infection* 1981;**9**(5):223-7. [MEDLINE: 7028634]

Hetey 1990

Hetey SK. Effect of ascorbic acid on urine pH in patients with injured spinal cords. *American Journal of Hospital Pharmacy* 1990;**37**(2):235-7. [MEDLINE: 7361797]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Jepson 2004

Jepson RG, Mihaljevic L, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD001321.pub3]

Kasanen 1974

Kasanen A, Mustakallio E, Koskinen EH, Soini V. Methenamine hippurate in the treatment of urinary tract infections. *Annals of Clinical Research* 1974;**6**(5):279-84. [MEDLINE: 4614694]

Lau 1998

Lau J, Ioannidis JPA, Schmid CH. Summing up evidence: One answer is not always enough. *Lancet* 1998;**351**(9096):123-7. [MEDLINE: 9439507]

Lefebvre 1996

Lefebvre C, McDonald S. Development of a sensitive search strategy for reports of randomized controlled trials in EMBASE. Fourth International Cochrane Colloquium, Adelaide Australia, 20-24 October. 1996.

Macfarlane 1985

Macfarlane DE. Prevention and treatment of catheter-associated urinary tract infections. *Journal of Infection* 1985;**10**(2):96-106. [MEDLINE: 3891871]

Mayrer 1982

Mayrer AR, Andriole VT. Urinary tract antiseptics. *Medical Clinics of North America* 1982;**66**(1):199-208. [MEDLINE: 7038329]

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

McEvoy 1999

Gerald K. McEvoy (Ed). AHFS Drug Information 1999. Bethesda: American Society of Hospital Pharmacists, 1999.

Nahata 1982

Nahata MC, Cummins BA, McLeod DC, Schondelmeyer SW, Butler R. Effect of urinary acidifiers on formaldehyde concentration and efficacy with methenamine therapy. *European Journal of Clinical Pharmacology* 1982;**22**(3):281-4. [MEDLINE: 7106162]

NHMRC 1999

Anonymous. Summarising and synthesising the studies. How to review the evidence: systematic identification and review of the scientific literature. Canberra: NHMRC, Nov 1999:27-36.

NIDRRS 1992

National Institute on Disability and Rehabilitation Research Statement (NIDRRS). The prevention and management of urinary tract infections amongst people with spinal cord injuries. *Journal of American Paraplegia Society* 1992;**15**(3):194-204. [MEDLINE: 1500945]

Niel-Weise 2005

Niel-Weise BS, van den Brock PJ. Antibiotic policies for short-term catheter bladder drainage in adults. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD005428]

Parfitt 1999

Kathleen Parfitt (ed). Martindale. London: Pharmaceutical Press, 1999.

Saint 1999

Saint S, Lipsky BA. Preventing catheter-related bacteriuria: should we? Can we? How?. *Archives of Internal Medicine* 1999;**159**(8):800-8. [MEDLINE: 10219925]

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12. [MEDLINE: 7823387]

Stamm 1988

Stamm WE. Protocol for diagnosis of urinary tract infection: Reconsidering the criterion for significant bacteriuria. *Urology* 1988;**32**(2 Suppl):6-10. [MEDLINE: 3043881]

Thom 1999

Thom JD, Wolfe V, Perkash I, Lin VW. Methicillin-resistant Staphylococcus aureus in patients with spinal cord injury. *Journal of Spinal Cord Medicine* 1999;**22**(2):125-31. [MEDLINE: 10826270]

Waites 1993

Waites KB, Canupp KC, Devivo MJ. Epidemiology and risk factors for urinary tract infection following spinal cord injury. *Archives of Physical Medicine & Rehabilitation* 1993;**74**(7):691-5. [MEDLINE: 8328888]

Waites 2000

Waites KB, Chen Y, DeVivo MJ, Canupp KC, Moser SA. Antimicrobial resistance in gram-negative bacteria isolated from the urinary tract in community-residing persons with spinal cord injury. *Archives of Physical Medicine & Rehabilitation* 2000;**81**(6):764-9. [MEDLINE: 10857521]

Wall 1990

Wall I, Tiselius HG. Long-term acidification of urine in patients treated for infected renal stones. *Urologia Internationalis* 1990;**45**(6):336-41. [MEDLINE: 2288050]

References to other published versions of this review

Lee 2001

Lee B, Bhuta T, Craig J, Simpson J. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD003265]

Lee 2002

Lee B, Bhuta T, Craig J, Simpson J. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database of Systematic Reviews* 2002, Issue 1. [DOI: 10.1002/14651858.CD003265]

Lee 2007

Lee BSB, Simpson JM, Craig JC, Bhuta T. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD003265.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Furness 1975

Methods	• Study design: RCT • Treatment and follow-up duration ill defined, but possibly several months
Participants	• 226 pregnant patients with asymptomatic bacteriuria (> 10^5 bacteria/mL) • The baseline characteristics of the populations were not well described.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Furness 1975 *(Continued)*

Interventions	1. Methenamine hippurate 1 g, twice daily 2. Methenamine mandelate 1 g, 4 times daily 3. No treatment
Outcomes	1. Symptomatic UTI: Poorly defined 2. Adverse events collected: birth weight, maturity at delivery and foetal mortality and abnormalities 3. See adverse events table for details
Notes	The inclusion criteria for this study was asymptomatic bacteriuria, which differed from the majority of studies analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Post-randomisation exclusions were 12%
Intention-to-treat analysis	Unclear risk	Unclear

Gundersen 1986

Methods	• Study design: RCT • Number of Centres: Uncertain • Follow-up period: 6 months
Participants	• 30 post-menopausal women in a general practice setting • All had at least 2 symptom giving, lower urine tract infections during the last 6 months • None of the patients had pathological urography, kidney insufficiency or pyelonephritis • The age of each group was comparable (74.5 in the treatment group and 74.0 in the placebo group) • Other baseline characteristics were not described
Interventions	1. Methenamine hippurate 1 g, twice daily 2. Placebo • One tablet twice daily was commenced when the patients had sterile urine (< 10^4 bacteria/mL) • The patients were told to take the tablets after urinating • Advice on hygiene and sufficient water intake were given

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gundersen 1986 *(Continued)*

	• The treatments lasted for 6 months
Outcomes	1. Symptomatic UTI: Criteria not well defined. Verified by positive bacteriological testing 2. Bacteriuria: > 10^5 bacteria/mL (one test/month for 6 months) 3. Adverse events collected: Potential side effects were recorded by indirect questions. See adverse events table for details
Notes	There is an "Episodes of Participant discrepancy" problem with this study (see discussion)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions post-randomisation; 3 losses, all accounted for
Intention-to-treat analysis	Low risk	ITT performed

Hoivik 1984

Methods	• Study design: RCT • Number of Centres: 8 • Losses post randomisation: 11 • Follow-up period: 1 year
Participants	• 52 premenopausal women • 4 centres compared methenamine hippurate 1 g twice daily with placebo • 4 other centres compared methenamine hippurate one tablet once/day with a twice daily dose • All were menstruating women who had at least 3 lower UTI in the last year Exclusion criteria • Patients with pathological urography, insufficient kidney function, vegetarians, pregnant women
Interventions	1. Methenamine hippurate one tablet (1 g) 2. Placebo control • Dose: Twice daily, or one of each respectively • Treatment began when patients had sterile urine (< 10^4 bacteria/mL)

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Hoivik 1984 *(Continued)*

	• Once symptoms of UTI were occurred and infection was confirmed by testing, the patient was treated with antibiotics, and prophylactic treatment continued
Outcomes	All bacteriological examinations were done on morning urine (midstream and wash test). Uricult was used as a screening method. When bacteria was > 10^5/mL, urine was sent away for resistance testing. 1. Symptomatic UTI was not defined 2. Adverse events: Side effects were assessed by indirect questions. See adverse events table for details
Notes	The outcomes of this study had an "episodes of participant discrepancy" problem (see discussion). Side effects were relatively well described compared to the other studies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated (this was clearly not centrally randomised). The centres had different treatments to randomise (see participants)
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses post-randomisation: 11/52
Intention-to-treat analysis	Unclear risk	Not stated

Kasanen 1982

Methods	• Study design: RCT • Number of centres: 2 • Follow-up: The follow-up procedure is described as a clinical and microbiological follow-up every 2 months for one year
Participants	• 290 patients attending an outpatients clinic of the regional hospital in Loimaa and the Nephrological outpatients clinic of Turku University (Finland) • The patients had a history of UTI (3 or more in the last year) and a mean age of 50.5 (51.1 in placebo, 49.7 in the methenamine hippurate groups) • 92% were female • The patient population has a background of UTI with 115 participants described as having chronic UTI (defined as cortical scars and pelvic changes on urography)
Interventions	The patients urine was first rendered sterile by antibiotic treatment. The patients were then allocated into 4 groups 1. Placebo

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kasanen 1982 *(Continued)*

	2. Nitrofurantoin 75 mg 3. Methenamine hippurate 1 g 4. Trimethoprim 100 mg
Outcomes	1. Bacteriuria: 10^5 bacteria/mL 2. Adverse events collected: The side effects (rash, nausea, abdominal pain, headache, leucorrhoea and fatigue) were collected by direct questions at each follow-up period although there are no descriptions of these questions being standardised. See adverse events table for details
Notes	"Episodes of participant discrepancy" (see discussion)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals are described as low (0% placebo, 1.4% in the hippurate group) however, it is not clear from the methodology whether all patients successfully completed all parts of this protocol.
Intention-to-treat analysis	Unclear risk	Unclear

Knoff 1985

Methods	• Study design: RCT • Follow-up period: 3-5 days
Participants	• 64 women post gynaecological operations (involving short-term catheterisation 1-3 days)
Interventions	1. Methenamine hippurate 2 g twice daily 2. Placebo 2 tablets twice daily Treatment continued for 7 days post surgery
Outcomes	• Symptomatic UTI: Poorly defined • Bacteriuria: > 10^5 bacteria/mL • See adverse events table for side effect details
Notes	Notes: The Authors have been contacted to account for the 4 post randomisation exclusions and to clarify outcome measures

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Knoff 1985 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Post randomisation exclusions: 6%.
Intention-to-treat analysis	Unclear risk	Unclear

Kuhlemeier 1985

Methods	• Study design: quasi-RCT • Follow-up of these patients does not seem consistent • Analysis: There were 202 trials conducted in 161 patients. This meant that some patients have contributed several times to both the number of events and the number of participants for the studies main outcome measure (Days free of infection)
Participants	• 161 male patients with traumatic spinal cord injuries who were managed by an intermittent catheterisation program • All had a history of at least one previous UTI • Inadequate description of baseline characteristics
Interventions	1. No-treatment controls 2. Ascorbic acid 1 g four times/day 3. Trimethoprim-sulfamethoxazole 80/400 mg two times daily 4. Nitrofurantoin 50 mg 4 times daily 5. Methenamine hippurate 1 g twice daily
Outcomes	Urine cultures were obtained weekly until the urine showed significant bacterial colonisation (≥ 1000 bacteria/mL for a catheter obtained specimen or 100,000 colonies/mL for a clean catch sample). 1. The primary outcome measure was days free of infection 2. A secondary outcome measure was the number of patients discharged with sterile urine. It was impossible to calculate length of follow-up for this outcome measure. Patients who were discharged with sterile urine were treated as losses for the calculation of days free of infection. 3. See adverse events table for side effect details
Notes	Episodes of participant discrepancy (see discussion) Significant problems with the outcome measures, follow-up and losses

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kuhlemeier 1985 *(Continued)*

Unpublished data regarding quasi randomised assignment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Assignment to the groups was sequential: first, seventh patient to group 1, second, eighth to group 2 etc (unpublished data)
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single blinded (unpublished data)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	There were between 38% to 20% losses to follow-up depending on outcome measure
Intention-to-treat analysis	Unclear risk	Unclear

Ladehoff 1984

Methods	• Study design: RCT • Follow-up period: 8-13 days
Participants	• 300 women undergoing a vaginal operation or radical hysterectomy • Catheterisation duration: 5 days for vaginal operations, 10 days for radical hysterectomy • More people were having radical hysterectomies (hence longer duration of catheterisation) in the control group (16 versus 10)
Interventions	1. Methenamine hippurate 500 mg, twice daily 2. No-treatment control group Treatment duration 8 to 13 days
Outcomes	1. Bacteriuria: $>10^5$ bacteria/mL 2. See adverse events table for side effect details
Notes	The higher number of hysterectomies in the control group may bias towards a treatment effect.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ladehoff 1984 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Post randomisation exclusions: 23%
Intention-to-treat analysis	High risk	No ITT

Lee 2007

Methods	• Study design: Factorial RCT, predominantly community dwelling patients • Time frame: November 2000 to August 2002 • Follow-up period: Time to outcome up to 6 months (time of first UTI)
Participants	• Country: Australia • SCI patients with neurogenic bladder • Stable bladder management with either indwelling urethral or suprapubic catheter, intermittent catheterisation, or reflex voiding with or without a condom drainage device. Absence of complex urological or serious renal of hepatic pathology. No prescribed antibiotics at time of enrolment • Number: 305 • Age: mean 43.5 years (SD 13.5; range 16-82) • Sex: 83% male • SCI: 55% tetraplegia, 49% had complete spinal injury • Time since SCI: median 12 years (range 1 month - 61 years) Exclusion criteria • Previous allergy to any of the test interventions
Interventions	1. Methenamine hippurate (2 g) + cranberry (1600 mg) 2. Methenamine hippurate (2 g) + cranberry placebo 3. Methenamine hippurate placebo + cranberry (1600 mg) 4. Methenamine hippurate placebo + cranberry placebo
Outcomes	1. Symptomatic UTI (definition provided) 2. Bacteriological urinary analysis at time of primary end point 3. Adverse events
Notes	• Exclusions post randomisation but pre-intervention: None • Stop or end point/s: Symptomatic UTI within 6 months from randomisation • Additional data requested from authors: Yes

Risk of bias

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Lee 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation, 4 groups factorial design
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Yes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Intention-to-treat analysis	Low risk	Yes

Pettersson 1989

Methods	• Study design: RCT • 1 month follow-up period for this outcome measure
Participants	• 149 patients with renal tract calculi undergoing • Extracorporeal shockwave lithotripsy (involving short-term catheterisation less than 1 day duration)
Interventions	1. Methenamine hippurate 1 g three times daily 2. Trimethoprim and sulphamethoxazole 3. No-treatment control Treatment continued for 7 days post surgery
Outcomes	1. Symptomatic UTI: Poorly defined 2. Bacteriuria: Poorly defined (no threshold level) 3. Adverse events collected: No mention of side effects. See adverse events table for side effect details
Notes	The poorly defined outcome measures are a major problem with this study The authors have been contacted for clarification

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate
Allocation concealment (selection bias)	Unclear risk	Not stated

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Pettersson 1989 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	no blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not well described (Between 94-100%completed follow-up). No post randomisation exclusions.
Intention-to-treat analysis	Unclear risk	Unclear

Sander 1976

Methods	• Study design: quasi-RCT • Follow-up period: 4 weeks and 8 weeks with urine tests
Participants	• 66 male patients operated on for prostate problems (transurethral resection in 44 patients and retropubic prostatectomy in 22 patients) • Patients with bacteriuria were not included in the survey • The patients were from 52-76 years (apparently evenly distributed - although this information was not summarised in a table of baseline characteristics) • Post operative catheter duration was approximately 3 days if a transurethral resections was performed, and 6 days if a retropubic prostatectomy was done • Days with catheter after operation were comparable between the treatment and control groups
Interventions	1. Methenamine hippurate 1 g twice daily with urinary acidification (0.3-0.5 g Vit C/day) 2. No-treatment control group Duration of treatment not explicitly stated
Outcomes	1. Bacteriuria: >10^4 bacteria/mL. Only the 4th week test is considered 2. Patients in the no treatment group with bacteriuria were treated between the 4th and 8th week with antibiotics. This invalidates the 8th week urine test 3. Adverse events collected: no side effects reported. See adverse events table for side effect details
Notes	The duration of exposure is not clear from this paper There are suggestions in the paper that treatment may have continued for the entire 8-week follow-up period, but these have not been explicitly stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	quasi-RCT
Allocation concealment (selection bias)	Unclear risk	not stated

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Sander 1976 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post randomisation exclusions
Intention-to-treat analysis	Unclear risk	Unclear

Schiotz 2002

Methods	• Study design: RCT • Follow-up period 1 month (clinical) • Universal bacteriological follow-up period was at day 3
Participants	• 150 female patients operated on for routine gynaecological laparotomy or vaginal plastic surgery • Inclusion criteria was elective surgery with use of a catheter and no antibiotic prophylaxis • Patient age and duration of surgery was reasonably matched between the groups
Interventions	1. Methenamine Hippurate 1 g twice daily for 5 days 2. No treatment control group (placebo tablets) twice daily for 5 days
Outcomes	1. Primary outcome measure: bacteruria (day 3) 2. Secondary outcome measure symptomatic UTI (within a 1 month period) The following is unpublished data: All patients had an outpatient appointment after 4-6 weeks, but not with urinary cultures if there had been no symptoms of UTI. Patients discharged with bacteriuria were instructed to contact the study team if symptoms of infection occurred. Two patients failed to do so, but details of their symptoms and cultures were obtained from their general practitioner and the laboratory and the patients were interviewed by the primary author
Notes	Notes: 150 participants randomised but only 145 analysed. 5 patients were excluded: 3 because of preoperative antibiotic treatment and 2 were not catheterised. additional detail regarding the randomisation group and the outcomes of these patients were sought from the authors who provided the allocation groups and the outcomes for these patients. This data (unpublished) is included in the analysis. The nature follow-up and how the symptomatic UTI diagnosis was collected has also been provided from the authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate
Allocation concealment (selection bias)	Low risk	Adequate

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Schiotz 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Post randomisation exclusions: unclear
Intention-to-treat analysis	Unclear risk	Unclear

Thomlinson 1968

Methods	• Study design: quasi-RCT • Follow-up period 7 days
Participants	• 130 women admitted for major gynaecological surgery • Duration of catheterisation was not specified • The operation types seemed well distributed
Interventions	1. Methenamine hippurate 1 g twice daily with urinary acidification (sodium acid phosphate 2 g three times daily) 2. No-treatment control Treatment continued for 7 days post surgery.
Outcomes	1. Bacteriuria: > 10^5 bacteria/mL 2. Side effects collected: No side effects reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	High risk	Alternate allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not stated

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Thomlinson 1968 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Post allocation exclusions: 23%
Intention-to-treat analysis	High risk	No ITT

Tyreman 1986

Methods	• Study design: RCT • Follow-up period: 7 days
Participants	• 109 females undergoing uterovaginal prolapse surgery (involving short term catheterisation usually 3 days)
Interventions	1. Methenamine hippurate 1 g three times daily 2. No-treatment control Treatment duration: continued for 5 days post surgery
Outcomes	1. Symptomatic UTI: Poorly defined 2. Bacteriuria: > 10^5 bacteria/mL 3. Adverse effects collected: no side-effects reported
Notes	No clarification of the methodology used to collect side effect data is given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Post randomisation exclusions: 14%
Intention-to-treat analysis	Unclear risk	Unclear

NS - not stated; SCI - spinal cord injury; UTI - urinary tract infection

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

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Banovac 1991	No mention of randomised or quasi randomised control. Marked differences were evident on a comparison between the treatment and control groups with regards to sex and level of spinal injury. ACC
Brumfitt 1981	RCT involving women with a frequent history of UTI did not include a "no treatment" control group. The comparison "control" group was nitrofurantoin.
Brumfitt 1983	RCT involving women with a frequent history of UTI did not include a "no treatment" control group. The comparison "control" group was frequent perineal povidone iodine application (for ethical reasons, as stated by the authors).
Casselman 1966	Probably a before and after study. No control (no treatment) group.
Chrapowicki 1975	No control. All participants were given vitamin C and cranberry juice as well (from German).
Christopher 1969	This (alternate allocation) study, compared methenamine hippurate to sulphamethizole in pregnant women. The study did not include a "no treatment" control group.
Cronberg 1987	Randomised double blind cross over design. This study could potentially be included if data at the first 6 month cross over could be provided. 33% drop out at 1 year but no drop out rate at 6 months. (ACC)
Elo 1978	Not RCT or quasi-RCT. No control (no treatment) group.
Genster 1970	This study on UTIs following transurethral prostatectomy did not mention using a randomised or quasi randomised control design. ACC
Gerstein 1968	Not RCT or quasi-RCT. It did not include the use of a "no treatment" control.
Gow 1974	This trial compared methenamine hippurate to methenamine mandelate, without the use of a "non treatment" control.
Horcickova 1986	This study compared methenamine hippurate with methenamine mandelate without a "no treatment" control group.
Kasanen 1974a	Comparison of long-term, low dosage nitrofurantoin, methenamine hippurate, trimethoprim and trimethoprim-sulphamethoxazole. Absence of a "no treatment" control group.
Kasanen 1974b	The main outcome measure is the urinary formaldehyde concentration, which is not an outcome measure specified by our review.
Klein 1976	No control group (from Germany)
Kostiala 1982	No mention of randomised or quasi randomised control. The method of allocation was not specified and there was no mention of randomisation in the methodology. ACC
Krechnakova 1979	14 patients. Chronic, relapsing pyelonephritis treated with methenamine hippurate on a long term basis. No control stated in this study.
LeBlanc 1964	Mandelamine not methenamine hippurate studied.
Murray 1977	A comparison of hexamine hippurate with sulphamethizole, a "no treatment" control comparison was not provided.
Nilsson 1975	This study is a 16 month cohort study on 24 patients given methenamine hippurate. It does not meet the inclusion criteria of this review, but may provide useful side effect data.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Norberg-A 1980	RCT, double blind study. Outcome measure was catheter life (not an outcome measure specified in this review). Incidentally, there appears to be an episodes to participants issue with this trial.
Norberg-B 1979a	Not RCT. The study involves the treatment of patients with infected urine rather than the prevention of UTI
Norberg-B 1979b	Non randomised crossover trial. The outcome measure is a quantified sediment of the urine from Geriatric patients with indwelling catheters. This does not match our predefined outcome measures.
Nyren 1981	No mention of randomised or quasi-randomised control. ACC
Olsen 1983	The comparison "control group" was cefotaxime, not "no treatment".
Parkhede 1982	RCT. The outcome measure is a reduction in urine viscosity. Although this may have an association with catheter blockage, it does not address directly the study question of this meta-analysis as defined by pre-study outcome measures.
Parvio 1976	Non randomised crossover trial. Of the original 52 patients, 12 did not complete the 6 month treatment course.
Pedersen 1977	Double blind, parallel experiment comparing methenamine hippurate and "phenylsalicylate" only. (lack of "no treatment" control).
Scetbon 1973	Not RCT or quasi-RCT (from France)
Stover 1980	This RCT did not provide a "no treatment" control group . The interventions included methenamine hippurate 1 g by mouth twice/day, or ascorbic acid 1 g by mouth 4 times/day. Other problems are a lack of blinding, lack of intention-to-treat analysis and in particular no clear description of the number and group of excluded patients.
Vainrub 1977	No mention of RCT or quasi-RCT. ACC
Wibell 1980	No mention of RCT or quasi-RCT. Non randomised cross over for the control (no treatment) group.

ACC - authors contacted for clarification

DATA AND ANALYSES

Comparison 1. Symptomatic UTI (confirmed by positive urine test)

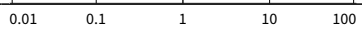
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic bacteruria	6	853	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.24, 1.18]
2 Symptomatic bacteruria: Renal tract abnormalities	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 No renal tract abnormalities	4	456	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.07, 0.89]
2.2 Renal tract abnormalities	2	397	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.38, 6.20]

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Sensitivity analysis: Symptomatic UTI including subjects unconfirmed by positive urine tests (for Lee 2006).	6	853	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.24, 1.17]
4 Duration of therapy	6	853	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.24, 1.18]
4.1 Short duration treatment (7 days or less)	4	411	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.06, 1.56]
4.2 Longer duration treatment (greater than 7 days)	2	442	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.25]
5 Short duration treatment (7 days or less): Upper renal tract abnormalities	4	411	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.06, 1.56]
5.1 No upper renal tract abnormalities	3	319	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.05, 0.38]
5.2 Upper renal tract abnormalities	1	92	Risk Ratio (M-H, Random, 95% CI)	4.79 [0.58, 39.40]

Analysis 1.1. Comparison 1 Symptomatic UTI (confirmed by positive urine test), Outcome 1 Symptomatic bacteruria.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Furness 1975	14/70	17/67		25.59%	0.79[0.42,1.47]
Knoff 1985	1/31	8/29		10.33%	0.12[0.02,0.88]
Lee 2007	53/150	55/155		29.05%	1[0.74,1.35]
Pettersson 1989	5/47	1/45		9.74%	4.79[0.58,39.4]
Schiotz 2002	2/75	10/75		14.8%	0.2[0.05,0.88]
Tyreman 1986	1/51	14/58		10.49%	0.08[0.01,0.6]
Total (95% CI)	**424**	**429**		**100%**	**0.53[0.24,1.18]**
Total events: 76 (Treatment), 105 (Control)					
Heterogeneity: Tau^2=0.55; Chi^2=17.74, df=5(P=0); I^2=71.81%					
Test for overall effect: Z=1.55(P=0.12)					



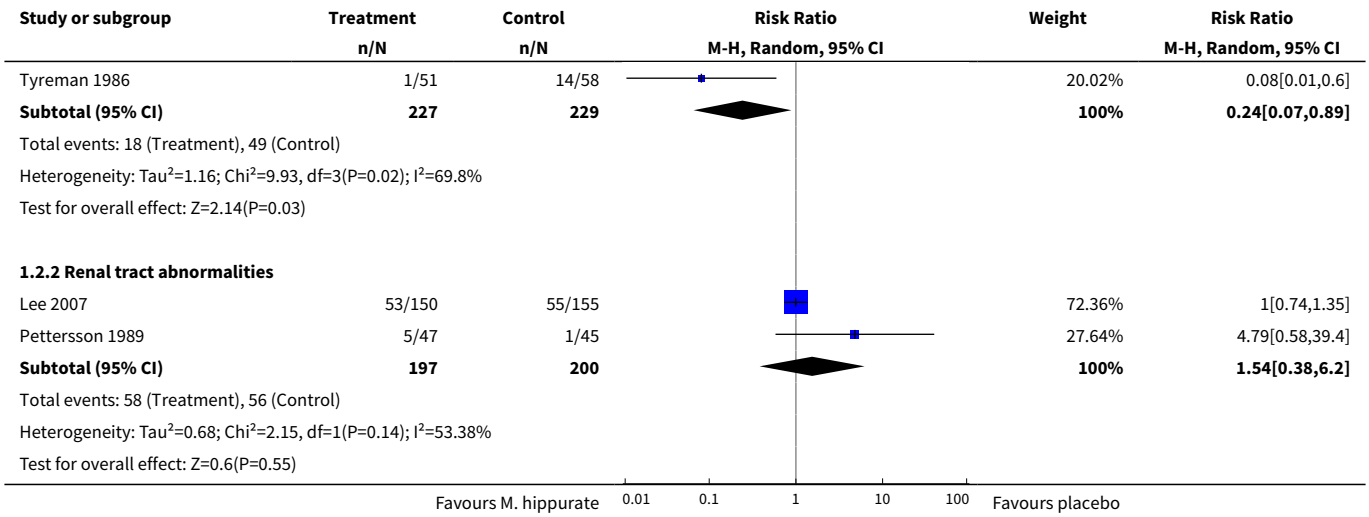
Favours treatment — Favours control

Analysis 1.2. Comparison 1 Symptomatic UTI (confirmed by positive urine test), Outcome 2 Symptomatic bacteruria: Renal tract abnormalities.

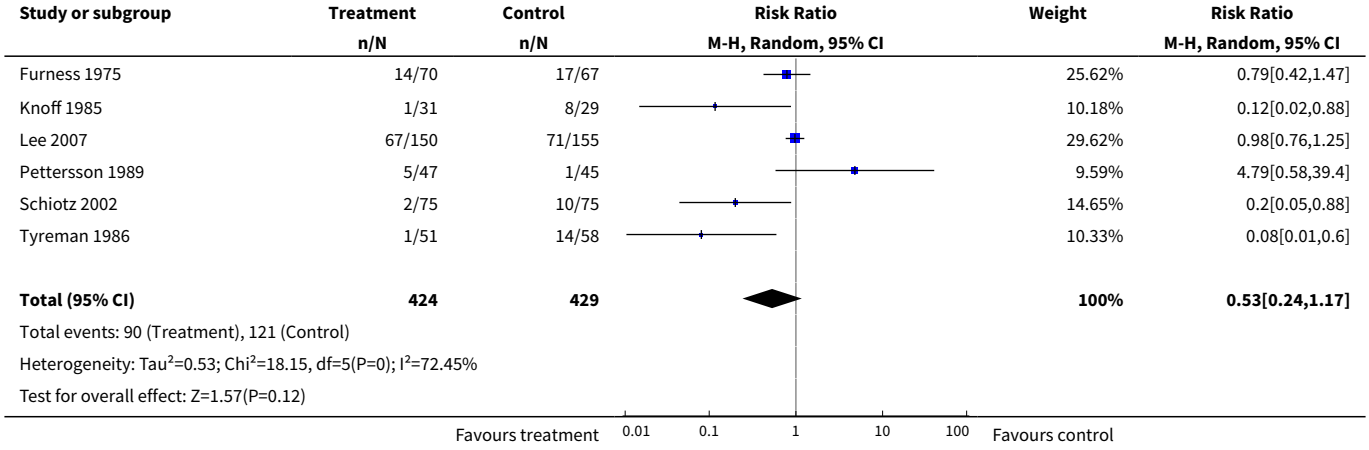
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 No renal tract abnormalities					
Furness 1975	14/70	17/67		34.82%	0.79[0.42,1.47]
Knoff 1985	1/31	8/29		19.81%	0.12[0.02,0.88]
Schiotz 2002	2/75	10/75		25.35%	0.2[0.05,0.88]

Favours M. hippurate — Favours placebo

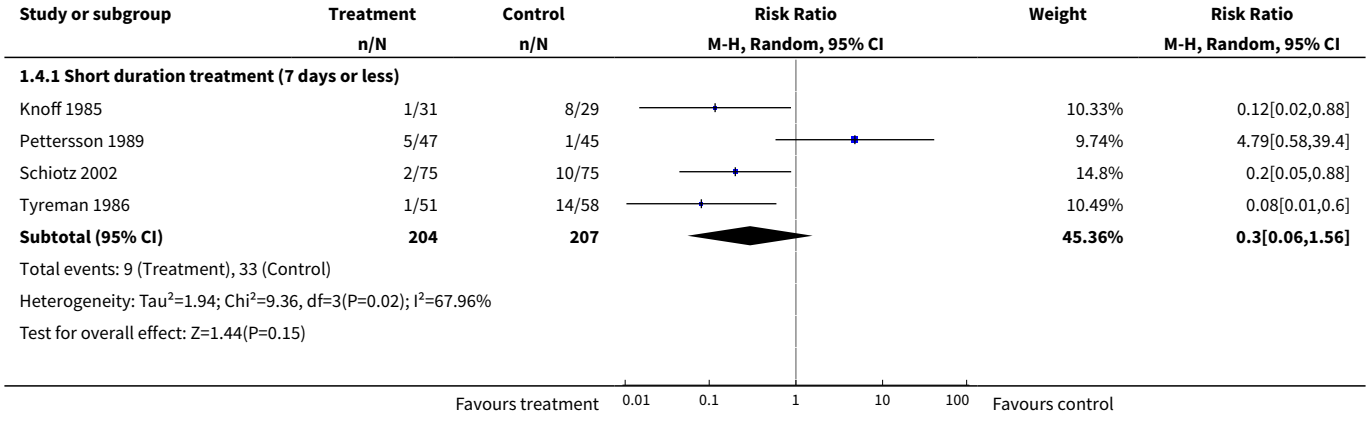
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.



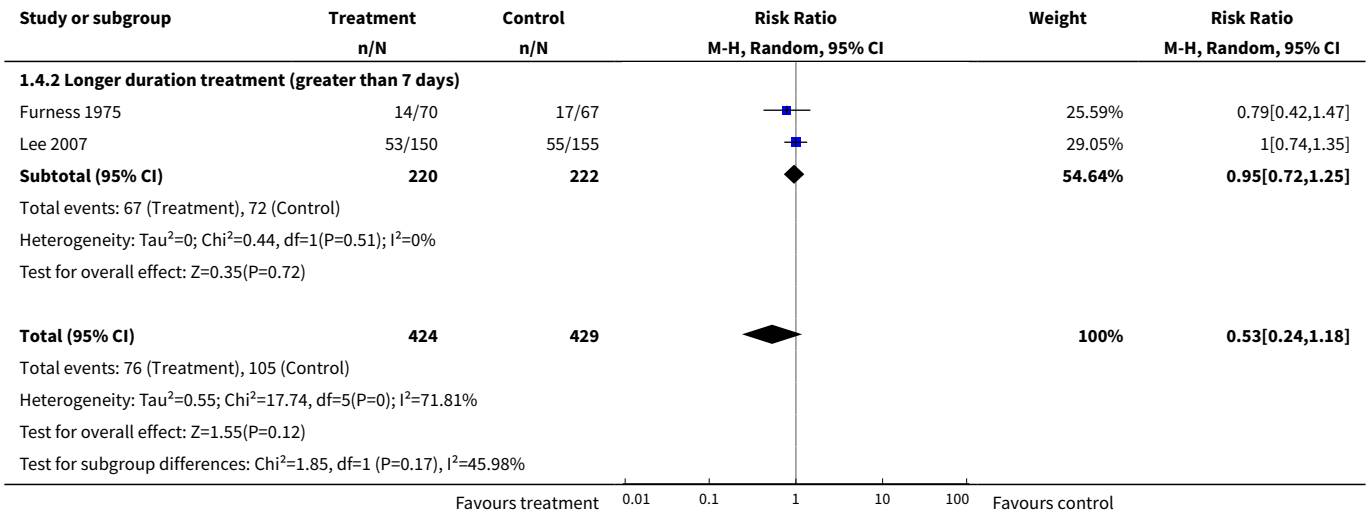
Analysis 1.3. Comparison 1 Symptomatic UTI (confirmed by positive urine test), Outcome 3 Sensitivity analysis: Symptomatic UTI including subjects unconfirmed by positive urine tests (for Lee 2006)..



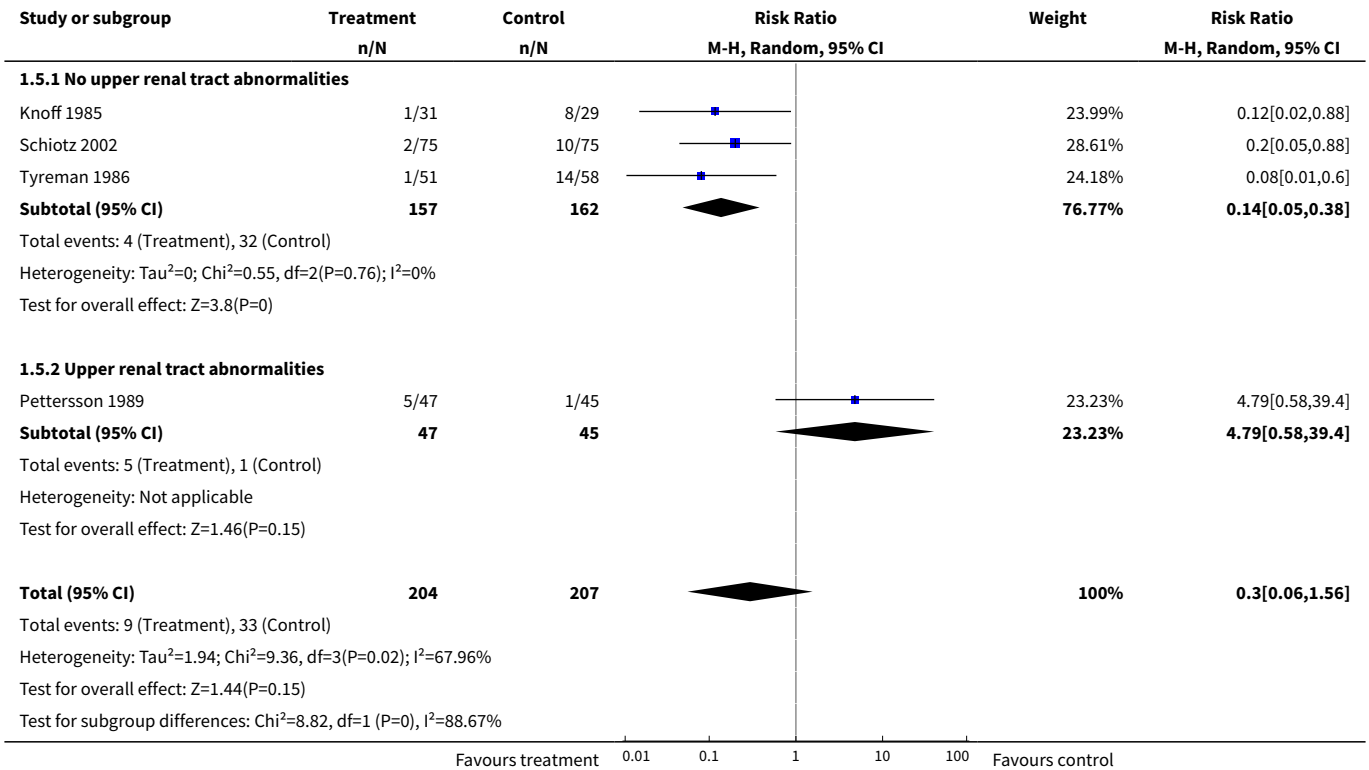
Analysis 1.4. Comparison 1 Symptomatic UTI (confirmed by positive urine test), Outcome 4 Duration of therapy.



Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.



Analysis 1.5. Comparison 1 Symptomatic UTI (confirmed by positive urine test), Outcome 5 Short duration treatment (7 days or less): Upper renal tract abnormalities.



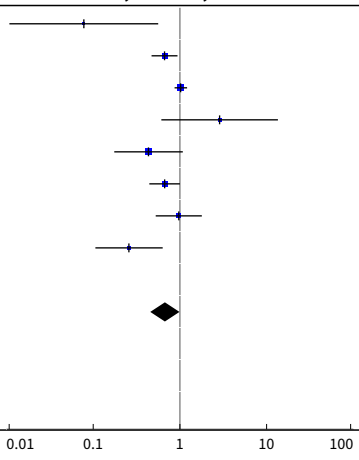
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Comparison 2. Bacteriuria

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome measure: Bacteriuria	8	1114	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 0.99]
2 Bacteriuria (renal tract abnormalities)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 No renal tract abnormality	6	717	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.37, 0.83]
2.2 Renal tract abnormality	2	397	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.54, 3.07]
3 Duration of therapy	7	1048	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.47, 1.06]
3.1 Short duration treatment (7 days or less)	5	511	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.29, 1.22]
3.2 Long duration treatment (greater than 7 days)	2	537	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.55, 1.31]
4 Short duration treatment (7 days or less): (upper renal tract abnormalities)	5	511	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.29, 1.22]
4.1 No upper renal tract abnormalities	4	419	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.23, 0.99]
4.2 Upper renal tract abnormalities	1	92	Risk Ratio (M-H, Random, 95% CI)	2.87 [0.61, 13.50]

Analysis 2.1. Comparison 2 Bacteriuria, Outcome 1 Outcome measure: Bacteriuria.

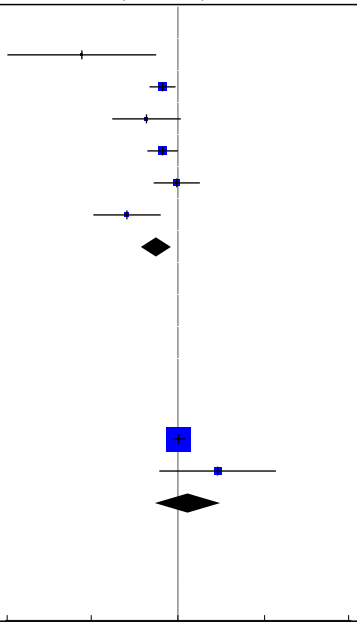
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Knoff 1985	1/31	12/29		3.28%	0.08[0.01,0.56]
Ladehoff 1984	33/109	56/123		18.72%	0.66[0.47,0.94]
Lee 2007	99/150	100/155		21.13%	1.02[0.87,1.21]
Pettersson 1989	6/47	2/45		4.89%	2.87[0.61,13.5]
Sander 1976	5/31	13/35		9.94%	0.43[0.17,1.08]
Schiotz 2002	24/75	36/75		17.72%	0.67[0.44,1]
Thomlinson 1968	14/49	15/51		14.18%	0.97[0.53,1.79]
Tyreman 1986	5/51	22/58		10.13%	0.26[0.11,0.63]
Total (95% CI)	**543**	**571**		**100%**	**0.67[0.45,0.99]**
Total events: 187 (Treatment), 256 (Control)					
Heterogeneity: Tau^2=0.18; Chi^2=28.55, df=7(P=0); I^2=75.48%					
Test for overall effect: Z=2.02(P=0.04)					



Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

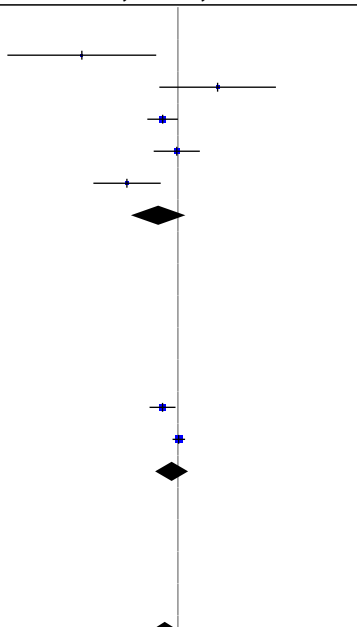
Analysis 2.2. Comparison 2 Bacteriuria, Outcome 2 Bacteriuria (renal tract abnormalities).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 No renal tract abnormality					
Knoff 1985	1/31	12/29		3.63%	0.08[0.01,0.56]
Ladehoff 1984	33/109	56/123		27.31%	0.66[0.47,0.94]
Sander 1976	5/31	13/35		12.28%	0.43[0.17,1.08]
Schiotz 2002	24/75	36/75		25.32%	0.67[0.44,1]
Thomlinson 1968	14/49	15/51		18.91%	0.97[0.53,1.79]
Tyreman 1986	5/51	22/58		12.55%	0.26[0.11,0.63]
Subtotal (95% CI)	**346**	**371**		**100%**	**0.56[0.37,0.83]**
Total events: 82 (Treatment), 154 (Control)					
Heterogeneity: Tau^2=0.12; Chi^2=11.44, df=5(P=0.04); I^2=56.3%					
Test for overall effect: Z=2.88(P=0)					
2.2.2 Renal tract abnormality					
Lee 2007	99/150	100/155		77.47%	1.02[0.87,1.21]
Pettersson 1989	6/47	2/45		22.53%	2.87[0.61,13.5]
Subtotal (95% CI)	**197**	**200**		**100%**	**1.29[0.54,3.07]**
Total events: 105 (Treatment), 102 (Control)					
Heterogeneity: Tau^2=0.25; Chi^2=1.78, df=1(P=0.18); I^2=43.81%					
Test for overall effect: Z=0.58(P=0.56)					

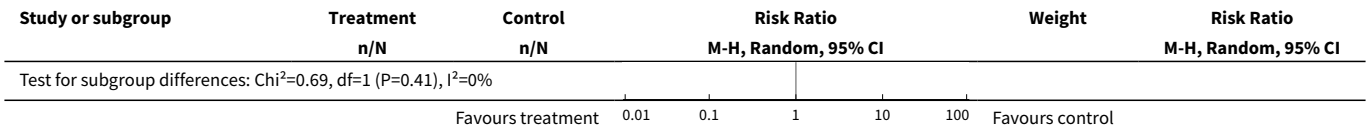


Analysis 2.3. Comparison 2 Bacteriuria, Outcome 3 Duration of therapy.

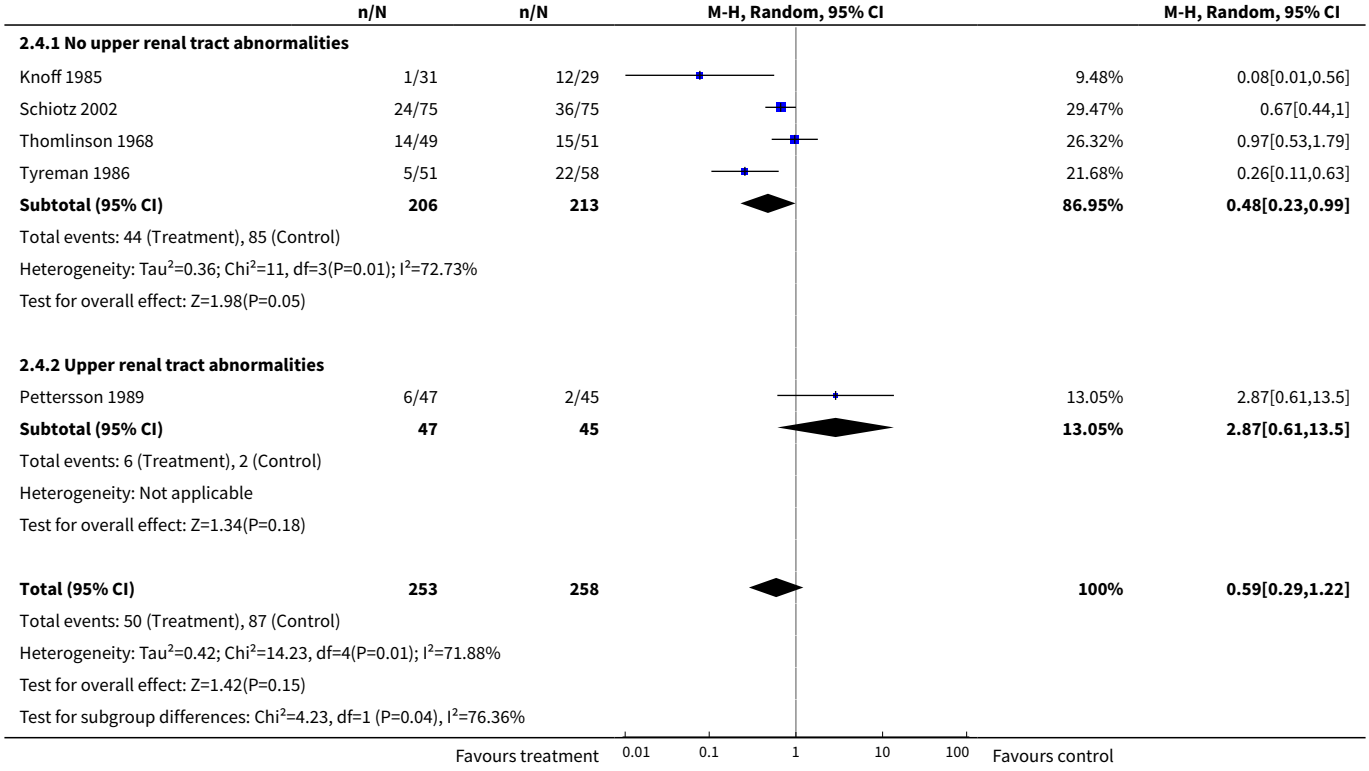
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Short duration treatment (7 days or less)					
Knoff 1985	1/31	12/29		3.59%	0.08[0.01,0.56]
Pettersson 1989	6/47	2/45		5.36%	2.87[0.61,13.5]
Schiotz 2002	24/75	36/75		19.71%	0.67[0.44,1]
Thomlinson 1968	14/49	15/51		15.7%	0.97[0.53,1.79]
Tyreman 1986	5/51	22/58		11.17%	0.26[0.11,0.63]
Subtotal (95% CI)	**253**	**258**		**55.53%**	**0.59[0.29,1.22]**
Total events: 50 (Treatment), 87 (Control)					
Heterogeneity: Tau^2=0.42; Chi^2=14.23, df=4(P=0.01); I^2=71.88%					
Test for overall effect: Z=1.42(P=0.15)					
2.3.2 Long duration treatment (greater than 7 days)					
Ladehoff 1984	33/109	56/123		20.86%	0.66[0.47,0.94]
Lee 2007	99/150	100/155		23.61%	1.02[0.87,1.21]
Subtotal (95% CI)	**259**	**278**		**44.47%**	**0.85[0.55,1.31]**
Total events: 132 (Treatment), 156 (Control)					
Heterogeneity: Tau^2=0.08; Chi^2=5.35, df=1(P=0.02); I^2=81.32%					
Test for overall effect: Z=0.75(P=0.45)					
Total (95% CI)	**512**	**536**		**100%**	**0.7[0.47,1.06]**
Total events: 182 (Treatment), 243 (Control)					
Heterogeneity: Tau^2=0.17; Chi^2=25.82, df=6(P=0); I^2=76.76%					
Test for overall effect: Z=1.69(P=0.09)					



Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.



Analysis 2.4. Comparison 2 Bacteriuria, Outcome 4 Short duration treatment (7 days or less): (upper renal tract abnormalities).



ADDITIONAL TABLES

Table 1. Population and adverse events

Studies	Adverse events	Population
Furness 1975	No significant difference in birth weight or maturity at delivery between the treatments. There was one major foetal abnormality (anencephaly), which occurred in the control group. Abortion: 1 occurred in the control group, and 1 in another study arm (not methenamine hippurate). Three intra-uterine deaths are mentioned, but they are not assigned to specific treatment arms.	Pregnant and post-natal women.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Population and adverse events *(Continued)*

Gundersen 1986	One patient with nausea/rash and 1 death (apoplexia cerebri: presumed unrelated) in the 15 patients in the methenamine hippurate group, and 1 episode of constipation and 1 person leaving the study due to lack of effect in the 15 patients in the placebo group	Post-menopausal women.
Hoivik 1984	Six patients leaving the study early from 28 patients in the methenamine hippurate 1 g twice daily group (21%), 1 from 12 in the methenamine hippurate 1 g daily group (8%) and 4 from 12 in the control group (33%). Three episodes of side-effects are described in the 1 g twice daily group (1 episode of intense stinging in the bladder region leading to the patient leaving the trial, and 2 unspecified). Two episodes of side effects are mentioned in the methenamine hippurate 1 g daily group and 3 in the placebo group, but these are only described as "minor".	Pre-menopausal women.
Kasanen 1982	Three episodes of side effects in the methenamine hippurate 1 g daily group (1 episode of rash and 2 of nausea), leading to 2 withdrawals from the study (from 73 participants). The placebo group in comparison suffered 2 episodes of side effects (1 episode of nausea and 1 of abdominal pain), leading to 2 withdrawals.	Recurrent UTI.
Knoff 1985	1/31 in the methenamine hippurate 2 g twice daily group with a sore throat and 1/29 in the placebo group.	Women post gynaecological operations.
Kuhlemeier 1985	Two patients in the methenamine hippurate group suffering nausea.	Male spinal cord-injured patients.
Ladehoff 1984	One patient left the study due to complications on methenamine hippurate 500 mg twice daily (nausea).	Women post gynaecological operations.
Lee 2007	Two patients in the methenamine hippurate group suffered constipation, diarrhoea or rash respectively. One suffered nausea (unpublished data).	Spinal Cord Injured Patients with neuropathic bladders.
Thomlinson 1968	No reported side effects	Women post gynaecological operations.
Tyreman 1986	No reported side effects	Women post gynaecological operations.
Sander 1976	No reported side effects	Men undergoing prostate operations.
Schiotz 2002	Eleven patients (7.6%) had an adverse event. Eight had nausea (5 in the treatment group and 3 in the placebo group). Three participants had a rash (1 methenamine versus 2 placebo). Two withdrawals (one from each group).	Women undergoing gynaecological laparotomy or vaginal plastic surgery.
Pettersson 1989	No mention of side effects	Patients undergoing extracorporeal shockwave lithotripsy.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

APPENDICES

Appendix 1. Electronic search strategies

Databases	Search terms
CENTRAL	#1 CYSTITIS MeSH #2 PYELONEPHRITIS MeSH #3 uti* #4 (urinary near infection*) #5 cystitis #6 pyelonephritis #7 bacteriuria #8 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8) #9 METHENAMINE MeSH #10 HIPPURATES MeSH #11 MANDELIC ACIDS MeSH #12 hiprex #13 (hippuric next acid) #14 hexamine #15 methenamine #16 hexamethylenetetramine #17 (mandelato near metenamina) #18 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #16 or #17 or #18) #19 (#9 and #19)
MEDLINE	1. exp Urinary Tract Infections/ 2. exp Cystitis/ 3. exp Pyelonephritis/ 4. (uti or utis).tw. 5. (urin$ adj5 infection$).tw. 6. cystitis.tw. 7. pyelonephritis.tw. 8. bacteriuria.tw. 9. pyuria.tw. 10. or/1-9 11. Methenamine/ 12. exp Hippurates/ 13. exp Mandelic Acids/ 14. hiprex.tw. 15. hippuric acid.tw. 16. hexamine.tw. 17. methenamine.tw. 18. hexamethylenetetramine.tw. 19. mandelato de metenamina.tw. 20. or/11-19 21. and/10,20

WHAT'S NEW

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Date	Event	Description
20 September 2012	Review declared as stable	As of June 2012 this Cochrane Review is no longer being updated. There have been no new studies published on this topic in the past five years and there are currently no registered ongoing studies.

HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 1, 2002

Date	Event	Description
7 June 2012	New citation required but conclusions have not changed	New search performed, no new studies identified
18 March 2010	Amended	Contact details updated.
14 October 2008	Amended	Converted to new review format.
1 August 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

- Dr Bonne Lee was involved in the following aspects of this project:
  * Design of the research question, formulation of the study protocol, design and repeated updates of the literature search, selection of articles and extraction of information, arranging translation of articles as appropriate, data analysis, interpretation and write up.
- A/Prof Judy Simpson was involved in protocol development, data analysis, statistical support, interpretation, document update and manuscript editing.
- A/Prof Jonathan Craig was involved in protocol development, data analysis, interpretation, document update and manuscript editing.
- Dr Tushar Bhuta was co-author, and was involved in literature searching, data selection, extraction and interpretation.

DECLARATIONS OF INTEREST

- Dr Lee is the lead investigator on the NHMRC Project Grant Application: 630448 Probiotic Prophylaxis of Spinal Cord Injury Urinary Tract-Infection TherapeUtic-Trial (ProSCIUTTU), which is an Australian government sponsored study looking at the effectiveness of Probiotic therapy in preventing Urinary tract infection and multi drug resistance (Lee 2007). This study was independently assessed by the Cochrane Renal Group's Review Group Coordinator to eliminate potential bias in the assessment of this study.
- Tushar Bhuta: none known
- Judy M Simpson: none known
- Jonathan C Craig: none known

SOURCES OF SUPPORT

Internal sources

- Royal North Shore Hospital Spinal Medicine Department (initial protocol and review), Australia.

External sources

- No sources of support supplied

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Infective Agents, Urinary [*therapeutic use]; Hippurates [*therapeutic use]; Methenamine [*analogs & derivatives] [therapeutic use]; Randomized Controlled Trials as Topic; Urinary Tract Infections [*prevention & control]

MeSH check words

Humans

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.