**PICO Search Assignment Worksheet Name: Sierra Teegarden**

**Brief description of patient problem/setting (summarize the case very briefly):**

A 24 y/o female with a history of recurrent urinary tract infections presents to the clinic with complaints of burning on urination. Urinalysis is positive for nitrites and leukocyte esterase. She admits to following all of the lifestyle modification guidance to decrease her risk of recurrence. This is her 6th UTI in the last year and the provider suggests daily low-dose antibiotics for prevention. The patient is hesitant because they believe it is harmful to be on antibiotics for that long and would like to know if there is another medication. The provider then suggests Methenamine Hippurate.

**Search Question**:

Is the efficacy and safety of Methenamine superior to that of standard low-dose antibiotic therapy for the prophylaxis of recurrent urinary tract infections in adult women?

**Question Type:** What kind of question is this?

Prevalence Screening Diagnosis

Prognosis Treatment Harms

I will initially set my search to include meta-analysis, systematic reviews, and randomized control trials. If results are limited, I will then expand my search criteria to include retrospective cohort studies. My time period will be set to within the last 12 years to capture relevant articles just out of the 10-year period but with a focus on the most recently published studies available to guide my current practice. My search will initially include the terms of my intervention, comparison, and outcome but I will omit certain terms of the search results are too narrow.

**PICO search terms:**

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| **P** | **I** | **C** | **O** |
| Recurrent UTI | Methenamine | antibiotics | UTI prevention |
| Recurrent cystitis | Methenamine Hippurate | antibacterial | Cystitis prevention |
| Recurrent urinary tract infection |  | antimicrobial | prophylaxis |

**Search tools and strategy used:**

**Filters/limits applied:**

1. Full text
2. Publication date: Within 12 years
3. Language: English
4. Article Type: Meta-Analysis, Systematic review, Randomized Control Trial, Randomized Control Study, Retrospective Study
5. Age: None selected

**Databases used:**

1. PubMed
2. Google Scholar
3. Science Direct
4. Wiley Online Library

**Results found:**

**Number of articles returned once relevant limits are added**

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| **Database** | **Filter** | **Terms Searched** | **Articles Returned** |
| **PubMed** | Full text/English/Meta-analysis/Systematic Review/Randomized control trial/Randomized control study/Sort by relevance | Methenamine antibiotic prophylaxis | 8 |
| methenamine | 126 |
| **Google Scholar** | 2010-2022/Include citations/All in title | methenamine | 116 |
| **ScienceDirect** | English/2010-2022/Research Articles/Medicine & Dentistry/Sort by relevance | Methenamine urinary tract infection | 113 |
| **Wiley Online Library** | English/Anywhere/Published 2010-2022/Journals/Open access content/Sorted by Relevance | Methenamine urinary tract infection | 265 |

My initial PubMed search was too narrow, so I omitted the comparison and outcome terms leaving only the intervention term “methenamine” which broadened my search results. Of the 126 results, I found five that were of relevance and met my inclusion/exclusion criteria for this PICO question. Google scholar, which normally yields high numbers of irrelevant results, yielded 116 search articles when setting the parameters to within the past 12 years. Although I prefer articles chosen to be as up to date as possible which is typically within the last 10 years, I expanded to 12 years to try and capture any meaningful articles that were just outside of this time window. ScienceDirect also offered a similar number of articles but fewer of them directly answered my question. Wiley Online Library had the highest number of returned articles but many of them were also irrelevant.

**Results found:**

**Article 1**

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| **Citation**: Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2012;10(10):CD003265. Published 2012 Oct 17. doi:10.1002/14651858.CD003265.pub3 |
| **Type of Study: Systematic Review** |
| **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:** Randomized 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.**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. |
| **Reason for Selection:** I chose this systematic review because it evaluated the benefits and harms of Methenamine in preventing UTI by comparing 13 RCTs. The sample size of 2032 total participants is relatively large. The data collection and analysis was adequate and included information on the heterogeneity as well as a detailed review of the results. |
| **Key Points:**   * 8/14 studies addressed reoccurrence of symptomatic UTIs and 6/8 of these studies found methenamine to be an effective prophylaxis for UTIs * 8 studies addressed bacteriuria as an outcome which all favored methenamine but in the face of significant heterogeneity * The frequency of reported side-effects was low compared to control but the data was of insufficient quality to perform formal statistical evaluation and side effects were poorly described * Methenamine was found to be more effective for short duration treatment in those without renal tract abnormalities * Methenamine does not appear to work in patients with neuropathic bladder or in patietns who have renal tract abnormalities |

**Article 2:**

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| **Citation**: Bakhit M, Krzyzaniak N, Hilder J, Clark J, Scott AM, Mar CD. Use of methenamine hippurate to prevent urinary tract infections in community adult women: a systematic review and meta-analysis. *Br J Gen Pract*. 2021;71(708):e528-e537. Published 2021 Jun 24. doi:10.3399/BJGP.2020.0833 |
| **Type of Study: Systematic Review & Meta-analysis** |
| **Abstract:**  **Background:** Urinary tract infections (UTIs) are often treated with antibiotics and are a source of antibiotic overuse. **Aim:** To systematically review randomised controlled trials (RCTs) of adult women in the community with a history of recurrent UTIs and who use methenamine hippurate prophylactically.**Design and setting:** Systematic review of women in the UK, Australia, Norway, and US (aged ≥18 years) with recurrent UTIs receiving methenamine hippurate against placebo or no treatment, and antibiotics.**Method:** The authors searched three databases, clinical trial registries, and performed forward–backward citation analysis on references of included studies.**Results:** Six studies involving 557 participants were included (447 were analysed). Of the six studies, five were published and one was an unpublished trial record with results, three compared methenamine hippurate against placebo or control, and three compared methenamine hippurate with antibiotics. For the number of patients who remained asymptomatic, methenamine hippurate showed a non-statistically significant trend of benefit versus antibiotics over 12 months (risk ratio [RR] 0.65, 95% confidence interval [CI] = 0.40 to 1.07, I2 49%), versus control over 6 or 12 months (RR 0.56, 95% CI = 0.13 to 2.35, I2 93%), and a non-statistically significant trend versus any antibiotic for abacteruria (RR 0.80, 95% CI = 0.62 to 1.03, I2 23%). A similar non-statistically significant trend of benefits for methenamine hippurate for the number of UTI or bacteriuric episodes was found, and a non-statistically significant difference in the number of patients experiencing adverse events between methenamine hippurate and any comparator, with a trend towards benefit for the methenamine hippurate, was identified. Antibiotic use and resistance were not consistently reported.**Conclusion:** There is insufficient evidence to be certain of the benefits of methenamine hippurate to prevent UTI. Further research is needed to test the drug’s effectiveness in preventing UTIs and as an alternative for antibiotic treatment for UTI. |
| **Reason for Selection:**I chose this meta-analysis/systematic review because it evaluates the use of prophylactic methenamine for women with a history of recurrent UTIs against both placebo and antibiotics. There were 6 studies included which is similar to the amount of studies from the first research article. Although the number of participants is lower (557) the studies appear to be higher quality than those evaluated in article one. |
| **Key Points:**   * There is not sufficient evidence to establish the benefits of methenamine use to prevent UTIs. * Antibiotic resistance was poorly reported among the individual studies but the studies that evaluated it did find higher resistance in the antibiotic groups than the methenamine group. * The most common adverse events were nausea, headache, and abdominal pain * There was no statistical difference in the number of adverse events between methenamine and antibiotics |

**Article 3:**

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| **Citation**: Harding C, Chadwick T, Homer T, Lecouturier J, Mossop H, Carnell S, *et al.* Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT. *Health Technol Assess* 2022;26(23) |
| **Type of Study: Randomized Control Trial** |
| **Abstract:**  **Background:**Daily, low-dose antibiotic prophylaxis is the current standard care for women with recurrent urinary tract infection. Emerging antimicrobial resistance is a global health concern, prompting research interest in non-antibiotic agents such as methenamine hippurate, but comparative data on their efficacy and safety are lacking.  **Objective:**To assess the clinical effectiveness and cost-effectiveness of methenamine hippurate (Hiprex®; Mylan NV, Canonsburg, PA, USA) compared with current standard care (antibiotic prophylaxis) for recurrent urinary tract infection prevention in adult women.  **Design:**Multicenter, pragmatic, open-label, randomized, non-inferiority trial of 12 months' treatment with the allocated intervention, including an early, embedded qualitative study and a 6-month post-treatment observation phase. The predefined non-inferiority margin was one urinary tract infection per person-year.  **Participants:**A total of 240 adult women with recurrent urinary tract infection requiring preventative treatment participated in the trial.  **Interventions:**A central randomization system allocated participants 1 : 1 to the experimental (methenamine hippurate: 1 g twice daily) or control (once-daily low-dose antibiotics: 50/100 mg of nitrofurantoin, 100 mg of trimethoprim or 250 mg of cefalexin) arm. Crossover between treatment arms was permitted.  **Main outcome measures:**The primary clinical outcome was incidence of symptomatic antibiotic-treated urinary tract infection during the 12-month treatment period. Cost-effectiveness was assessed by incremental cost per quality-adjusted life-year gained, extrapolated over the patient's expected lifetime using a Markov cohort model. Secondary outcomes included post-treatment urinary tract infections, total antibiotic use, microbiologically proven urinary tract infections, antimicrobial resistance, bacteriuria, hospitalizations and treatment satisfaction.  **Results:**Primary modified intention-to-treat analysis comprised 205 (85%) randomized participants [102/120 (85%) participants in the antibiotics arm and 103/120 (86%) participants in the methenamine Hippurate arm] with at least 6 months' data available. During treatment, the incidence rate of symptomatic, antibiotic-treated urinary tract infections decreased substantially in both arms to 1.38 episodes per person-year (95% confidence interval 1.05 to 1.72 episodes per person-year) for methenamine Hippurate and 0.89 episodes per person year (95% confidence interval 0.65 to 1.12 episodes per person-year) for antibiotics (absolute difference 0.49; 90% confidence interval 0.15 to 0.84). This absolute difference did not exceed the predefined, strict, non-inferiority limit of one urinary tract infection per person-year. On average, methenamine Hippurate was less costly and more effective than antibiotics in terms of quality-adjusted life-years gained; however, this finding was not consistent over the longer term. The urinary tract infection incidence rate 6 months after treatment completion was 1.72 episodes per year in the methenamine hippurate arm and 1.19 in the antibiotics arm. During treatment, 52% of urine samples taken during symptomatic urinary tract infections were microbiologically confirmed and higher proportions of participants taking daily antibiotics (46/64; 72%) demonstrated antibiotic resistance in *Escherichia coli* cultured from perineal swabs than participants in the methenamine hippurate arm (39/70; 56%) (*p*-value = 0.05). Urine cultures revealed that during treatment higher proportions of participants and samples from the antibiotic arm grew *E. coli* resistant to trimethoprim/co-trimoxazole and cephalosporins, respectively. Conversely, post treatment, higher proportions of participants in the methenamine hippurate arm (9/45; 20%) demonstrated multidrug resistance in *E. coli* isolated from perineal swabs than participants in the antibiotic arm (2/39; 5%) (*p* = 0.06). All other secondary outcomes and adverse events were similar in both arms.  **Limitations:**This trial could not define whether or not one particular antibiotic was more beneficial, and progressive data loss hampered economic evaluation.  **Conclusions:**This large, randomized, pragmatic trial in a routine NHS setting has clearly shown that methenamine hippurate is not inferior to current standard care (daily low-dose antibiotics) in preventing recurrent urinary tract infections in women. The results suggest that antimicrobial resistance is proportionally higher in women taking prophylactic antibiotics. |
| **Reason for Selection:**I selected this RCT because it evaluates the clinical and cost effectiveness of methenamine compared to antibiotics for the prophylaxis of UTIs. The sample size is acceptable for an RCT with 240 participants and the population is that of adult women. |
| **Key Points:**   * Methenamine is not inferior to antibiotic therapy for the prophylactic treatment of recurrent UTIs * Microbial resistance is proportionally higher in women taking prophylactic antibiotics compared to women taking methenamine * During treatment higher proportions of participants from the antibiotic group grew E. coli resistant to Bactrim and cephalosporins. * Post treatment, higher proportions of participants in the methenamine group demonstrated multidrug resistance in E. coli isolated from perineal swabs than in the antibiotic group |

**Article 4:**

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| **Citation**: Harding C, Mossop H, Homer T, et al. Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial. *BMJ*. 2022;376:e068229. Published 2022 Mar 9. doi:10.1136/bmj-2021-0068229 |
| **Type of Study: Randomized Clinical Trial** |
| **Abstract:** **Objective:** To test and compare the efficacy of methenamine hippurate for prevention of recurrent urinary tract infections with the current standard prophylaxis of daily low dose antibiotics.**Design:** Multicentre, open label, randomised, non-inferiority trial.**Setting:** Eight centres in the UK, recruiting from June 2016 to June 2018.**Participants:** Women aged ≥18 years with recurrent urinary tract infections, requiring prophylactic treatment.**Interventions:** Random assignment (1:1, using permuted blocks of variable length via a web based system) to receive antibiotic prophylaxis or methenamine hippurate for 12 months. Treatment allocation was not masked and crossover between arms was allowed.**Main outcome measure:** Absolute difference in incidence of symptomatic, antibiotic treated, urinary tract infections during treatment. A patient and public involvement group predefined the non-inferiority margin as one episode of urinary tract infection per person year. Analyses performed in a modified intention-to-treat population comprised all participants observed for at least six months.**Results:** Participants were randomly assigned to antibiotic prophylaxis (n=120) or methenamine hippurate (n=120). The modified intention-to-treat analysis comprised 205 (85%) participants (antibiotics, n=102 (85%); methenamine hippurate, n=103 (86%)). Incidence of antibiotic treated urinary tract infections during the 12 month treatment period was 0.89 episodes per person year (95% confidence interval 0.65 to 1.12) in the antibiotics group and 1.38 (1.05 to 1.72) in the methenamine hippurate group, with an absolute difference of 0.49 (90% confidence interval 0.15 to 0.84) confirming non-inferiority. Adverse reactions were reported by 34/142 (24%) in the antibiotic group and 35/127 (28%) in the methenamine group and most reactions were mild.**Conclusion:** Non-antibiotic prophylactic treatment with methenamine hippurate might be appropriate for women with a history of recurrent episodes of urinary tract infections, informed by patient preferences and antibiotic stewardship initiatives, given the demonstration of non-inferiority to daily antibiotic prophylaxis seen in this trial. |
| **Reason for Selection:**I selected this RCT because it evaluates the efficacy of methenamine to standard low dose daily antibiotics for the prevention of recurrent UTIs. The sample population is that of adult women. The duration of the trial was for an acceptable amount of time (12 months). There is also 240 participants in this trial which is equal to the sample size of the RCT from article 3. This article also shares the same primary author as Article 3 who has utilized similar methods which increases my confidence in results occurring by methodology rather than by chance. |
| **Key Points:**   * Methenamine was found to be non-inferior to daily low dose antibiotics for the prevention of recurrent UTIs * Rates of adverse events and reactions were low and comparable across treatment groups. * Of the two serious adverse reactions reported, both were in the antibiotic treatment group. * Although the methenamine group had a 55% higher rate of UTI episodes than the antibiotic group, the absolute difference was just 0.49 UTI episodes per year, which has limited clinical consequence. |

**Article 5:**

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| **Citation**: Muller AE, Verhaegh EM, Harbarth S, Mouton JW, Huttner A. Nitrofurantoin's efficacy and safety as prophylaxis for urinary tract infections: a systematic review of the literature and meta-analysis of controlled trials. Clin Microbiol Infect. 2017 Jun;23(6):355-362. doi: 10.1016/j.cmi.2016.08.003. Epub 2016 Aug 17. PMID: 27542332. |
| **Type of Study: Systematic Review & Meta-analysis** |
| **Abstract:**  **Objectives:**Nitrofurantoin has been used for the prevention of urinary tract infection (UTI) for over 60 years. We conducted a systematic review and meta-analysis to assess its efficacy and safety in the prophylaxis of UTI.  **Methods:**We performed a systematic review of all controlled trials in humans assessing nitrofurantoin for UTI prophylaxis published from 1946 to 2015. We further reviewed population-level cohort studies evaluating nitrofurantoin's toxicity. Meta-analyses assessing efficacy and adverse events were conducted on controlled trials.  **Results:**Twenty-six controlled trials including 3052 patients fulfilled entry criteria for the systematic review and meta-analysis on efficacy and toxicity, and 16 population-level cohort studies were identified for review of toxicity. Overall quality was poor, with all studies at increased risk for various biases. When compared with no prophylaxis, nitrofurantoin is effective in the prevention of UTI (risk ratio 0.38 in favor of nitrofurantoin, 95% CI 0.30-0.48). Its prophylactic efficacy is superior to that of methenamine hippurate and comparable to that of other antibacterials. Compared with patients receiving other antibacterials, those receiving nitrofurantoin had an increased risk of 2.24 (95% CI 1.77-2.83) for a non-severe adverse effect. In all controlled trials, only one patient experienced a severe adverse effect (interstitial pneumonia). Cohort studies reported severe adverse effect frequencies of 0.02-1.5 per 1000 nitrofurantoin users.  **Conclusions:**Nitrofurantoin is effective in the prevention of UTI. Its use may be associated with increased non-severe adverse effects; severe adverse effects occur infrequently. The risk of severe toxicity seems to increase with the duration of nitrofurantoin prophylaxis. |
| **Reason for Selection:**I chose this systematic review/meta-analysis because it evaluates Nitrofurantoin, a common antibiotic used for UTIs, efficacy and safety as prophylaxis compared to other prophylactic options including methenamine. The sample size is very large including 26 RCTs and 3052 participants over a long period of time from 1946-2015. |
| **Key Points:**   * This study found that Nitrofurantoin has superior efficacy to methenamine and is comparable to that of other antibacterials commonly used * In all controlled trials, only one patient experienced a severe adverse effect with Nitrofurantoin * Nitrofurantoin did have a 2.24 increased risk of non-severe adverse effects when compared to other prophylactic options |

**Weighing the evidence**

Of the five articles selected in this PICO, articles 1, 2, & 5 hold the most weight being systematic reviews/meta-analysis. Of these three articles, articles 1 & 2 answer my PICO question more than article 3 does. Overall, article 1 holds the most weight because it has a larger participant size, more included studies, and is over a longer time period than article 2. Articles 3 & 4 are both randomized controlled trials with the same participant size published within the last year, however I am giving article 3 more weight because it includes U.S. participants while article 4 is only based in the UK which may make the findings not as relevant to my patient population. While article 1 (highest level of evidence) suggests that Methenamine is an effective prophylactic agent against recurrent UTIs, article 2 (second highest level of evidence) states there is not enough data to draw this conclusion. Article 5 (third highest level of evidence) states that while Methenamine is effective, antibiotics are a more effective treatment. Both articles 3 & 4 found Methenamine to be at least equal in efficacy to daily low dose antibiotics. Regarding safety, all articles that evaluated this outcome found that Methenamine has lower adverse events and reactions compared to antibiotics. Additionally, articles that evaluated microbial resistance found higher rates in the antibiotic group than the Methenamine group.

**What is the clinical “bottom line” derived from these articles in answer to your question?**

The clinical bottom line is that the overall trend of the articles found Methenamine to be an effective alternative to antibiotic prophylaxis in the prevention of recurrent UTIs. They also found antibiotics have increased adverse events, side effects, and microbial resistance. Based on these findings, I would recommend Methenamine to my patients as the more favorable option because it appears to have equal efficacy and increased safety compared with antibiotics. The clinical exception to this would be for patients with neuropathic bladder because article 1 found that methenamine is not effective in this patient population. For the rest of my patient population, I would opt for Methenamine as the first choice and consider antibiotic prophylaxis as second line therapy if Methenamine does not adequately prevent their recurrences.

**Links:**

Article 1

Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2012;10(10):CD003265. Published 2012 Oct 17. doi:10.1002/14651858.CD003265.pub3

Link: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003265.pub3/full

Article 2

Bakhit M, Krzyzaniak N, Hilder J, Clark J, Scott AM, Mar CD. Use of methenamine hippurate to prevent urinary tract infections in community adult women: a systematic review and meta-analysis. *Br J Gen Pract*. 2021;71(708):e528-e537. Published 2021 Jun 24. doi:10.3399/BJGP.2020.0833

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8136580/

Article 3

Harding C, Chadwick T, Homer T, Lecouturier J, Mossop H, Carnell S, *et al.* Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT. *Health Technol Assess* 2022;26(23)

Link: https://www.journalslibrary.nihr.ac.uk/hta/QOIZ6538#/abstract

Article 4

Harding C, Mossop H, Homer T, et al. Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial. *BMJ*. 2022;376:e068229. Published 2022 Mar 9. doi:10.1136/bmj-2021-0068229

Link: https://www.bmj.com/content/376/bmj-2021-0068229

Article 5

Muller AE, Verhaegh EM, Harbarth S, Mouton JW, Huttner A. Nitrofurantoin's efficacy and safety as prophylaxis for urinary tract infections: a systematic review of the literature and meta-analysis of controlled trials. Clin Microbiol Infect. 2017 Jun;23(6):355-362. doi: 10.1016/j.cmi.2016.08.003. Epub 2016 Aug 17. PMID: 27542332.

Link: https://linkinghub.elsevier.com/retrieve/pii/S1198-743X(16)30304-4