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Methenamine Hippurate for the Management and Prophylaxis of Recurrent Urinary Tract Infections: a Scoping Review Protocol

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Abstract

Introduction: Recurrent urinary tract infections (rUTIs) are typically treated using antibiotics. Given the growing issue of antimicrobial resistance, nonantibiotic management options for rUTIs have faced a recent resurgence in popularity. Methenamine hippurate is a urinary antiseptic used as a nonantibiotic prophylactic measure in those with rUTIs. The results of a recent randomised controlled trial showed methenamine hippurate to perform on par with antibiotic prophylaxis in adult women with rUTIs. However, little is known about the efficacy of methenamine hippurate in vulnerable patient populations, such as children, the elderly, patients with indwelling catheters and those with renal tract abnormalities. Moreover, an up-to-date, comprehensive evaluation of the entirety of the literature surrounding methenamine hippurate has yet to be carried out. As such, key trends within the literature, such as common side effects and specific avenues for future research, are difficult to determine. Therefore, we developed the methodology for a scoping review to map the entirety of the existing evidence base for methenamine hippurate.

Methods and analysis: The protocol for this scoping review was developed in accordance with the framework set out by Arksey and O'Malley. We will search MEDLINE, Embase, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception until August 2024, with no language restrictions applied. Studies including patients of any age and sex receiving methenamine hippurate treatment, either as a primary or adjunct treatment for recurrent Urinary Tract Infections, will be eligible for inclusion. Interventional studies, such as randomised controlled trials and their protocols, non-randomised clinical trials, cohort studies, case-control studies and observational studies of any design will be included. Two independent reviewers blinded to each other's decisions will assess the eligibility of articles at each stage using the Covidence review platform. After the relevant data from each study has been extracted, we will report the results of our scoping review using descriptive summary statistics and a narrative thematic analysis.

Ethics and dissemination: Ethical approval was not required for this scoping review. The final manuscript of this scoping review will be published in an international, peer-reviewed journal, and the findings of the review presented in relevant national and international conferences.

Data sources/availability statement: No public dataset was used in the creation of this manuscript.

This scoping review was prospectively registered on the Open Science Framework (OSF): https://doi.org/10.17605/OSF.IO/NWMB8.

Strengths and Limitations

- The primary aim of our scoping review is novel; we aim to map the entirety of the evidence base and identify gaps in knowledge regarding methenamine hippurate's use as a nonantibiotic management option for rUTIs, with a particular focus on the patient populations methenamine hippurate has so far been evaluated in.
- The methodology for this scoping review was developing in accordance with the frameworks set out by Arksey and O'Malley in 2005 and further expanded upon by Levac et al. in 2010 and the Joanna Briggs Institute in 2021.
- In order to capture the full breadth of the evidence base, we developed database-specific search strategies and did not restrict our searches to any particular language or time period.
- We will not assess the weight (by conducting a meta-analysis, for example) or quality of the identified evidence, as this falls outside of the purview of a scoping review.

Introduction

Urinary tract infections (UTIs) are one of the most common forms of bacterial infection worldwide (1). UTIs can be classified as affecting the upper or lower urinary tract (2). In the absence of comorbidities or renal tract abnormalities, UTIs are classified as being uncomplicated; in their presence, a UTI is considered complicated (2). Approximately 50-60% of all women will experience a UTI in their lifetime (3). A recurrent UTI (rUTI) is defined as two or more UTIs in a 6-month period, or three or more UTIs within one year (4). Whilst the true prevalence is difficult to determine, it is thought that 20-30% of women with a UTI will experience a recurrence (5). In addition to impairments in quality of life for an individual, rUTIs also exert a significant psychological burden on a patient as well as an economic burden on the broader healthcare system (5). The gold standard treatment for rUTIs is daily low-dose antibiotic suppression (1). However, given the ever-developing issue of antimicrobial resistance (6), there is a growing interest in nonantibiotic management options for rUTIs.

One such nonantibiotic management option for rUTIs is methenamine hippurate. Preparations of methenamine, a cyclic hydrocarbon, have been utilised as a urinary antiseptic for decades (7, 8). In the environment of acidic urine, a salt preparation of methenamine degrades to form ammonia and formaldehyde; the latter is thought to act as a bacteriostatic agent by inhibiting bacterial cell division (9). Methenamine hippurate is often thought to have gone overlooked by most clinicians (10), with most guidelines providing no strong recommendation regarding the use of methenamine hippurate for long-term rUTI prevention in women (11). Nonetheless, methenamine hippurate is widely prescribed in some Scandinavian countries (12), particularly in Norway (13). Following the resolution of a four-month drug shortage of methenamine hippurate in Norway, the number of prescriptions for methenamine hippurate rose as prescriptions for UTI antibiotics fell sharply (14).

Recently, methenamine hippurate has faced a resurgence in popularity. The ALTAR non-inferiority randomised controlled trial (RCT) found methenamine hippurate to be equivalent to antibiotic therapy at reducing the incidence of rUTIs in a large cohort of adult women (12). Two recent systematic reviews of the literature, similarly focused on adult women with uncomplicated rUTIs, identified that methenamine hippurate performed on-par with antibiotic prophylaxis (15, 16). Recent reviews, both systematic reviews and those looking broadly at nonantibiotic treatments for rUTIS (7, 8), have not investigated the efficacy of methenamine hippurate in vulnerable patient populations. rUTIs are a common problem in the elderly, and diagnosis and management can prove to be challenging in the presence of multiple comorbidities, contraindications to antibiotic treatment and the increased risk of *clostridium difficile* infections due to prolonged antibiotic use (17-19). Indeed, elderly women are particularly vulnerable to UTIs, with the prevalence of UTIs being almost three-fold higher in this population (4). In children, long-term infection of the urinary

tract can have, albeit rare, negative consequences on kidney function in later life (20), and long-term prophylactic antibiotic regimens are typically not recommended (21). Moreover, patients with indwelling catheters are at greater risk for developing bacteriuria and subsequent catheter related UTIs (22, 23). It is unclear to what extent the literature has evaluated methenamine hippurate's viability in these vulnerable patient subgroups.

In the existing literature, a Cochrane review of RCTs last updated in 2012 did identify a number of studies that evaluated methenamine hippurate's effectiveness in diverse populations of patients with both complicated and uncomplicated UTIs (24). Given methenamine hippurate's recent resurgence in popularity, an updated review of the literature is warranted. Moreover, non-randomised studies, cohort studies and institutional experiences have likely gone overlooked by systematic reviews of RCTs (15, 16) and reviews of only the most recent evidence (25, 26). As a result, there is difficulty in ascertaining the necessity of systematic reviews focusing on methenamine hippurate's efficacy in the aforementioned subgroups; indeed, it is unclear whether the recent evidence base has evaluated methenamine hippurate's effectiveness in these patients at all. These knowledge gaps are the primary focuses of our scoping review.

Scoping reviews are conducted to identify a breadth of studies within a field of research (27, 28). Scoping reviews can be applicable to any domain, including the implementation of healthcare practices (29), surgical procedures (30) or the effects of a particular medication (31, 32), and employ a systematic methodology but forego a subsequent meta-analyses in favour of characterising the breadth of and trends within the extant literature (27, 28). Scoping reviews are commonly used to identify whether systematic reviews, which typically focus on a specific patient population, are warranted (33). As such, scoping reviews are perfectly suited to both characterise a broad evidence base and, as a result, to identify gaps that exist. Thus, we identified that a scoping review framework provided a methodologically sound, systematic method to characterise and summarise the evidence surrounding methenamine hippurate. To date, a rigorous, inclusive assessment of methenamine hippurate's evidence base has yet to be undertaken.

We will conduct a scoping review to systematically map the existing evidence base surrounding methenamine Hippurate as a treatment for or prophylactic measure against rUTIs. Assessing the literature in this holistic manner will allow for identification of patient populations that have and have not been evaluated in the literature thus far. Our work will identify avenues for future research into methenamine hippurate's efficacy in these patient subgroups, including focused systematic reviews and novel RCTs. Moreover, we will characterise how methenamine Hippurate has been evaluated up until now, including whether it is more commonly utilised as a standalone medication for prophylaxis, alongside antibiotics, or alongside other nonantiobiotic treatments for rUTIs. Moreover, no review to date

has yet covered in detail whether methenamine hippurate can utilised to prevent postoperative UTIs or to manage or prevent bacteriuria. By characterising the literature in this rigorous, detailed manner, we seek to provide specific suggestions to guide future research. In this paper, we outline the methodological approach of our scoping review in keeping with the guidance originally set out by Arksey and O'Malley (27) and further expanded upon by Levac et al. (34) and the Joanna Briggs Institute (28). The framework for this protocol outlines our approach to the four stages of a scoping review (27): identifying the research questions, identifying relevant studies, study selection and reporting the data. This scoping review protocol was prospectively registered on the Open Science Framework (OSF) (https://doi.org/10.17605/OSF.IO/NWMB8).

Methods

This protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews checklist (PRISMA-ScR) (35) (Supplementary File 1).

Research questions

As outlined by Arksey and O'Malley (27), the first stage of conducting a scoping review involves identifying the pertinent research questions. Based on our understanding of the current evidence surrounding methenamine hippurate as a management option for rUTIs, we developed the following research questions that our scoping review seeks to address:

1. In what patient populations has the efficacy of methenemaine hippurate already been investigated and, conversely, in what patient demographics is there a lack of research into the efficacy of methenamine hippurate for the management of rUTIs?
2. In what manner is methenamine hippurate evaluated? I.e., as a standalone prophylactic measure, an adjunct to antibiotic treatment or alongside other nonantibiotic treatments for rUTI?
3. What dosage of and over what time course is methenamine hippurate commonly given in the extant literature, and does this vary between studies?
4. What are the commonly reported side effects of methenamine hippurate?
5. What are the geographical and temporal trends in research investigating the efficacy of methenamine hippurate? In other words, is methenamine hippurate evidently more popular in certain countries, and is there a reason for this?

Study Selection

In order to identify potentially eligible studies for inclusion in our scoping review, we will conduct a systematic search of four databases: MEDLINE, Embase, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL). A thorough search strategy for each database was developed using key terms identified from our research questions and Medical Subject Heading (MeSH) terms and was adapted to suit each database accordingly using the appropriate Boolean operators, database-specific MeSH terms and database-specific syntax (Supplementary File 2). Key terms included but were not limited to 'methenamine hippurate', 'recurrent urinary tract infections', 'rUTIs' and 'urinary tract infections'. The polyglot search translator was used to aid the process of constructing the search strategy. Databases will be searched from inception up until 10th August 2024, and no language filters will be applied. Prior to the final analysis, the searches will be re-run up until the present day and any additional studies meeting the eligibility criteria will be included. Unpublished studies will not be sought. In addition to database searching, citations of relevant articles will be manually exported and included within the screening process. For studies not given in the English language, a suitable translated version will be sought, either from the authors themselves or using Google's inbuilt translation software.

Eligibility criteria

Identified studies will be assessed for eligibility using the Population, Concept and Context (PCC) framework set out by Arksey and O'Malley (27) and the Joanna Brigg's Institute (28). The full details of the inclusion and exclusion criteria are provided in Table 1.

Table 1: Inclusion and Exclusion criteria for assessing eligibility of studies

	Inclusion Criteria	Exclusion Criteria
Population	• Studies including patients of any age and sex. • This includes the adult population (>18) and the paediatric population (<18). • Our inclusion criteria is **not** limited to patients of any age, sex or those with any specific comorbidities.	• Studies conducted in non-human participants (e.g *in vivo* research) and *in vitro* research.

Concept	• Patients given methenamine hippurate for the prophylaxis and/or management of rUTIs. • Patients given methenamine hippurate for the postoperative prevention of UTIs or the prevention/management of recurrent bacteriuria. • Patients with Urinary Tract Infections (UTIs) of any aetiology (complicated, uncomplicated, upper and lower). • We will include studies that utilise methenamine hippurate as a control arm or as an adjunct medication (alongside, for example, conventional antibiotic prophylactic therapy).	• Studies involving patients given methenamine hippurate for any indication other than rUTIs (as defined by the study), UTI prevention/prophylaxis or bacteriuria. • Studies that focus exclusively on other nonantibiotic treatments for rUTIs, e.g. cranberry products or D-mannose not utilised alongside methenamine hippurate.
Context	• Studies conducted in the hospital or community setting, in patients of any age or demographic. • Studies reporting an outcome measure related to rUTIs; this includes but is not limited to the frequency, duration, the growth of drug-resistant bacteria, and adverse side effects.	• Qualitative studies exclusively investigating personal views or satisfaction with a treatment regimen of methenamine hippurate.

Study Type	• Randomised Controlled Trials (RCTs) • Protocols for ongoing RCTs • Cohort studies • Case-Control studies • Observational studies • Non-randomised clinical trials • Protocols for planned or ongoing trials	• *in vitro* studies • Case reports and case series < 5 patients • Letters, Editorials, and short communications • Systematic reviews and literature reviews • Abstracts and conference proceedings • Rapid reviews

Study Selection

Retrieved articles from each database will be exported and uploaded to Covidence, a digital platform built to facilitate and streamline the process of carrying out systematic reviews (36). Firstly, duplicate articles will be removed. Remaining articles will undergo title and abstract screening as per the eligibility criteria (Table 1). This will be undertaken by two independent reviewers (AC, IA, FW, PN) who will be blinded to each other's decisions. A disagreement between reviewers will be resolved either via a third independent reviewer or by discussion amongst researchers. Included articles will then undergo full-text screening by two independent reviewers, again blinded to each other's decisions, with conflicts resolved by discussion amongst reviewers or, if this is unsuccessful, by a third reviewer. At the full-text review stage, the specific reason for exclusion will be recorded. The details of the screening process will be reported using a PRISMA flowchart (28).

Charting the data

Data will be extracted from each included study using a data extraction form. This data extraction form contains key information regarding each study, and was developed in line with our Population, Concept and Context framework. This includes but is not limited to information regarding the nature of the study design, the year of publication, whether patients were randomly assigned to a treatment or not, the characteristics of the included patients, the dosage and time course of methenamine hippurate treatment, UTI frequency pre- and post- intervention, outcome measures utilised and reported side effects. Further details of the data extraction fields are given in Table 2.

Table 2: Data extraction fields

Category	Data extraction fields
Study characteristics	• Study citation • Year of publication • Country of origin • Study design • Treatment allocation randomisation (Y/N) • Protocol for an ongoing study (Y/N)
Participant characteristics	• Control group characteristics (if applicable) • Intervention group characteristics • UTI aetiology control group (if applicable) • UTI aetiology intervention group • Control group sample size • Intervention group sample size • Follow-up time
Methenamine hippurate regimen	• Control group medication details (including dosage, adjunct therapy, time course) • Intervention group methenamine hippurate details (including dosage, adjunct therapy, time course)
Outcomes	• Outcome measure(s) utilised • Control group UTI frequency pre-intervention • Intervention group UTI frequency pre-intervention • Control group UTI frequency post intervention • Intervention group UTI frequency post intervention
Side effects	• Side effects reported (Y/N) • Details of reported minor side effects • Details of reported severe side effects • Minor side effects (individual and overall rate) • Severe side effects (individual and overall rate)

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This data extraction tool will be implemented into Covidence and initially piloted by two authors (AC, PN) on five included studies to internally assess its validity prior to the commencement of data extraction, in line with recommendations from Levac et al. in 2010 (34). If needed, the data extraction fields will be expanded upon or edited by the senior authors. Once this is complete, data extraction will be undertaken by one reviewer for each study (AC, IA, FW, PN) with a second independent author checking the extracted data against the original study. The data extraction process will be iterative and collaborative (34), with any disagreements or difficulty in extracting heterogenous data being resolved through discussion and consideration between the authors.

Collating, summarising, and reporting the results

After charting of the data, reporting of the results of a scoping review is separated into three phases (34): 1) Descriptive numerical summary analysis and qualitative thematic analysis, 2) Reporting the results in line with the research questions and 3) Discussion of the future implications of the findings of the scoping review.

Firstly, the extracted data will be exported as a CSV file to undergo further analysis. Data analysis will be undertaken using a combination of R (37) and Microsoft Excel. Initially, study characteristics will be grouped together (for example: methodological approach, patient characteristics, methenamine hippurate regimen, reported outcomes), tabularised and presented in the final manuscript. Where possible, we will calculate and present simple descriptive summary statistics (for example, the proportion of patients reporting side effects of methenamine hippurate across studies). We will use the extracted data to construct evidence maps and simple descriptive figures that will holistically outline the key trends and patterns within the extant literature surrounding methenamine hippurate. Depending on the nature and intrinsic heterogeneity of the extracted evidence, we may construct bar charts, line graphs, word clouds, network diagrams and conceptual frameworks, all popular methods of data visualisation within scoping reviews (38). Qualitative thematic analysis will also be undertaken. Key themes between studies will be identified by discussion amongst the reviewers, and these will be grouped in accordance with the research questions of our scoping review. These themes will be addressed in a narrative manner in the final manuscript and their implications for future research addressed accordingly.

Trial Status:

Preliminary searches: Started

Piloting of the study selection process: Started

Formal screening: Started

Data extraction: Not started

Data analysis: Not started

Ethics and dissemination

Ethical approval was not required for this scoping review. The final manuscript of this scoping review will be published in an international, peer-reviewed journal, and the findings of the review presented in relevant national and international conferences.

Patient and public involvement

There was neither patient nor public involvement in the development of this scoping review protocol.

Competing Interests

J M Norris has received funding from the MRC (UK) and RCSEng.

Data Availability Statement

No public dataset was used in the creation of this manuscript.

Author Statement

AC and PN were responsible for conceptualisation of the protocol. AC was responsible for the initial draft of the manuscript. IA, AAT, NC, KM, SB, DDC, NZ, JMN and PN provided feedback on the manuscript. All authors read and approved the final version of the manuscript. AC is the guarantor of the review.

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Table S1: Database-specific search strategies

Database	Search Strategy
MEDLINE	1 exp Mandelic Acids/ or Mandelic acid.mp. 2 exp Hippurates/ or Hippuric acid.mp. 3 Hexamine.mp. or exp Methenamine/ 4 methenamine.mp. 5 hexamethylenetetramine.mp. 6 aminoform.mp. 7 hexamethylenetetramine.mp. 8 hexamine silver.mp. 9 methenamine, silver.mp. 10 silver, hexamine.mp. 11 silver methenamine.mp. 12 urotropin.mp. 13 methenamine hippurate.mp. 14 haiprex.mp. 15 hipeksal.mp. 16 hippramine.mp. 17 hippuran.mp. 18 hip-Rex.mp. 19 urotractan.mp. 20 hexydal.mp. 21 lemandine.mp. 22 mandameth.mp. 23 mandelamine.mp. 24 metanamin.mp. 25 cystitis.mp. or exp Cystitis/ 26 urethritis.mp. or exp Urethritis/ 27 exp Pyelonephritis/ or pyelonephritis.mp. 28 (rUTI or rUTI*).mp. 29 Bacteriuria/ or bacteriurea.mp. 30 (recur* or ongoing or repeated or repeat* or recurrent).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 31 urinary tract infection.mp. 32 urinary tract infections.mp. or exp Urinary Tract Infections/ 33 31 or 32 34 30 and 33 35 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 36 25 or 26 or 27 or 28 or 29 or 31 or 32 or 34 37 35 and 36
Embase	1 mandelic acid.mp. or exp mandelic acid/ 2 hippuric acid.mp. or exp hippuric acid/ 3 Hexamine.mp. 4 hexamethylenetetramine.mp. 5 exp methenamine/ or exp methenamine hippurate/ or methenamine.mp. 6 methenamine hippurate.mp. 7 hiprex.mp. 8 urinary tract infection.mp. or exp urinary tract infection/ 9 UTI.mp. 10 rUTI.mp. 11 exp cystitis/ or cystitis.mp. 12 recur* UTI.mp. 13 bacteriuria.mp. or exp bacteriuria/ 14 urethritis.mp. or exp urethritis/ or exp nonspecific urethritis/

	15 pyelonephritis.mp. or exp pyelonephritis/ 16 (methenamine hippurate or methenamine or haiprex or hipeksal or hippramine or hippuran or hip-Rex or urotractan or hexydal or lemandine or mandameth or mandelamine or metanamin).mp. 17 hippurates.mp. or exp hippuric acid derivative/ 18 urinary tract infections.mp. 19 aminoform.mp. 20 aminoformaldehyde.mp. 21 ammoform.mp. 22 antihydral.mp. 23 cystamin.mp. 24 formamine.mp. 25 formin.mp. 26 hexaloid.mp. 27 hexamethylene tetramine.mp. 28 hexamethyleneamine.mp. 29 hexamethylenetetramine.mp. 30 hexamine.mp. 31 hexamine soap.mp. 32 methenamine hydrochloride.mp. 33 metramine.mp. 34 mictasol.mp. 35 naphthamine.mp. 36 uralysol.mp. 37 uraseptine.mp. 38 urisol.mp. 39 uritone.mp. 40 urogenine.mp. 41 urotropin.mp. 42 utropine.mp. 43 vesalvine.mp. 44 (recur* or ongoing or repeated or repeat* or recurrent).mp. 45 1 or 2 or 3 or 4 or 5 or 6 or 7 or 16 or 17 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 46 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 18 47 44 and 46 48 46 or 47 49 45 and 48
Scopus	(INDEXTERMS (methenamine) OR TITLE-ABS-KEY (hiprex) OR TITLE-ABS-KEY (hiprex) OR TITLE-ABS-KEY ("methenamine hippurate") OR TITLE-ABS-KEY (methenamine) OR TITLE-ABS-KEY (hiprex) OR TITLE-ABS-KEY (dispersal) OR TITLE-ABS-KEY (hippadine) OR TITLE-ABS-KEY (hippuran) OR TITLE-ABS-KEY (hip-rex) OR TITLE-ABS-KEY (neurotractin) OR TITLE-ABS-KEY (hexyl) OR TITLE-ABS-KEY (leueandine) OR TITLE-ABS-KEY (mandameth) OR TITLE-ABS-KEY (mandelamine) OR TITLE-ABS-KEY (metanamin) OR INDEXTERMS (hippurates) OR TITLE-ABS-KEY ("Hippuric acid") OR TITLE-ABS-KEY (hexamine) OR INDEXTERMS (methenamine)) AND (INDEXTERMS (bacteriuria) OR INDEXTERMS ("Urinary Tract Infections") OR TITLE-ABS-KEY (cystitis) OR INDEXTERMS (cystitis) OR TITLE-ABS-KEY (urethritis) OR INDEXTERMS (urethritis) OR TITLE-ABS-KEY (ruti) OR TITLE-ABS-KEY (ruti*) OR INDEXTERMS (pyelonephritis) OR TITLE-ABS-KEY (pyelonephritis) OR TITLE-ABS-KEY ("urinary tract infection") OR TITLE-ABS-KEY ("urinary tract infections") OR INDEXTERMS ("Urinary Tract Infections"))
Cochrane Central Register of Controlled Trials	#1 MeSH descriptor: [Methenamine] explode all trees #2 MeSH descriptor: [Bacteriuria] explode all trees #3 MeSH descriptor: [Cystitis] explode all trees #4 MeSH descriptor: [Pyelonephritis] explode all trees #5 MeSH descriptor: [Urinary Tract Infections] explode all tree

	#6 MeSH descriptor: [Urethritis] explode all trees #7 bacteriuria:ti,ab OR cystitis:ti,ab OR pyelonephritis:ti,ab OR urinary NEXT tract NEXT infection*:ti,ab OR UTI*:ti,ab OR urethritis:ti,ab #8 methenamine:ti,ab OR hiprex:ti,ab OR methenamine NEXT hippurate:ti,ab #9 #2 OR #3 OR #4 OR #5 OR #6 OR #7 #10 #1 OR #8 #11 #9 AND #10

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4-6
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	6-7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	6-7
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	2, 6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	6-7
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplementary File 1
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	8-9
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	10-11
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	9-10
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	10, 11

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	N/A
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	N/A
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	N/A
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	N/A
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	N/A
Limitations	20	Discuss the limitations of the scoping review process.	2
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	N/A
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	1

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

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Methenamine Hippurate for the Management and Prophylaxis of Recurrent Urinary Tract Infections: a Scoping Review Protocol

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Methenamine Hippurate for the Management and Prophylaxis of Recurrent Urinary Tract Infections: a Scoping Review Protocol

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Abstract

Introduction: Recurrent urinary tract infections (rUTIs) are typically treated using antibiotics. Given the growing issue of antimicrobial resistance, nonantibiotic management options for rUTIs have faced a recent resurgence in popularity. Methenamine hippurate is a urinary antiseptic used as a nonantibiotic prophylactic measure in those with rUTIs. The results of a recent randomised controlled trial showed methenamine hippurate to perform on par with antibiotic prophylaxis in adult women with rUTIs. However, little is known about the efficacy of methenamine hippurate in vulnerable patient populations, such as children, the elderly, patients with indwelling catheters and those with renal tract abnormalities. Moreover, an up-to-date, comprehensive evaluation of the entirety of the literature surrounding methenamine hippurate has yet to be carried out. As such, key trends within the literature, such as common side effects and specific avenues for future research, are difficult to determine. Therefore, we developed the methodology for a scoping review to map the entirety of the existing evidence base for methenamine hippurate.

Methods and analysis: The protocol for this scoping review was developed in accordance with the framework set out by Arksey and O'Malley. We will search MEDLINE, Embase, Scopus , the Cochrane Central Register of Controlled Trials (CENTRAL) and ProQuest Dissertation and Theses from inception until August 2024, with no language restrictions applied. Studies including patients of any age and sex receiving methenamine hippurate treatment, either as a primary or adjunct treatment for recurrent Urinary Tract Infections, will be eligible for inclusion. Interventional studies, such as randomised controlled trials and their protocols, non-randomised clinical trials, cohort studies, case-control studies and observational studies of any design will be included. Grey literature, systematic reviews and qualitative studies will also be included. Two independent reviewers blinded to each other's decisions will assess the eligibility of articles at each stage using the Covidence review platform. After the relevant data from each study has been extracted, we will report the results of our scoping review using descriptive summary statistics and a narrative thematic analysis.

Ethics and dissemination: Due to the nature of the present study, ethical approval was not required for this scoping review. The final manuscript of this scoping review will be published in an international, peer-reviewed journal, and the findings of the review presented in relevant national and international conferences.

Data sources/availability statement: No public dataset was used in the creation of this manuscript.

This scoping review was prospectively registered on the Open Science Framework (OSF): https://doi.org/10.17605/OSF.IO/NWMB8.

Strengths and Limitations

- The methodology for this scoping review was developed in accordance with the frameworks set out by Arksey and O'Malley in 2005, and further expanded upon by Levac et al. in 2010 and the Joanna Briggs Institute in 2021.
- In order to capture the full breadth of the evidence base, we developed database-specific search strategies and did not restrict our searches to any particular language or time period.
- We will not assess the weight (by conducting a meta-analysis, for example) of the identified evidence, as this falls outside of the purview of a scoping review.

Introduction

Urinary tract infections (UTIs) are one of the most common forms of bacterial infection worldwide [1]. UTIs can be classified as affecting the upper or lower urinary tract [2]. Lower UTIs in female patients can be classified as uncomplicated, provided they occur in the absence of comorbidities or renal tract abnormalities [2]. Lower UTIs in every other patient population, irrespective of existing comorbidities, are considered to be complicated [3]. Upper UTIs, regardless of the population in which they occur, are always considered to be complicated [2]. Approximately 50-60% of all women will experience a UTI in their lifetime [4]. A recurrent UTI (rUTI) is defined as two or more UTIs in a 6-month period, or three or more UTIs within one year [5]. Whilst the true prevalence is difficult to determine, it is thought that 20-30% of women with a UTI will experience a recurrence [6]. In addition to impairments in quality of life for an individual, rUTIs also exert a significant psychological burden on a patient as well as an economic burden on the broader healthcare system [6]. The role of antibiotics in rUTI management is prominent; acute treatment of each recurrence with antibiotics and prophylactic low-dose daily antibiotic suppression are both common mainstays of treatment [1]. However, given the ever-developing issue of antimicrobial resistance [7], there is a growing interest in nonantibiotic management options for rUTIs.

One such nonantibiotic management option for rUTIs is methenamine hippurate. Preparations of methenamine, a cyclic hydrocarbon, have been utilised as a urinary antiseptic for decades [8, 9]. In the environment of acidic urine, a salt preparation of methenamine degrades to form ammonia and formaldehyde; the latter is thought to act as a bacteriostatic agent by inhibiting bacterial cell division [10]. Methenamine hippurate is often thought to have gone overlooked by most clinicians [11], with most guidelines providing no strong recommendation regarding the use of methenamine hippurate for long-term rUTI prevention in women [12]. Nonetheless, methenamine hippurate is widely prescribed in some Scandinavian countries [13], particularly in Norway [14]. Following the resolution of a four-month drug shortage of methenamine hippurate in Norway, the number of prescriptions for methenamine hippurate rose as prescriptions for UTI antibiotics fell sharply [15].

Recently, methenamine hippurate has faced a resurgence in popularity. The ALTAR non-inferiority randomised controlled trial (RCT) found methenamine hippurate to be equivalent to antibiotic therapy at reducing the incidence of rUTIs in a large cohort of adult women [13]. Two recent systematic reviews of the literature, similarly focused on adult women with uncomplicated rUTIs, identified that methenamine hippurate performed on-par with antibiotic prophylaxis [16, 17]. Recent reviews, both systematic reviews and those looking broadly at nonantibiotic treatments for rUTIS [8, 9], have not investigated the efficacy of methenamine hippurate in vulnerable patient populations. rUTIs are a common problem in the elderly, and diagnosis and management can prove to be challenging in the presence of

multiple comorbidities, contraindications to antibiotic treatment and the increased risk of *clostridium difficile* infections due to prolonged antibiotic use [18-20]. Indeed, elderly women are particularly vulnerable to UTIs, with the prevalence of UTIs being almost three-fold higher in this population [5]. In children, long-term infection of the urinary tract can have, albeit rare, negative consequences on kidney function in later life [21], and long-term prophylactic antibiotic regimens are typically not recommended [22]. Moreover, patients with indwelling catheters are at greater risk for developing catheter related UTIs [23, 24]. It is unclear to what extent the literature has evaluated methenamine hippurate's viability in these vulnerable patient subgroups.

In the existing literature, a Cochrane review of RCTs last updated in 2012 did identify a number of studies that evaluated methenamine hippurate's effectiveness in diverse populations of patients with both complicated and uncomplicated UTIs [25]. Given methenamine hippurate's recent resurgence in popularity, an updated review of the literature is warranted. Moreover, non-randomised studies, cohort studies and institutional experiences have likely gone overlooked by systematic reviews of RCTs [16, 17] and reviews of only the most recent evidence [26, 27]. As a result, there is difficulty in ascertaining the necessity of systematic reviews focusing on methenamine hippurate's efficacy in the aforementioned subgroups; indeed, it is unclear whether the recent evidence base has evaluated methenamine hippurate's effectiveness in these patients at all. These knowledge gaps are the primary focuses of our scoping review.

Scoping reviews are conducted to identify a breadth of studies within a field of research [28, 29]. Scoping reviews can be applicable to any domain, including the implementation of healthcare practices [30], surgical procedures [31] or the effects of a particular medication [32, 33], and employ a systematic methodology but forego a subsequent meta-analyses in favour of characterising the breadth of and trends within the extant literature [28, 29]. Scoping reviews are commonly used to identify whether systematic reviews, which typically focus on a specific patient population, are warranted [34]. As such, scoping reviews are perfectly suited to both characterise a broad evidence base and, as a result, to identify gaps that exist. Thus, we identified that a scoping review framework provided a methodologically sound, systematic method to characterise and summarise the evidence surrounding methenamine hippurate. To date, a rigorous, inclusive assessment of methenamine hippurate's evidence base has yet to be undertaken.

We will conduct a scoping review to systematically map the existing evidence base surrounding methenamine Hippurate as a treatment for or prophylactic measure against rUTIs. Assessing the literature in this holistic manner will allow for identification of patient populations that have and have not been evaluated in the literature thus far. Our work will identify avenues for future research into methenamine hippurate's efficacy in these patient subgroups, including focused systematic reviews and novel RCTs. Moreover, we will characterise how methenamine Hippurate

has been evaluated up until now, including whether it is more commonly utilised as a standalone medication for prophylaxis, alongside antibiotics, or alongside other nonantiobiotic treatments for rUTIs. Moreover, no review to date has yet covered in detail whether methenamine hippurate can be utilised to prevent UTIs postoperatively, or to prevent catheter associated UTIs. By characterising the literature in this rigorous, detailed manner, we seek to provide specific suggestions to guide future research. In this paper, we outline the methodological approach of our scoping review in keeping with the guidance originally set out by Arksey and O'Malley [28] and further expanded upon by Levac et al. [35] and the Joanna Briggs Institute [29]. The framework for this protocol outlines our approach to the four stages of a scoping review [28]: identifying the research questions, identifying relevant studies, study selection and reporting the data. This scoping review protocol was prospectively registered on the Open Science Framework (OSF) (https://doi.org/10.17605/OSF.IO/NWMB8).

Methods

This protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews checklist (PRISMA-ScR) [36] (Supplementary File 1).

Research questions

As outlined by Arksey and O'Malley [28], the first stage of conducting a scoping review involves identifying the pertinent research questions. Based on our understanding of the current evidence surrounding methenamine hippurate as a management option for rUTIs, we developed the following research questions that our scoping review seeks to address:

1. In what patient populations has the efficacy of methenemaine hippurate already been investigated and, conversely, in what patient demographics is there a lack of research into the efficacy of methenamine hippurate for the management of rUTIs?
2. How effective is methenamine hippurate in managing rUTIs in these patients (as defined by each study's endpoints), and does its efficacy vary between different patient populations?
3. In what manner is methenamine hippurate evaluated? I.e., as a standalone prophylactic measure, an adjunct to antibiotic treatment or alongside other nonantibiotic treatments for rUTIs?
4. What dosage of and over what time course is methenamine hippurate commonly given in the extant literature, and does this vary between studies?
5. What are the commonly reported side effects of methenamine hippurate?

6. What are the geographical and temporal trends in research investigating the efficacy of methenamine hippurate? In other words, is methenamine hippurate evidently more popular in certain countries, and is there a reason for this?

Search strategy

In order to identify potentially eligible studies for inclusion in our scoping review, we will conduct a systematic search of four databases: MEDLINE, Embase, Scopus, the Cochrane Central Register of Controlled Trials (CENTRAL) and ProQuest Dissertation and Theses Global. A thorough search strategy for each database was developed using key terms identified from our research questions and Medical Subject Heading (MeSH) terms and was adapted to suit each database accordingly using the appropriate Boolean operators, database-specific MeSH terms and database-specific syntax (Supplementary File 2, Table S1). Key terms included but were not limited to 'methenamine hippurate', 'recurrent urinary tract infections', 'rUTIs' and 'urinary tract infections'. The polyglot search translator was used to aid the process of constructing the search strategy. Databases will be searched from inception up until 10th August 2024, and no language filters will be applied. Prior to the final analysis, the searches will be re-run up until the present day and any additional studies meeting the eligibility criteria will be included. Unpublished studies will not be sought. In addition to database searching, citations of relevant articles will be manually exported and included within the screening process. For studies not given in the English language, a suitable translated version will be sought, either from the authors themselves or using Google's inbuilt translation software.

Identification of eligible studies

Identified studies will be assessed for eligibility using the Population, Concept and Context (PCC) framework set out by Arksey and O'Malley [28] and the Joanna Brigg's Institute [29]. With respect to the population, we will include studies investigating patients with rUTIs, with the strict definition of rUTI being defined by each study individually. Owing to the broad nature of our scoping review, we will include studies investigating both adult (>16) and paediatric (<16) patients with both complicated and uncomplicated rUTIs receiving methenamine hippurate for UTI prophylaxis (i.e. long-term). We will also include studies where methenamine hippurate is used as an adjunct (e.g. alongside conventional antibiotics) or as a control arm. As methodology is likely to be heterogenous between studies, we have no specific exclusion criteria relating to a comparator; this may be a placebo, conventional antibiotic suppression or no treatment at all. Studies investigating methenamine hippurate for UTI prophylaxis, for example, following surgery or in those with long-term catheters (irrespective of whether these patients have a history of rUTIs or not) will also be included. We will exclude studies conducted exclusively *in vitro* and in non-human participants. Studies in which

patients are given methenamine hippurate for any indication other than rUTI management or UTI prophylaxis will be similarly excluded.

With regards to the context, we will include studies conducted in any healthcare or community setting. We will also include grey literature (in the form of conference abstracts) and systematic reviews of the literature (irrespective of whether a subsequent meta-analysis was undertaken). In order to capture the full breadth of the evidence base, qualitative studies investigating patient or clinician perspectives on methenamine hippurate will also be included. Narrative literature reviews, case reports and case series with fewer than 5 patients and research letters containing no novel research will be excluded. The full details of the inclusion and exclusion criteria are provided in Table 1.

Table 1: Inclusion and Exclusion criteria for assessing eligibility of studies

	Inclusion Criteria	Exclusion Criteria
Population	• Male, female, and paediatric patients with recurrent Urinary Tract Infections (rUTIs). • Male, female, and paediatric patients at higher risk for UTIs (e.g. postoperatively, or with indwelling or long-term catheters) who are eligible for UTI prophylaxis.	• Studies conducted in non-human participants (e.g *in vivo* research) and *in vitro* research.
Concept	• Patients given methenamine hippurate for the prophylaxis and/or management of rUTIs. • Patients at higher risk for UTIs (such as those with long-term catheters, or postoperatively) receiving methenamine hippurate for UTI prophylaxis.	• Studies involving patients given methenamine hippurate for any indication other than rUTIs (for example, exclusively asymptomatic bacteriuria) or UTI prophylaxis. • Studies that focus exclusively on other nonantibiotic treatments for rUTIs, e.g. cranberry products or D-mannose not

	• We will include studies that utilise methenamine hippurate as a control arm or as an adjunct medication (alongside, for example, conventional antibiotic prophylactic therapy).	utilised alongside methenamine hippurate.
Context	• Studies conducted in primary (e.g. patients in the community), secondary (e.g. hospitalised patients) and tertiary care (e.g. specialist centres) settings will be included. • Studies conducted in ambulatory care settings, pharmacies and nursing homes will also be included. • Studies must report an outcome measure related to rUTIs; this includes but is not limited to the frequency, duration, the growth of drug-resistant bacteria, and adverse side effects. • Qualitative studies exclusively investigating personal views or satisfaction with a treatment regimen of methenamine hippurate, from either the patient or provider perspective. • Systematic reviews of the literature regarding methenamine hippurate.	• Narrative (i.e. lacking systematic review methodology, including formal database searching and prospective registration in the PROSPERO database) reviews of the literature surrounding methenamine hippurate.

Study Type	• Randomised Controlled Trials (RCTs) • Protocols for ongoing RCTs • Cohort studies • Case-Control studies • Observational studies • Non-randomised clinical trials • Protocols for planned or ongoing trials/studies • Qualitative studies • Systematic reviews (with or without accompanying meta-analyses) of the literature • Conference abstracts	• *in vitro* studies • Case reports and case series < 5 patients • Letters, Editorials, and short communications • Narrative (i.e. non-systematic) reviews of the literatures • Rapid reviews

Retrieved articles from each database will be exported and uploaded to Covidence, a digital platform built to facilitate and streamline the process of carrying out systematic reviews [37]. Firstly, duplicate articles will be removed. Remaining articles will undergo title and abstract screening as per the eligibility criteria (Table 1). This will be undertaken by two independent reviewers (AC, IA, FW, PN) who will be blinded to each other's decisions. A disagreement between reviewers will be resolved either via a third independent reviewer or by discussion amongst researchers. Included articles will then undergo full-text screening by two independent reviewers, again blinded to each other's decisions, with conflicts resolved by discussion amongst reviewers or, if this is unsuccessful, by a third reviewer. At the full-text review stage, the specific reason for exclusion will be recorded. The details of the screening process will be reported using a PRISMA flowchart [29].

Charting the data

Data will be extracted from each included study using a data extraction form. This data extraction form contains key information regarding each study, and was developed in line with our Population, Concept and Context framework. This includes but is not limited to information regarding the nature of the study design, the year of publication, whether patients were randomly assigned to a treatment or not, the characteristics of the included patients, the dosage and time course of methenamine hippurate treatment, UTI frequency pre- and post- intervention, outcome

measures utilised and reported side effects (Table 2). Data from included qualitative studies and systematic reviews will be extracted using separate data extraction forms (Supplementary File 2, Tables S2 and S3 respectively) owing to their distinct methodology.

Table 2: Data extraction fields

Category	Data extraction fields
Study characteristics	• Study citation • Year of publication • Country of origin • Study design • Treatment allocation randomisation (Y/N) • Protocol for an ongoing study (Y/N)
Participant characteristics	• Control group characteristics (if applicable) • Intervention group characteristics • UTI aetiology control group (if applicable) • UTI aetiology intervention group • Control group sample size • Intervention group sample size • Follow-up time
Methenamine hippurate regimen	• Control group medication details (including dosage, adjunct therapy, time course) • Intervention group methenamine hippurate details (including dosage, adjunct therapy, time course)
Outcomes	• Outcome measure(s) utilised • Control group UTI frequency pre-intervention • Intervention group UTI frequency pre-intervention • Control group UTI frequency post intervention • Intervention group UTI frequency post intervention
Side effects	• Side effects reported (Y/N) • Details of reported minor side effects

	• Details of reported severe side effects • Minor side effects (individual and overall rate) • Severe side effects (individual and overall rate)

This data extraction tool will be implemented into Covidence and initially piloted by two authors (AC, PN) on five included studies to internally assess its validity prior to the commencement of data extraction, in line with recommendations from Levac et al. in 2010 [35]. If needed, the data extraction fields will be expanded upon or edited by the senior authors. Once this is complete, data extraction will be undertaken by one reviewer for each study (AC, IA, FW, PN) with a second independent author checking the extracted data against the original study. The data extraction process will be iterative and collaborative [35], with any disagreements or difficulty in extracting heterogenous data being resolved through discussion and consideration between the authors. In addition to extracting data from each study, we will also assess the quality of included trials and observational studies. This will be conducted in duplicate for each study (AC, IA, FW, PN), with any disagreements being resolved by consensus amongst reviewers. For Randomised Controlled Trials (RCTs), the Cochrane Risk of Bias 2 (RoB 2) tool will be used [38]. For non-randomised trials, the Risk of Bias in non-randomised studies – of interventions (ROBINS-I) tool will be utilised [39].

Collating, summarising, and reporting the results

After charting of the data, reporting of the results of a scoping review is separated into three phases [35]: 1) Descriptive numerical summary analysis and qualitative thematic analysis, 2) Reporting the results in line with the research questions and 3) Discussion of the future implications of the findings of the scoping review.

Firstly, the extracted data will be exported as a CSV file to undergo further analysis. Data analysis will be undertaken using a combination of R [40] and Microsoft Excel. Initially, study characteristics will be grouped together (for example: methodological approach, patient characteristics, methenamine hippurate regimen, reported outcomes), tabularised and presented in the final manuscript. Where possible, we will calculate and present simple descriptive summary statistics (for example, the proportion of patients reporting side effects of methenamine hippurate across studies). We will use the extracted data to construct evidence maps and simple descriptive figures that will holistically outline the key trends and patterns within the extant literature surrounding methenamine hippurate. Depending on the nature and intrinsic heterogeneity of the extracted evidence, we may construct bar charts, line graphs, word clouds, network diagrams and conceptual frameworks, all popular methods of data visualisation within scoping reviews [41]. Qualitative thematic analysis will also be undertaken. Key themes between studies will be identified by discussion

amongst the reviewers, and these will be grouped in accordance with the research questions of our scoping review. These themes will be addressed in a narrative manner in the final manuscript and their implications for future research addressed accordingly.

Trial Status:

Preliminary searches: Started

Piloting of the study selection process: Started

Formal screening: Started

Data extraction: Not started

Data analysis: Not started

Study start date: 1st July 2025

Anticipated completion date: 1st January 2026

Ethics and dissemination

Due to the nature of the present study, ethical approval was not required for this scoping review. The final manuscript of this scoping review will be published in an international, peer-reviewed journal, and the findings of the review presented in relevant national and international conferences.

Patient and public involvement

There was neither patient nor public involvement in the development of this scoping review protocol.

Competing Interests

J M Norris has received funding from the MRC (UK) and RCSEng. All other authors have no competing interests to declare.

Data Availability Statement

No public dataset was used in the creation of this manuscript.

Author Statement

AC, JMN and PN were responsible for conceptualisation of the protocol. AC was responsible for the initial draft of the manuscript. IA, AAT, NC, KM, SB, DDC, NZ, and PN provided feedback on the manuscript. All authors read and approved the final version of the manuscript. AC is the guarantor of the review.

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4-6
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	7
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	8-11
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	8
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplementary File 1
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	8-9
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	12-13
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	9-10
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	13
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	11-14

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	N/A
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	N/A
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	N/A
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	N/A
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	N/A
Limitations	20	Discuss the limitations of the scoping review process.	4
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	N/A
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	1

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Table S1: Database-specific search strategies

Database	Search Strategy
MEDLINE	1 exp Mandelic Acids/ or Mandelic acid.mp. 2 exp Hippurates/ or Hippuric acid.mp. 3 Hexamine.mp. or exp Methenamine/ 4 methenamine.mp. 5 hexamethylenetetramine.mp. 6 aminoform.mp. 7 hexamethylenetetramine.mp. 8 hexamine silver.mp. 9 methenamine, silver.mp. 10 silver, hexamine.mp. 11 silver methenamine.mp. 12 urotropin.mp. 13 methenamine hippurate.mp. 14 haiprex.mp. 15 hipeksal.mp. 16 hippramine.mp. 17 hippuran.mp. 18 hip-Rex.mp. 19 urotractan.mp. 20 hexydal.mp. 21 lemandine.mp. 22 mandameth.mp. 23 mandelamine.mp. 24 metanamin.mp. 25 cystitis.mp. or exp Cystitis/ 26 urethritis.mp. or exp Urethritis/ 27 exp Pyelonephritis/ or pyelonephritis.mp. 28 (rUTI or rUTI*).mp. 29 Bacteriuria/ or bacteriurea.mp. 30 (recur* or ongoing or repeated or repeat* or recurrent).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 31 urinary tract infection.mp. 32 urinary tract infections.mp. or exp Urinary Tract Infections/ 33 31 or 32 34 30 and 33 35 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 36 25 or 26 or 27 or 28 or 29 or 31 or 32 or 34 37 35 and 36 (*598 articles)*
Embase	1 mandelic acid.mp. or exp mandelic acid/ 2 hippuric acid.mp. or exp hippuric acid/ 3 Hexamine.mp. 4 hexamethylenetetramine.mp. 5 exp methenamine/ or exp methenamine hippurate/ or methenamine.mp. 6 methenamine hippurate.mp. 7 hiprex.mp. 8 urinary tract infection.mp. or exp urinary tract infection/ 9 UTI.mp. 10 rUTI.mp. 11 exp cystitis/ or cystitis.mp. 12 recur* UTI.mp. 13 bacteriuria.mp. or exp bacteriuria/ 14 urethritis.mp. or exp urethritis/ or exp nonspecific urethritis/ 15 pyelonephritis.mp. or exp pyelonephritis/ 16 (methenamine hippurate or methenamine or haiprex or hipeksal or hippramine or hippuran or hip-Rex or urotractan or hexydal or lemandine or mandameth or mandelamine or metanamin).mp. 17 hippurates.mp. or exp hippuric acid derivative/ 18 urinary tract infections.mp. 19 aminoform.mp.

	20 aminoformaldehyde.mp. 21 ammoform.mp. 22 antihydral.mp. 23 cystamin.mp. 24 formamine.mp. 25 formin.mp. 26 hexaloid.mp. 27 hexamethylene tetramine.mp. 28 hexamethyleneamine.mp. 29 hexamethylenetetramine.mp. 30 hexamine.mp. 31 hexamine soap.mp. 32 methenamine hydrochloride.mp. 33 metramine.mp. 34 mictasol.mp. 35 naphthamine.mp. 36 uralysol.mp. 37 uraseptine.mp. 38 urisol.mp. 39 uritone.mp. 40 urogenine.mp. 41 urotropin.mp. 42 utropine.mp. 43 vesalvine.mp. 44 (recur* or ongoing or repeated or repeat* or recurrent).mp. 45 1 or 2 or 3 or 4 or 5 or 6 or 7 or 16 or 17 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 46 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 18 47 44 and 46 48 46 or 47 49 45 and 48 *(1094 articles)*
Scopus	(INDEXTERMS (methenamine) OR TITLE-ABS-KEY (hiprex) OR TITLE-ABS-KEY (hiprex) OR TITLE-ABS-KEY ("methenamine hippurate") OR TITLE-ABS-KEY (methenamine) OR TITLE-ABS-KEY (hiprex) OR TITLE-ABS-KEY (dispersal) OR TITLE-ABS-KEY (hippadine) OR TITLE-ABS-KEY (hippuran) OR TITLE-ABS-KEY (hip-rex) OR TITLE-ABS-KEY (neurotractin) OR TITLE-ABS-KEY (hexyl) OR TITLE-ABS-KEY (leueandine) OR TITLE-ABS-KEY (mandameth) OR TITLE-ABS-KEY (mandelamine) OR TITLE-ABS-KEY (metanamin) OR INDEXTERMS (hippurates) OR TITLE-ABS-KEY ("Hippuric acid") OR TITLE-ABS-KEY (hexamine) OR INDEXTERMS (methenamine)) AND (INDEXTERMS (bacteriuria) OR INDEXTERMS ("Urinary Tract Infections") OR TITLE-ABS-KEY (cystitis) OR INDEXTERMS (cystitis) OR TITLE-ABS-KEY (urethritis) OR INDEXTERMS (urethritis) OR TITLE-ABS-KEY (ruti) OR TITLE-ABS-KEY (ruti*) OR INDEXTERMS (pyelonephritis) OR TITLE-ABS-KEY (pyelonephritis) OR TITLE-ABS-KEY ("urinary tract infection") OR TITLE-ABS-KEY ("urinary tract infections") OR INDEXTERMS ("Urinary Tract Infections")) *(1108 articles)*
Cochrane Central Register of Controlled Trials	#1 MeSH descriptor: [Methenamine] explode all trees #2 MeSH descriptor: [Bacteriuria] explode all trees #3 MeSH descriptor: [Cystitis] explode all trees #4 MeSH descriptor: [Pyelonephritis] explode all trees #5 MeSH descriptor: [Urinary Tract Infections] explode all tree #6 MeSH descriptor: [Urethritis] explode all trees #7 bacteriuria:ti,ab OR cystitis:ti,ab OR pyelonephritis:ti,ab OR urinary NEXT tract NEXT infection*:ti,ab OR UTI*:ti,ab OR urethritis:ti,ab #8 methenamine:ti,ab OR hiprex:ti,ab OR methenamine NEXT hippurate:ti,ab #9 #2 OR #3 OR #4 OR #5 OR #6 OR #7 #10 #1 OR #8 #11 #9 AND #10 *(79 articles)*
ProQuest Dissertation and Theses	((methenamine OR "methenamine hippurate" OR hiprex OR hexamine OR "methenamine mandelate" OR "methenamine hippurate" OR haiprex) AND (bacteriuria OR cystitis OR pyelonephritis OR urethritis OR "urinary tract infection" OR "urinary tract infections" OR UTI OR UTIs OR "recurrent urinary tract infections")) *(247 articles)*

Table S2: Data extraction fields for systematic reviews

Category	Data Extraction Fields
Study characteristics	• Study citation • Year of publication • Country of origin • PROSPERO ID • Databases searched • Search period • Key research questions as per protocol/final text
Eligibility (PCC framework)	• Inclusion criteria relating to population (i.e. patients, and indication for antimicrobial treatment) • Exclusion criteria relating to population • Inclusion criteria relating to concept (i.e. intervention – methenamine hippurate regimen) • Exclusion criteria relating to concept • Inclusion criteria related to context (i.e. study setting) • Exclusion criteria related to context
Outcomes	• Total number of retrieved articles • Number of articles included • Key outcomes interpreted, including relevant summary statistics • Key conclusions from review
Meta-analysis	• Was a meta-analysis conducted? (Y/N) • Description of meta-analysis (narrative) and primary effects (eg. Odds ratios, Risk ratios, standardised mean differences) obtained from pooled results and accompanying markers of between-study heterogeneity.

Table S3: Data extraction fields for qualitative studies

Category	Data extraction fields
Study characteristics	• Study citation • Year of publication • Country of origin
Description of source population	• Description of source population as per the PCC framework • Origin of population (e.g. primary or secondary care) • Sampling method and recruitment time frame
Questionnaire methodology	• Modality of questionnaire dissemination • Response rate (%) including proportion of partial and complete responses, if applicable • Key outcomes investigated within questionnaire
Outcomes	• Narrative description of key results with relevant summary statistics and between-group differences