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Efficacy of carbapenems and alternative antimicrobials for treating complicated urinary tract infections caused by antimicrobial-resistant Gram-negative bacteria: Protocol for a systematic review and meta-analysis

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Efficacy of carbapenems and alternative antimicrobials for treating complicated urinary tract infections caused by antimicrobial-resistant Gram-negative bacteria: Protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Complicated urinary tract infections (cUTIs) are associated with poor prognosis. The widespread infection of multidrug-resistant Gram-negative uropathogens such as extended-spectrum beta-lactamase (ESBL)-producing bacteria has limited the efficacy of antibiotics used for treating cUTI. Considering the existence of antimicrobial-resistant (AMR) uropathogens, carbapenem is the last-resort antibiotic for cUTI. Given that carbapenem overuse has facilitated the spread of carbapenem-resistant Gram-negative bacteria, carbapenem dependence should be urgently reduced. However, improvement on the clinical outcomes of alternative antibiotics against cUTI caused by AMR uropathogens has not yet been systematically evaluated. Thus, this systematic review and meta-analysis aims to explore and compare the clinical outcomes of cUTI caused by AMR uropathogens between carbapenem and noncarbapenem antibiotics.

Methods and analysis

The study inclusion criteria will be considered based on the PICO model. P (population): adult patients with cUTIs caused by Gram-negative uropathogens; I (intervention): noncarbapenem class of antimicrobial agents with in vitro activities against Gram-negative uropathogens; C (comparison): treatment of carbapenem class antibiotics; O

(outcome): clinical and microbiologic cure. Relevant articles published until December 2022 will be systematically searched in February 2023, using electronic databases such as PubMed, the Cochrane Library, EMBASE, and ClinicalTrials.gov. Two independent reviewers will screen the select literature and then assess the full-text article to meet the inclusion criteria. The risk of bias will be assessed using the Cochrane risk-of-bias assessment tool. The treatment effects of antibiotics will be estimated as a risk ratio with a 95% confidence interval, using the random-effects model.

Ethics and dissemination

This protocol and systematic review will not include direct patient data; thus, informed consent will be waived. The results of this study will be published in an international peer-reviewed journal for wider information dissemination.

PROSPERO registration number: CRD42022356064

Keywords: complicated urinary tract infection, carbapenem, antimicrobial resistant

Word Count: 1269

Strengths and limitations of this study

This new protocol will evaluate the effectiveness of carbapenem and alternative antibiotics against cUTI caused by antimicrobial-resistant (AMR) uropathogens.

The analysis of efficacy of carbapenems and alternative antibiotics will contribute to both improving patient outcomes and developing treatment strategies that are effective for cUTIs caused by AMR uropathogens.

The protocol method is conducted robustly in accordance with the Cochrane Handbook for Systematic Reviews.

Given that the inclusion criteria will include articles published and uploaded to the database, studies such as those in conference presentations and not written in English may be missed.

INTRODUCTION

Complicated urinary tract infections (cUTIs) are associated with morbidity, mortality, and excessive healthcare costs.[1-4] Guidelines for cUTIs recommend that the empirical treatment should target Gram-negative uropathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, and non-Enterobacterales. Therefore, broad-spectrum antibiotics are frequently selected for empirical treatment.[5]

Over the past few decades, the widespread use of multidrug-resistant Gram-negative bacteria have been limiting the efficacy of antibiotics in cUTI treatment.[6] In particular, the burden of a disease caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria, which have become resistant to almost all beta-lactam antibiotics, is alarming.[7] Carbapenems as a representative of beta-lactam antibiotics exhibit an in vitro activity against most of the Gram-negative bacteria, including AMR uropathogens such as the ESBL-producing bacteria. In fact, carbapenem is the last-resort antibiotic for cUTI caused by antimicrobial-resistant (AMR) uropathogens, including ESBL-producing *E. coli* and *K. pneumoniae*.[8] Consequently, carbapenems have been increasingly used, but their widespread use has facilitated the proliferation of carbapenem-resistant Gram-negative bacteria.[9] The global spread of carbapenem-resistant bacteria reinforces the urgent need to reduce carbapenem dependence. An important strategy to reduce carbapenem overuse is to evaluate alternative antibiotics.[10] Several systematic reviews and meta-analyses were conducted to evaluate and compare the efficacy between carbapenems and alternative antibiotics for the treatment of cUTIs.[11-14] The study results consistently indicated that the efficacy of alternative antibiotics was noninferior to that of carbapenem in patients with cUTIs. Nevertheless, the population of these meta-analyses included both resistant and nonresistant strains. Considering that various antibiotics can treat cUTI caused by nonresistant bacteria, focusing on resistant bacteria is needed to evaluate the efficacy of carbapenem and its alternative antibiotics. Presently, specific data on the efficacy of alternative antibiotics for cUTIs caused by AMR uropathogens remain unavailable. In addition, improvement of the clinical outcomes of patients taking alternative antibiotics for cUTI caused by AMR uropathogens has not yet been systematically evaluated. Thus, we would like to conduct a systematic review and meta-analysis of the clinical outcomes of cUTI caused by AMR uropathogens between carbapenem and noncarbapenem antibiotics. Our meta-analysis will provide useful information for the proper selection of antibiotics used for treating cUTI in a clinical setting, as well as a future direction for the development of alternative antibiotics for AMR cUTI.

METHODS AND ANALYSIS

This protocol adheres to the Preferred Reporting Items for Systematic review and Meta-

Analysis Protocols (PRISMA-P) guidelines. We prepared this protocol manuscript according to the PRISMA-P checklist.[15]

Population

For the study population, we will include adult patients with cUTIs, including acute pyelonephritis, caused by Gram-negative uropathogens that are resistant to third-generation cephalosporin. [16]

Interventions

The intervention involves the noncarbapenem class of antimicrobial agents with in vitro activities against Gram-negative uropathogens that are resistant to third-generation cephalosporin.

Controls

The control is the treatment of carbapenem class antibiotics.

Outcomes

The primary outcome will be the composite outcome of clinical and microbiologic cure defined by the US Food and Drug Administration as follows: resolution of cUTI symptoms present at trial entry (and no new symptoms) and the reduction of bacterial pathogens found at trial entry to fewer than 10^3 CFU/mL on urine culture.[17] The secondary outcomes will be the microbiologic outcome responses and death at each endpoint.

Study designs

This review will only include individual and cluster randomized controlled trials.

Search strategy

Literature published until December 2022 will be searched in February 2023 in the following databases: MEDLINE/PubMed, the Cochrane Library (Cochrane Central Register of Controlled Trials, CENTRAL), EMBASE, and ClinicalTrials.gov. The systematic search strategy will be mainly done in MEDLINE/PubMed and the Cochrane Library database. The comprehensive search strategies will use the developed search terms shown in Table 1.

Table 1 Search strategy methods in PubMed

No.	Search queries
#1	Urinary Tract Infections[mh] OR "urinary tract infection*"[tiab] OR cUTI*[tiab] OR Pyelonephritis[mh] OR pyelonephritis*[tiab]
#2	Drug Resistance[mh] OR resistan*[tiab]
#3	Carbapenems[mh] OR carbapenem*[tw] OR CS-533[tw] OR CS533[tw] OR Imipenem[mh] OR imipenem*[tw] OR MK-0787[tw] OR MK0787[tw] OR N-Formimidoylthienamycin[tw] OR doripenem*[tw] OR "S 4661"[tw] OR S4661[tw] OR ertapenem*[tw] OR invanz[tw] OR panipenem*[tw] OR meropenem*[tw] OR merrem[tw] OR penem[tw] OR ronem[tw] OR SM-7338[tw] OR SM7338[tw] OR biapenem*[tw] OR L-627[tw] OR L627[tw] OR LJC-10627[tw] OR LJC10627[tw]
#4	#1 AND #2 AND #3
#5	(controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR clinical trials as topic[mesh:noexp] OR trial[ti] OR placebo[tiab]) NOT (Animals[mh] NOT Humans[mh])
#6	#4 AND #5
#7	Sepsis[mh] OR sepsis*[tiab] OR "blood poisoning*"[tiab] OR "bloodstream Infect*"[tiab] OR pyaemi*[tiab] OR pyemi*[tiab] OR pyohemi*[tiab] OR pyohaemi*[tiab] OR septicemi*[tiab] OR "bloodstream infection*"[tiab] OR bacteremi*[tiab] OR bacteraemi*[tiab]
#8	#6 AND #7

Screening of the retrieved articles

Independent researchers will review the screening search results. The title and abstract will be screened and scrutinized to meet the study criteria, using the reference management software Rayyan.[18] If they differ in decision on whether or not the study meets the inclusion criteria, another reviewer will do the screening.

Data extraction

The selected data will be extracted using Microsoft Excel, conforming to guidelines of the Cochrane Handbook for Systematic Reviews.[19] The following data will be extracted from the selected studies: author names, publication year, study population, baseline characteristics, study settings, intervention details, outcomes, and subgroup analysis stratified by AMR pathogens.

Assessment of risk of bias

Independent researchers will assess the risk of bias by using the Cochrane risk-of-bias assessment tool. The assessment domain consists of the following: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment of self-reported outcomes and reaction time (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases, such as imbalance of baseline characteristics and overdiagnosis bias.[20] The included studies will be divided into low risk, high risk, and unclear risk according to the reviewers' judgment. Any discord will be resolved through a discussion between them.

Data analysis

For dichotomous data, the treatment effects will be estimated as a risk ratio with a 95% confidence interval, using the random effects model. Heterogeneity will be assessed using the chi-square test and I^2 statistics. The heterogeneity will be addressed through meta-regression and subgroup analyses. Publication bias will be assessed in forest plots using Egger's test. Forest plots and funnel plots will be generated using the Review Manager (RevMan) software.

Grading of evidence

The strength of the body of evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) to judge the quality of evidence for outcomes. GRADE will then be assessed according to the risk of bias among studies, inconsistency, imprecision, indirectness, and publication bias.

Patient and public involvement

No patients or citizens will be involved in this research. Only data that are already published will be used. For this systematic review, the estimation of the efficacy of the treatment will benefit patients with cUTI.

ETHICS AND DISSEMINATION

This meta-analysis will not include direct patient data because it will only use studies that are already published. Therefore, informed consent will be waived. The results of this study will be published in an international peer-reviewed journal for wider information dissemination. This work will influence the national guidelines for the treatment of

cUTIs.[16]

Contributorship statement:
Conception of the study: MM. Statistical concept: TH, HN, and EO. Construction of search strategy: MM. Drafting manuscript: MM and TH. Review and finalization: TH, HN, and EO. All authors reviewed and approved the final version of the manuscript. Guarantor of the review: MM.

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Competing interests statement
None declared.

Patient and public involvement
Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this protocol.

Patient consent for publication
Not applicable

Provenance and peer review
Not commissioned; externally peer reviewed.

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	7
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	7
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	2,3

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3,4
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3,4
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	5

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	3,4
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3,4
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	6

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

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5 The Tokyo Foundation for Policy Research, Tokyo, Japan

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Word Count: 1418

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The control is the treatment of carbapenem class antibiotics.

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The primary outcome will be the composite outcome of clinical and microbiologic cure defined by the US Food and Drug Administration as follows: resolution of cUTI symptoms present at trial entry (and no new symptoms) and the reduction of bacterial pathogens found at trial entry to fewer than 10^3 CFU/mL on urine culture.[18] The secondary outcomes will be the microbiologic outcome responses and death at each endpoint.

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Table 1 Comprehensive search strategy methods for Medline/PubMed

No.	Search queries
#1	Urinary Tract Infections[mh] OR "urinary tract infection*"[tiab] OR cUTI*[tiab] OR Pyelonephritis[mh] OR pyelonephritis*[tiab]
#2	Drug Resistance[mh] OR resistan*[tiab]
#3	Carbapenems[mh] OR carbapenem*[tw] OR CS-533[tw] OR CS533[tw] OR Imipenem[mh] OR imipenem*[tw] OR MK-0787[tw] OR MK0787[tw] OR N-Formimidoylthienamycin[tw] OR doripenem*[tw] OR "S 4661"[tw] OR S4661[tw] OR ertapenem*[tw] OR invanz[tw] OR panipenem*[tw] OR meropenem*[tw] OR merrem[tw] OR penem[tw] OR ronem[tw] OR SM-7338[tw] OR SM7338[tw] OR biapenem*[tw] OR L-627[tw] OR L627[tw] OR LJC-10627[tw] OR LJC10627[tw]
#4	#1 AND #2 AND #3
#5	(controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR clinical trials as topic[mesh:noexp] OR trial[ti] OR placebo[tiab]) NOT (Animals[mh] NOT Humans[mh])
#6	#4 AND #5
#7	Sepsis[mh] OR sepsis*[tiab] OR "blood poisoning*"[tiab] OR "bloodstream Infect*"[tiab] OR pyaemi*[tiab] OR pyemi*[tiab] OR pyohemi*[tiab] OR pyohaemi*[tiab] OR septicemi*[tiab] OR "bloodstream infection*"[tiab] OR bacteremi*[tiab] OR bacteraemi*[tiab]
#8	#6 AND #7

Screening of the retrieved articles

Two independent researchers will screen the retrieved articles. The title and abstract will be screened and scrutinized to meet the study criteria, using the online software Rayyan, which helps to conduct systematic reviews.[19] Two researchers will independently review the full-text manuscripts according to the eligibility criteria for this review. If they differ in the decision on whether or not the study meets the inclusion criteria, another reviewer will resolve the conflicts.

Data extraction

The selected data will be extracted by two independent researchers using Microsoft Excel, conforming to guidelines of the Cochrane Handbook for Systematic Reviews.[20] The following data will be extracted from the selected studies: author names, publication year,

study population, baseline characteristics, study settings, intervention details, outcomes, and subgroup analysis stratified by AMR pathogens.

Assessment of risk of bias

Two independent researchers will assess the risk of bias using the Cochrane risk-of-bias assessment tool. The assessment domain consists of the following: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment of self-reported outcomes and reaction time (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases, such as imbalance of baseline characteristics and overdiagnosis bias.[21] The included studies will be divided into low risk, high risk, and unclear risk according to the reviewers' judgment. Any discord will be resolved through a discussion between them.

Data analysis

For dichotomous data, the treatment effects will be estimated as a risk ratio with a 95% confidence interval, using the random effects model. We will use the random-effects model to address the possible between-studies heterogeneity. We cannot assess how statistical heterogeneity exists before seeing the datasets; thus, we will adopt the random-effect model for the primary statistical analyses. Heterogeneity will be assessed using the chi-square test and I^2 statistics. The heterogeneity will be addressed through meta-regression and subgroup analyses. We will conduct a sensitivity analysis to determine the impact of the exclusion of studies at an overall high risk of bias and outliers for the primary outcome. Publication bias will be assessed in forest plots using Egger's test. Forest plots and funnel plots will be generated using the Review Manager (RevMan) software. We will perform the synthesis analyses when at least four studies are eligible. After the preliminary assessments of publication biases, we will perform the meta-analyses if there are no serious systematic biases. We will present summary data and assess individual studies in detail if a meta-analysis is not feasible.[20]

Grading of evidence

The strength of the body of evidence will be assessed by two independent researchers using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) to judge the quality of evidence for outcomes. [22] GRADE will then be assessed according to the risk of bias among studies, inconsistency, imprecision, indirectness, and publication bias. We will generate a summary of the findings table using the GRADEpro

software.

Patient and public involvement

No patients or citizens will be involved in this research. Only data that are already published will be used. For this systematic review, the estimation of the efficacy of the treatment will benefit patients with cUTI.

ETHICS AND DISSEMINATION

This systematic review and meta-analysis will not include direct patient data because it will only use studies that are already published. Therefore, informed consent will be waived. The results of this study will be published in an international peer-reviewed journal for wider information dissemination. This work will influence the national guidelines for the treatment of cUTIs.[17]

Contributorship statement:

Conception of the study: MM. Statistical concept: TH, HN, and EO. Construction of search strategy: MM. Drafting manuscript: MM and TH. Review and finalization: TH, HN, and EO. All authors reviewed and approved the final version of the manuscript. Guarantor of the review: MM.

Funding statement:

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Competing interests statement

None declared.

Patient consent for publication

Not applicable

Provenance and peer review

Not commissioned; externally peer reviewed.

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Supplemental material - bmjopen-2022-069166

Table 1 Comprehensive search strategy methods for Cochrane Library (Cochrane Central Register of Controlled Trials, CENTRAL)

No.	Search queries
#1	[mh "Urinary Tract Infections"] OR [mh Pyelonephritis] OR ((urinary NEXT tract NEXT infection*) OR cUTI* OR APEKS-cUTI* OR pyelonephritis*):ti,ab,kw
#2	[mh "Drug Resistance"] OR resistan*:ti,ab,kw
#3	[mh Carbapenems] OR [mh Imipenem] OR (carbapenem* OR CS?533 OR imipenem* OR MK?0787 OR N-Formimidoylthienamycin OR doripenem* OR S?4661 OR ertapenem* OR invanz OR panipenem* OR meropenem* OR merrem OR penem OR ronem OR SM?7338 OR biapenem* OR L?627 OR LJC?10627 OR CLI?86815):ti,ab,kw
#4	#1 AND #2 AND #3
#5	[mh sepsis] OR (sepsis* OR (blood NEXT poisoning*) OR (bloodstream NEXT Infect*) OR pyaemi* OR pyemi* OR pyohemi* OR pyohaemi* OR septicemi* OR (bloodstream NEXT infection*) OR bacteremi* OR bacteraemi* OR (blood NEXT stream NEXT Infect*)):ti,ab,kw
#6	#4 AND #5

Table 2 Comprehensive search strategy methods for EMBASE.

No.	Search queries
#1	'urinary tract infection'/exp OR 'urinary tract infection' OR cuti* OR 'pyelonephritis'/exp OR pyelonephritis
#2	'drug resistance'/exp OR 'drug resistance' OR 'resistance'/exp OR resistance
#3	'carbapenems'/exp OR carbapenems OR 'cs 533'/exp OR 'cs 533' OR 'cs533'/exp OR cs533 OR 'panipenem'/exp OR panipenem OR 'imipenem'/exp OR imipenem OR 'mk 0787'/exp OR 'mk 0787' OR mk0787 OR 'n formimidoylthienamycin'/exp OR 'n formimidoylthienamycin' OR 'doripenem'/exp OR doripenem OR 's 4661'/exp OR 's 4661' OR 's4661'/exp OR s4661 OR 'ertapenem'/exp OR ertapenem OR 'invanz'/exp OR invanz OR 'meropenem'/exp OR meropenem OR 'merrem'/exp OR merrem OR penem OR ronem OR 'sm 7338'/exp OR 'sm 7338' OR 'sm7338'/exp OR sm7338 OR 'biapenem'/exp OR biapenem OR 'l 627'/exp OR 'l 627' OR 'l627'/exp OR l627 OR 'ljc 10627'/exp OR 'ljc 10627' OR 'ljc10627'/exp OR ljc10627

#4	#1 AND #2 AND #3
#5	'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR ('randomi?ed controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo*
#6	#4 AND #5
#7	'sepsis'/exp OR sepsis OR 'blood poisoning' OR 'bloodstream infection'/exp OR 'bloodstream infection' OR 'pyemia'/exp OR pyemia OR 'pyohemia'/exp OR pyohemia OR 'septicemia'/exp OR septicemia OR 'bacteremia'/exp OR bacteremia OR 'bacteraemia'/exp OR bacteraemia
#8	#6 AND #7

Table 3 Comprehensive search strategy methods for ClinicalTrials.gov.

Search fields	Search queries
Condition or disease	("Urinary Tract Infections" OR Bacteriuria OR Pyuria OR cUTI OR Pyelonephritis)
Other terms	(resistant OR resistance)
Intervention/treatment	(carbapenem OR doripenem OR ertapenem OR Imipenem OR doripenem OR ertapenem OR meropenem OR biapenem)

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	7
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	7
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	2,3

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3,4
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3,4
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	5

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	3,4
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3,4
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	6

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

BMJ Open

Efficacy of carbapenems versus alternative antimicrobials for treating complicated urinary tract infections caused by antimicrobial-resistant Gram-negative bacteria: Protocol for a systematic review and meta-analysis

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Urology
Keywords:	Urinary tract infections < UROLOGY, INFECTIOUS DISEASES, Pyelonephritis < NEPHROLOGY

Efficacy of carbapenems versus alternative antimicrobials for treating complicated urinary tract infections caused by antimicrobial-resistant Gram-negative bacteria: Protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Complicated urinary tract infections (cUTIs) are associated with poor prognosis. The widespread infection of multidrug-resistant Gram-negative uropathogens such as extended-spectrum beta-lactamase (ESBL)-producing bacteria has limited the efficacy of antibiotics used for treating cUTI. Considering the existence of antimicrobial-resistant (AMR) uropathogens, carbapenem is the last-resort antibiotic for cUTI. Given that carbapenem overuse has facilitated the spread of carbapenem-resistant Gram-negative bacteria, carbapenem dependence should be urgently reduced. However, improvement on the clinical outcomes of alternative antibiotics against cUTI caused by AMR uropathogens has not yet been systematically evaluated. Thus, this systematic review and meta-analysis aims to explore and compare the clinical outcomes of cUTI caused by AMR uropathogens between carbapenem and noncarbapenem antibiotics.

Methods and analysis

The study inclusion criteria will be considered based on the PICO model consisting the following elements; population: adult patients with cUTIs caused by Gram-negative uropathogens; intervention: noncarbapenem class of antimicrobial agents with in vitro activities against Gram-negative uropathogens; comparison: treatment of carbapenem

class antibiotics; outcome: a clinical and microbiologic cure. Relevant articles published until December 2022 will be systematically searched in February 2023, using electronic databases such as PubMed, the Cochrane Library, EMBASE, and ClinicalTrials.gov. Two independent reviewers will screen the select literature and then assess the full-text article to meet the inclusion criteria. The risk of bias will be assessed using the Cochrane risk-of-bias assessment tool. The treatment effects of antibiotics will be estimated as a risk ratio with a 95% confidence interval, using the random-effects model.

Ethics and dissemination

This protocol and systematic review will not include direct patient data; thus, informed consent will be waived. The results of this study will be published in an international peer-reviewed journal for wider information dissemination.

PROSPERO registration number: CRD42022356064

Keywords: complicated urinary tract infection, carbapenem, antimicrobial resistant

Word Count: 1418

Strengths and limitations of this study

This new protocol will only include randomised controlled trials and endeavor to address a gap in the current evidence by focusing on complicated urinary tract infections caused by antimicrobial-resistant uropathogens.

The protocol method is conducted robustly in accordance with the Cochrane Handbook for Systematic Reviews.

Given that the inclusion criteria will include articles published and uploaded to the database, studies such as those in conference presentations and not written in English may be missed.

INTRODUCTION

Complicated urinary tract infections (cUTIs) are associated with morbidity, mortality, and excessive healthcare costs.[1-4] Guidelines for cUTIs recommend that the empirical treatment should target Gram-negative uropathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, and non-Enterobacterales. Therefore, broad-spectrum antibiotics are frequently selected for empirical treatment.[5]

Over the past few decades, the widespread use of multidrug-resistant Gram-negative bacteria have been limiting the efficacy of antibiotics in cUTI treatment.[6] In particular, the burden of a disease caused by extended-spectrum beta-lactamase (ESBL)-producing

bacteria, which have become resistant to almost all beta-lactam antibiotics, is alarming.[7] Carbapenems as a representative of beta-lactam antibiotics exhibit an in vitro activity against most of the Gram-negative bacteria, including AMR uropathogens such as the ESBL-producing bacteria. In fact, carbapenem is the last-resort antibiotic for cUTI caused by antimicrobial-resistant (AMR) uropathogens, including ESBL-producing *E. coli* and *K. pneumoniae*.[8] Consequently, carbapenems have been increasingly used, but their widespread use has facilitated the proliferation of carbapenem-resistant Gram-negative bacteria.[9] The global spread of carbapenem-resistant bacteria reinforces the urgent need to reduce carbapenem dependence. An important strategy to reduce carbapenem overuse is to evaluate alternative antibiotics.[10] Several systematic reviews and meta-analyses were conducted to evaluate and compare the efficacy between carbapenems and alternative antibiotics for the treatment of cUTIs.[11-14] The study results consistently indicated that the efficacy of alternative antibiotics was noninferior to that of carbapenem in patients with cUTIs. Nevertheless, the population of these meta-analyses included both resistant and nonresistant strains. Considering that various antibiotics can treat cUTI caused by nonresistant bacteria, focusing on resistant bacteria is needed to evaluate the efficacy of carbapenem and its alternative antibiotics. Presently, specific data on the efficacy of alternative antibiotics for cUTIs caused by AMR uropathogens remain unavailable. In addition, improvement of the clinical outcomes of patients taking alternative antibiotics for cUTI caused by AMR uropathogens has not yet been systematically evaluated. Thus, we would like to conduct a systematic review and meta-analysis of the clinical outcomes of cUTI caused by AMR uropathogens between carbapenem and noncarbapenem antibiotics. Our meta-analysis will provide useful information for the proper selection of antibiotics used for treating cUTI in a clinical setting, as well as a future direction for the development of alternative antibiotics for AMR cUTI.

METHODS AND ANALYSIS

This protocol adheres to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines. We prepared this protocol manuscript according to the PRISMA-P checklist.[15,16]

Population

For the study population, we will include adult patients with cUTIs, including acute pyelonephritis, caused by Gram-negative uropathogens that are resistant to third-generation cephalosporin. [17]

Interventions

The intervention involves the noncarbapenem class of antimicrobial agents with in vitro activities against Gram-negative uropathogens that are resistant to third-generation cephalosporin.

Controls

The control is the treatment of carbapenem class antibiotics.

Outcomes

The primary outcome will be the composite outcome of clinical and microbiologic cure defined by the US Food and Drug Administration as follows: resolution of cUTI symptoms present at trial entry (and no new symptoms) and the reduction of bacterial pathogens found at trial entry to fewer than 10^3 CFU/mL on urine culture.[18] The secondary outcomes will be the microbiologic outcome responses and death at each endpoint.

Study designs

This review will only include individual and cluster randomized controlled trials.

Search strategy

Literature published until December 2022 will be searched in February 2023 in the following databases: MEDLINE/PubMed, the Cochrane Library (Cochrane Central Register of Controlled Trials, CENTRAL), EMBASE, and ClinicalTrials.gov. The comprehensive search strategies will use the developed search terms shown in Table 1 and Supplemental File 1.

Table 1 Comprehensive search strategy methods for Medline/PubMed

No.	Search queries
#1	Urinary Tract Infections[mh] OR "urinary tract infection*"[tiab] OR cUTI*[tiab] OR Pyelonephritis[mh] OR pyelonephritis*[tiab]
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#4	#1 AND #2 AND #3
#5	(controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR clinical trials as topic[mesh:noexp] OR trial[ti] OR placebo[tiab]) NOT (Animals[mh] NOT Humans[mh])
#6	#4 AND #5
#7	Sepsis[mh] OR sepsis*[tiab] OR "blood poisoning*"[tiab] OR "bloodstream Infect*"[tiab] OR pyaemi*[tiab] OR pyemi*[tiab] OR pyohemi*[tiab] OR pyohaemi*[tiab] OR septicemi*[tiab] OR "bloodstream infection*"[tiab] OR bacteremi*[tiab] OR bacteraemi*[tiab]
#8	#6 AND #7

Screening of the retrieved articles

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The selected data will be extracted by two independent researchers using Microsoft Excel, conforming to guidelines of the Cochrane Handbook for Systematic Reviews.[20] The following data will be extracted from the selected studies: author names, publication year,

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Two independent researchers will assess the risk of bias using the Cochrane risk-of-bias assessment tool. The assessment domain consists of the following: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment of self-reported outcomes and reaction time (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases, such as imbalance of baseline characteristics and overdiagnosis bias.[21] The included studies will be divided into low risk, high risk, and unclear risk according to the reviewers' judgment. Any discord will be resolved through a discussion between them.

Data analysis

For dichotomous data, the treatment effects will be estimated as a risk ratio with a 95% confidence interval, using the random effects model. We will use the random-effects model to address the possible between-studies heterogeneity. We cannot assess how statistical heterogeneity exists before seeing the datasets; thus, we will adopt the random-effect model for the primary statistical analyses. Heterogeneity will be assessed using the chi-square test and I^2 statistics. The heterogeneity will be addressed through meta-regression and subgroup analyses. We will conduct a sensitivity analysis to determine the impact of the exclusion of studies at an overall high risk of bias and outliers for the primary outcome. Publication bias will be assessed in forest plots using Egger's test. Forest plots and funnel plots will be generated using the Review Manager (RevMan) software. We will perform the synthesis analyses when at least four studies are eligible. After the preliminary assessments of publication biases, we will perform the meta-analyses if there are no serious systematic biases. We will present summary data and assess individual studies in detail if a meta-analysis is not feasible.[20]

Grading of evidence

The strength of the body of evidence will be assessed by two independent researchers using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) to judge the quality of evidence for outcomes. [22] GRADE will then be assessed according to the risk of bias among studies, inconsistency, imprecision, indirectness, and publication bias. We will generate a summary of the findings table using the GRADEpro

software.

Patient and public involvement

No patients or citizens will be involved in this research. Only data that are already published will be used. For this systematic review, the estimation of the efficacy of the treatment will benefit patients with cUTI.

ETHICS AND DISSEMINATION

This systematic review and meta-analysis will not include direct patient data because it will only use studies that are already published. Therefore, informed consent will be waived. The results of this study will be published in an international peer-reviewed journal for wider information dissemination. This work will influence the national guidelines for the treatment of cUTIs.[17]

Contributorship statement:

Conception of the study: MM. Statistical concept: TH, HN, and EO. Construction of search strategy: MM. Drafting manuscript: MM and TH. Review and finalization: TH, HN, and EO. All authors reviewed and approved the final version of the manuscript. Guarantor of the review: MM.

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Competing interests statement

None declared.

Patient consent for publication

Not applicable

Provenance and peer review

Not commissioned; externally peer reviewed.

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Table 1 Comprehensive search strategy methods for Cochrane Library (Cochrane Central Register of Controlled Trials, CENTRAL)

No.	Search queries
#1	[mh "Urinary Tract Infections"] OR [mh Pyelonephritis] OR ((urinary NEXT tract NEXT infection*) OR cUTI* OR APEKS-cUTI* OR pyelonephritis*):ti,ab,kw
#2	[mh "Drug Resistance"] OR resistan*:ti,ab,kw
#3	[mh Carbapenems] OR [mh Imipenem] OR (carbapenem* OR CS?533 OR imipenem* OR MK?0787 OR N-Formimidoylthienamycin OR doripenem* OR S?4661 OR ertapenem* OR invanz OR panipenem* OR meropenem* OR merrem OR penem OR ronem OR SM?7338 OR biapenem* OR L?627 OR LJC?10627 OR CLI?86815):ti,ab,kw
#4	#1 AND #2 AND #3
#5	[mh sepsis] OR (sepsis* OR (blood NEXT poisoning*) OR (bloodstream NEXT Infect*) OR pyaemi* OR pyemi* OR pyohemi* OR pyohaemi* OR septicemi* OR (bloodstream NEXT infection*) OR bacteremi* OR bacteraemi* OR (blood NEXT stream NEXT Infect*)):ti,ab,kw
#6	#4 AND #5

Table 2 Comprehensive search strategy methods for EMBASE.

No.	Search queries
#1	'urinary tract infection'/exp OR 'urinary tract infection' OR cuti* OR 'pyelonephritis'/exp OR pyelonephritis
#2	'drug resistance'/exp OR 'drug resistance' OR 'resistance'/exp OR resistance
#3	'carbapenems'/exp OR carbapenems OR 'cs 533'/exp OR 'cs 533' OR 'cs533'/exp OR cs533 OR 'panipenem'/exp OR panipenem OR 'imipenem'/exp OR imipenem OR 'mk 0787'/exp OR 'mk 0787' OR mk0787 OR 'n formimidoylthienamycin'/exp OR 'n formimidoylthienamycin' OR 'doripenem'/exp OR doripenem OR 's 4661'/exp OR 's 4661' OR 's4661'/exp OR s4661 OR 'ertapenem'/exp OR ertapenem OR 'invanz'/exp OR invanz OR 'meropenem'/exp OR meropenem OR 'merrem'/exp OR merrem OR penem OR ronem OR 'sm 7338'/exp OR 'sm 7338' OR 'sm7338'/exp OR sm7338 OR 'biapenem'/exp OR biapenem OR 'l 627'/exp OR 'l 627' OR 'l627'/exp OR l627 OR 'ljc 10627'/exp OR 'ljc 10627' OR 'ljc10627'/exp OR ljc10627

#4	#1 AND #2 AND #3
#5	'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR ('randomi?ed controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo*
#6	#4 AND #5
#7	'sepsis'/exp OR sepsis OR 'blood poisoning' OR 'bloodstream infection'/exp OR 'bloodstream infection' OR 'pyemia'/exp OR pyemia OR 'pyohemia'/exp OR pyohemia OR 'septicemia'/exp OR septicemia OR 'bacteremia'/exp OR bacteremia OR 'bacteraemia'/exp OR bacteraemia
#8	#6 AND #7

Table 3 Comprehensive search strategy methods for ClinicalTrials.gov.

Search fields	Search queries
Condition or disease	("Urinary Tract Infections" OR Bacteriuria OR Pyuria OR cUTI OR Pyelonephritis)
Other terms	(resistant OR resistance)
Intervention/treatment	(carbapenem OR doripenem OR ertapenem OR Imipenem OR doripenem OR ertapenem OR meropenem OR biapenem)

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	7
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	7
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	2,3

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3,4
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3,4
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	5

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	3,4
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3,4
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	6

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6