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Untargeted antifungal therapy versus placebo or no treatment in adult patients with complicated intra-abdominal infection: protocol for a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis

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TITLE

Untargeted antifungal therapy versus placebo or no treatment in adult patients with complicated intra-abdominal infection: protocol for a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis

PROSPERO registration number: CRD42016053508

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ABSTRACT

Introduction

Intra-abdominal infections are the second most frequent cause of sepsis. In a recent cohort, fungal specimens were found in 51.9% of all septic patients with peritonitis. Current systematic reviews comparing untargeted antifungal treatment with placebo or no treatment in critically ill patients have provided conflicting results, and clinical equipoise exists. Accordingly, we aim to assess patient-important benefits and harms of untargeted antifungal therapy versus placebo or no treatment in adult patients with complicated intra-abdominal infection.

Methods and analysis

We will conduct a systematic review with meta-analysis and trial sequential analysis of randomised clinical trials assessing any untargeted antifungal therapy compared to placebo or no treatment in adult patients with complicated intra-abdominal infections. The primary outcome is all-cause mortality, and secondary outcomes include adverse events, duration of mechanical ventilation and inotropic support, need for renal replacement therapy, emergence of antibiotic resistance and ICU and hospital length-of-stay. Conventional meta-analysis, including sensitivity and subgroup analyses, and assessment of the risk of systematic (bias) and random errors will be conducted. The review will be prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, the Cochrane methodology, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Ethics and dissemination

Ethical approval is not required as this systematic review only includes previously published data. We aim to publish the review in an international peer-reviewed journal.

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STRENGHTS AND LIMITATIONS OF THIS STUDY

Strenghts

- The protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement.
- The systematic review will be conducted in accordance with recommendations from the Cochrane Collaboration, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines.
- Exclusively patient-important outcome measures will be evaluated.

Limitations

- The included trials may be heterogeneous.
- Many outcome measures will be assessed.
- New as well as older antifungal agents will be assessed.

BACKGROUND

Description of the condition

Intra-abdominal infections are the second most frequent cause of sepsis in critically ill patients.[1] Complicated intra-abdominal infection or peritonitis is characterised by inflammation of the peritoneum, most often caused by bacteria or fungi. Primary or spontaneous bacterial peritonitis occurs due to hematogenous dissemination of bacteria or translocation of bacteria through the enteric wall and is managed without surgical intervention.[2] Secondary peritonitis is the most common form. It develops in relation to disease or injury due to breach of the intestinal wall and requires immediate source control.[2] Tertiary peritonitis is defined as persistent or reoccurring peritonitis within 48 hours of adequate surgical source control.[2] All forms are associated with high morbidity and mortality despite administration of relevant antibiotics and/or surgical interventions.[1-3]

In a recent retrospective cohort of critically ill patients with sepsis due to peritonitis, fungal specimens were found in 52% of all patients.[4] Candida spp. constituted the majority of isolates, in particular C. albicans (60%), C. glabrata (24%) and C. tropicalis (9%).[4] Patients with fungal infection had a significantly higher rate of tertiary peritonitis and a higher overall mortality compared to patients without fungal infection.[4]

Description of the intervention

Untargeted antifungal treatment is defined as any antifungal intervention initiated before definitive microbiological evidence of fungi exists.[5-7] Currently, three different untargeted treatment strategies have been defined, namely prophylaxis, pre-emptive and empirical therapy.[5-7] Antifungal prophylaxis is used in patients with high risk of developing invasive fungal infections, including critical illness, recent abdominal surgery, hematologic malignancy, organ transplantation and treatment with glucocorticoids or broad-spectrum antibiotics.[5-8] Pre-emptive antifungal treatment is administered in response to direct or indirect microbiological evidence of fungi without clinical suspicion of invasive fungal infection.[5-7] Lastly, empirical antifungal treatment is used in

patients with known risk factors and suspicion of fungal infection.[5-7]

How the intervention might work

Diagnosing fungal infection is challenging, as symptoms and signs are non-specific and mimic bacterial infections.[8] Also, the time to acquire definite diagnosis takes several days as it is still largely based on cultures. Thus, untargeted therapy strategies appear intuitively attractive.

In a prospective, population-based surveillance study of patients with Candida bloodstream infection, early administration of untargeted antifungal treatment was associated with reduced mortality.[9 10] Similarly, two previous systematic reviews investigating prophylactic antifungal treatment with fluconazole or ketoconazole in non-neutropenic critically ill patients demonstrated a reduction in both invasive fungal infection and all-cause mortality compared to placebo or no treatment.[11 12] However, in a recently updated systematic review including a total of 2761 non-neutropenic critically ill adults and children, untargeted antifungal treatment did not significantly reduce mortality (moderate quality of evidence). The results did indicate a reduction in rates of invasive fungal infections (low quality of evidence).[5] In conclusion, existing evidence have provided conflicting results regarding the use of untargeted antifungal therapy.[5 11 12]

Why it is important to do this review

Several disadvantages of antifungal treatment exist, including drug interactions, side effects, and economical expenses. In addition, resistance is increasing, in particular to fluconazole, highlighting the need for balancing benefits and harms of untargeted antifungal therapy.[1] Existing systematic reviews and meta-analysis on the matter are confined to critically ill patients. It remains to be elucidated if all or certain subgroups of adult patients with complicated intra-abdominal infection would benefit from treatment with untargeted antifungal therapy.

Objectives

We aim to assess patient-important benefits and harms of untargeted antifungal therapy versus placebo or no treatment in adult patients with complicated intra-

abdominal infection.

METHODS

This protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement.[13] The systematic review will be conducted in accordance with recommendations from the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [14], and the quality of evidence will be evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. [15] This protocol has also been registered in the International Prospective Register of Systematic Reviews (PROSPERO) on the 21st of December, 2016 (registration number CRD42016053508).

Types of studies

We aim to include randomised clinical trials (RCTs) assessing untargeted antifungal therapy in adult patients with complicated intra-abdominal infections (as defined by the original trials). RCTs regardless of publication status, publication period, blinding and language will be included. Crossover trials and quasi-randomised trials will be excluded.

Types of participants

We will include trials conducted in adult patients (as defined by the original trials) with complicated intra-abdominal infection. RCTs conducted in animals, children and healthy subjects will be excluded.

Types of interventions

The interventions of interest include any type of untargeted antifungal therapy, including azoles, echinocandins, polyenes, allylamines and nucleoside analogues in any dose, timing, formulation and duration. Trials are permitted to have more than one intervention group. The comparators are patients receiving either placebo or no treatment.

Types of outcome measures

The primary outcome measure is all-cause short-term mortality (≤ 90 days, including in-ICU and in-hospital mortality). Secondary outcomes include 1) long-term mortality (>90 days), 2) adverse events (as defined by the original trials) at longest follow-up, 3) duration of mechanical ventilation, 4) days free of mechanical ventilation, 5) need for renal replacement therapy at longest follow-up, 6) days free of renal replacement therapy, 7) duration of vasopressor/inotropic support, 8) days free of vasopressors/inotropes, 9) emergence of antibiotic resistance at longest follow-up, 10) emergence of fungi not susceptible to given antifungal agent, 11) ICU length-of-stay (LOS), 12) hospital LOS and 13) quality of life (as defined by the original trials) at longest follow-up.

Search methods for identification of studies

Electronic searches

We will systematically search the Cochrane Library (Wiley interface, current issue), MEDLINE (OVID interface, 1946 onwards), EMBASE (OVID interface, 1980 onwards) and Epistemonikos. Refer to Appendix for example of full search strategy performed in MEDLINE.

Searching other resources

Additionally, we will hand-search reference lists of relevant trials and other systematic reviews of untargeted antifungal therapy. Unpublished trials will be sought identified by performing an equivalent search strategy in other registers (e.g. clinicaltrials.gov, European Clinical Trials Database etc.).

Data collection and analysis

Selection of studies

Two independent authors will screen titles and abstracts of identified trials. Relevant trials will be evaluated in full-text for eligibility. Disagreements will be resolved by discussion between authors and finally by consensus among all authors.

Data extraction and management

Two independent authors will extract data from included trials in duplicate using a standardised data extraction form. Data items abstracted will include trial characteristics, patient characteristics, details of intervention(s) and comparator(s), risk of bias and the predefined patient-important outcome measures. We aim to include data from intention-to-treat analysis rather than per-protocol. Disagreements will be resolved by discussion between data extracting authors and finally by consensus among all authors.

Measures of treatment effect

Dichotomous data will be analysed by calculating the cumulative relative risk (RR) with 95% confidence interval (CI). For continuous data, we will calculate the mean difference (MD) with corresponding standard deviation (SD).

Assessment of risk of bias in included studies

Two authors will independently assess risk of bias of the included trials in accordance with the recommendations from the Cochrane Collaboration. [16] The domains reviewed include 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessors, 5) incomplete outcome data, 6) selective outcome reporting, and 7) other bias, including baseline imbalance, early stopping, bias due to vested financial interest and academic bias. If one or more domains are judged as being high or unclear, we will classify the trial as having overall high risk of bias.

Assessment of the risk of random errors

The risk of random errors will be assessed by trial sequential analysis (TSA).[17] TSA is a sample size calculation (interim analysis) for meta-analyses that widens the confidence intervals in case data are too sparse to draw firm conclusions.[17]

We will apply trial sequential monitoring boundaries according to an information size suggested by the trials with low risk of bias and an a priori 20% relative risk reduction, alfa 5%, beta 90%, and a control event proportion as per the control arm.[17]

Dealing with missing data

Authors will be contacted for additional data if relevant.

Assessment of heterogeneity

We will calculate inconsistency factor (I^2) and diversity factor (D^2) to quantify heterogeneity among included trials. We will use both fixed effect and random effects modeling, and report the most conservative estimate.

Assessment of small trial bias

We will assess the risk of small trial bias (publication bias) if ten or more trials are included by visually examining the funnel plots for asymmetry.[18]

Data synthesis

Review Manager (RevMan 5.3) will be used as statistical software to conduct the meta-analyses, including subgroup analyses (summary estimates). For the trial sequential analyses we will use the TSA software available from Copenhagen Trial Unit, Denmark.

Subgroup analysis

We will perform the following subgroup analyses by comparing estimates of the pooled intervention effect in each subgroup, if two of more trials exist:

- Overall low risk of bias versus overall high risk of bias. Hypothesised direction of subgroup effect: increased intervention effect in trials with high risk of bias.
- Prophylactic versus pre-emptive versus empirical treatment strategies. Hypothesised direction of subgroup effect: increased intervention effect in trials assessing empirical antifungal treatment.
- Non-ICU trials versus ICU trials. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted in the ICU.
- Trials published before the year 2000 versus in and after the year 2000. Hypothesised direction of subgroup: increased intervention effect in trials published before the year 2000.
- Patients with primary versus secondary versus tertiary peritonitis.

Hypothesised direction of subgroup effect: increased intervention effect in trials conducted in patients with tertiary peritonitis.

- Patients with versus without septic shock. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted in patients with septic shock.
- Median/mean Mannheim Peritonitis Index (MPI) score > 25 versus trials with a median/mean baseline MPI score ≤ 25. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted on patients with a MPI score > 25.

We will use Chi-square test to assess statistical heterogeneity between studies (test-of-interaction) with a p-value of 0.10 considered statistically significant.

Sensitivity analysis

In the zero event trials, empirical continuity correction will be applied.[19]

Summary of findings

The quality of evidence for each outcome will be assessed according to GRADE.[15] The domains assessed include risk of bias, inconsistency, indirectness, imprecision and publication bias.[15]

Ethics and dissemination

Ethical approval is not required as this systematic review only includes previously published data. We aim to publish the systematic review in an international peer-reviewed journal.

Author contributions: MW, FS, AP and MH drafted the protocol. MH and FS developed the idea for the review and is the guarantor of the review.

Funding statement: This research project received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None

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APPENDIX

Example of search strategy performed in MEDLINE

(("peritonitis"[MeSH Terms] OR "peritonitis"[All Fields]) OR ("intraabdominal infections"[MeSH Terms] OR ("intraabdominal"[All Fields] AND "infections"[All Fields]) OR "intraabdominal infections"
[All Fields] OR ("intra"[All Fields] AND "abdominal"[All Fields] AND "infection"[All Fields]) OR "intra abdominal infection"[All Fields])) AND (("antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR ("antifungal"[All Fields] AND "agents"[All Fields]) OR "antifungal agents"[All Fields] OR "antifungal"[All Fields]) OR antimycotic[All Fields] OR ("azoles"[MeSH Terms] OR "azoles"[All Fields] OR "azole"[All Fields]) OR ("echinocandins"[MeSH Terms] OR "echinocandins"[All Fields] OR "echinocandin"[All Fields]) OR ("polyenes"[MeSH Terms] OR "polyenes"[All Fields] OR "polyene"[All Fields]) OR ("allylamine"[MeSH Terms] OR "allylamine"[All Fields]) OR ("caspofungin"[Supplementary Concept] OR "caspofungin"[All Fields]) OR ("anidulafungin"[Supplementary Concept] OR "anidulafungin"[All Fields]) OR ("micafungin"[Supplementary Concept] OR "micafungin"[All Fields]) OR ("amphotericin b"[MeSH Terms] OR "amphotericin b"[All Fields]) OR ("nystatin"[MeSH Terms] OR "nystatin"[All Fields]) OR ("itraconazole"[MeSH Terms] OR "itraconazole"[All Fields]) OR ("posaconazole"[Supplementary Concept] OR "posaconazole"[All Fields]) OR ("fluconazole"[MeSH Terms] OR "fluconazole"[All Fields]) OR ("ketoconazole"[MeSH Terms] OR "ketoconazole"[All Fields]) OR ("clotrimazole"[MeSH Terms] OR "clotrimazole"[All Fields]) OR isavuconazonium[All Fields] OR ("miconazole"[MeSH Terms] OR "miconazole"[All Fields]) OR ("voriconazole"[MeSH Terms] OR "voriconazole"[All Fields]) OR ("terbinafine"[Supplementary Concept] OR "terbinafine"[All Fields]) OR ("flucytosine"[MeSH Terms] OR "flucytosine"[All Fields]) OR ("griseofulvin"[MeSH Terms] OR "griseofulvin"[All Fields])

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
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	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
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	6-7
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	7
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	13
Study records:			
Data	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8

management			
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)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
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	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	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 I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9-10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Limitations

- The included trials may be heterogeneous.
- Different antifungal treatment strategies (i.e. prophylaxis, pre-emptive and empirical therapy) will be assessed.
- Many outcome measures will be assessed.
- New as well as older antifungal agents will be assessed.

BACKGROUND

Description of the condition

Intra-abdominal infections are the second most frequent cause of sepsis in critically ill patients.[1] Complicated intra-abdominal infection or peritonitis is characterised by inflammation of the peritoneum, most often caused by bacteria or fungi. Primary or spontaneous bacterial peritonitis occurs due to hematogenous dissemination of bacteria or translocation of bacteria through the enteric wall and is managed without surgical intervention.[2] Secondary peritonitis is the most common form. It develops in relation to disease or injury due to breach of the intestinal wall and requires immediate source control.[2] Tertiary peritonitis is defined as persistent or reoccurring peritonitis within 48 hours of adequate surgical source control.[2] All forms are associated with high morbidity and mortality despite administration of relevant antibiotics and/or surgical interventions.[1-3]

In a recent retrospective cohort of critically ill patients with sepsis due to peritonitis, fungal specimens were found in 52% of all patients.[4] Candida spp. constituted the majority of isolates, in particular C. albicans (60%), C. glabrata (24%) and C. tropicalis (9%).[4] Patients with fungal infection had a significantly higher rate of tertiary peritonitis and a higher overall mortality compared to patients without fungal infection.[4]

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Untargeted antifungal treatment is defined as any antifungal intervention initiated before definitive microbiological evidence of fungi exists.[5-8] Currently, three different untargeted treatment strategies have been defined, namely prophylaxis, pre-emptive and empirical therapy.[5-8] Antifungal prophylaxis is used in patients with high risk of developing invasive fungal infections, including critical illness, recent abdominal surgery, hematologic malignancy, organ transplantation and treatment with glucocorticoids or broad-spectrum antibiotics.[5-9] Pre-emptive antifungal treatment is administered in response to direct or indirect microbiological evidence of fungi without clinical suspicion of invasive fungal infection.[5-8] Lastly, empirical antifungal treatment is used in

patients with known risk factors and suspicion of fungal infection.[5-8] In daily clinical practice, it is often difficult to distinguish the different untargeted antifungal treatment strategies.

How the intervention might work

Diagnosing fungal infection is challenging, as symptoms and signs are non-specific and mimic bacterial infections.[9] Also, the time to acquire definite diagnosis takes several days as it is still largely based on cultures. Thus, untargeted therapy strategies appear intuitively attractive.

In a prospective, population-based surveillance study of patients with Candida bloodstream infection, early administration of untargeted antifungal treatment was associated with reduced mortality.[10 11] Similarly, two previous systematic reviews investigating prophylactic antifungal treatment with fluconazole or ketoconazole in non-neutropenic critically ill patients demonstrated a reduction in both invasive fungal infection and all-cause mortality compared to placebo or no treatment.[12 13] However, in a recently updated Cochrane review including a total of 2761 non-neutropenic critically ill adults and children, untargeted antifungal treatment did not significantly reduce mortality (moderate quality of evidence). The results did indicate a reduction in rates of invasive fungal infections (low quality of evidence).[5] In conclusion, existing evidence have provided conflicting results regarding the use of untargeted antifungal therapy.[5 12 13]

Why it is important to do this review

Several disadvantages of antifungal treatment exist, including drug interactions, side effects, and economical expenses. In addition, resistance is increasing, in particular to fluconazole, highlighting the need for balancing benefits and harms of untargeted antifungal therapy.[1] Existing systematic reviews and meta-analysis on the matter are confined to critically ill patients. It remains to be elucidated if all or certain subgroups of adult patients with complicated intra-abdominal infection would benefit from treatment with untargeted antifungal therapy.

Objectives

We aim to assess patient-important benefits and harms of untargeted antifungal

therapy versus placebo or no treatment in adult patients with complicated intra-abdominal infection.

METHODS

This protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement.[14] The systematic review will be conducted in accordance with recommendations from the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [15], and the quality of evidence will be evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. [16] This protocol has also been registered in the International Prospective Register of Systematic Reviews (PROSPERO) on the 21st of December, 2016 (registration number CRD42016053508).

Types of studies

We aim to include randomised clinical trials (RCTs) assessing untargeted antifungal therapy in adult patients with complicated intra-abdominal infections (as defined by the original trials). RCTs regardless of publication status, publication period, blinding and language will be included. Crossover trials and quasi-randomised trials will be excluded.

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Types of interventions

The interventions of interest include any type of untargeted antifungal therapy, including azoles, echinocandins, polyenes, allylamines and nucleoside analogues in any dose, timing, formulation and duration. Trials are permitted to have more than one intervention group. The comparators are patients receiving either

placebo or no treatment.

Types of outcome measures

The primary outcome measure is all-cause short-term mortality (≤ 90 days, including in-ICU and in-hospital mortality). Secondary outcomes include 1) long-term mortality (>90 days), 2) adverse events (as defined by the original trials) at longest follow-up, 3) duration of mechanical ventilation, 4) days free of mechanical ventilation, 5) need for renal replacement therapy at longest follow-up, 6) days free of renal replacement therapy, 7) duration of vasopressor/inotropic support, 8) days free of vasopressors/inotropes, 9) emergence of antibiotic resistance at longest follow-up, 10) emergence of fungi not susceptible to given antifungal agent, 11) ICU length-of-stay (LOS), 12) hospital LOS and 13) quality of life (as defined by the original trials) at longest follow-up. If multiple time points are reported, we will use and report the outcome with longest follow-up.

Search methods for identification of studies

Electronic searches

We will systematically search the Cochrane Library (Wiley interface, current issue), MEDLINE (OVID interface, 1946 onwards), EMBASE (OVID interface, 1980 onwards) and Epistemonikos. Refer to Appendix for example of full search strategy performed in MEDLINE.

Searching other resources

Additionally, we will hand-search reference lists of relevant trials and other systematic reviews of untargeted antifungal therapy. Unpublished trials will be sought identified by performing an equivalent search strategy in other registers (e.g. clinicaltrials.gov, European Clinical Trials Database etc.).

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Dichotomous data will be analysed by calculating the cumulative relative risk (RR) with 95% confidence interval (CI). For continuous data, we will calculate the mean difference (MD) with corresponding standard deviation (SD).

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Two authors will independently assess risk of bias of the included trials in accordance with the recommendations from the Cochrane Collaboration. [17] The domains reviewed include 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessors, 5) incomplete outcome data, 6) selective outcome reporting, and 7) other bias, including baseline imbalance, early stopping, bias due to vested financial interest and academic bias. If one or more domains are judged as being high or unclear, we will classify the trial as having overall high risk of bias.

Assessment of the risk of random errors

The risk of random errors will be assessed by trial sequential analysis (TSA).[18] TSA is a sample size calculation (interim analysis) for meta-analyses that widens the confidence intervals in case data are too sparse to draw firm conclusions.[18]

We will apply trial sequential monitoring boundaries according to an information size suggested by the trials with low risk of bias and an a priori 20%

relative risk reduction, alfa 5%, beta 90%, and a control event proportion as per the control arm.[18]

Dealing with missing data

Authors will be contacted for additional data if relevant.

Assessment of heterogeneity

We will calculate inconsistency factor (I^2) and diversity factor (D^2) to quantify heterogeneity among included trials. We will use both fixed effect and random effects modeling, and report the most conservative estimate.

Assessment of small trial bias

We will assess the risk of small trial bias (publication bias) if ten or more trials are included by visually examining the funnel plots for asymmetry.[19]

Data synthesis

Review Manager (RevMan 5.3) will be used as statistical software to conduct the meta-analyses, including subgroup analyses (summary estimates). For the trial sequential analyses we will use the TSA software available from Copenhagen Trial Unit, Denmark.

Subgroup analysis

We will perform the following subgroup analyses by comparing estimates of the pooled intervention effect in each subgroup, if two of more trials exist:

- Overall low risk of bias versus overall high risk of bias. Hypothesised direction of subgroup effect: increased intervention effect in trials with high risk of bias.
- Prophylactic versus pre-emptive versus empirical treatment strategies. Hypothesised direction of subgroup effect: increased intervention effect in trials assessing empirical antifungal treatment.
- Non-ICU trials versus ICU trials. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted in the ICU.
- Trials published before the year 2000 versus in and after the year 2000.

Hypothesised direction of subgroup: increased intervention effect in trials published before the year 2000.

- Patients with primary versus secondary versus tertiary peritonitis. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted in patients with tertiary peritonitis.
- Patients with versus without septic shock. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted in patients with septic shock.
- Median/mean Mannheim Peritonitis Index (MPI) score > 25 versus trials with a median/mean baseline MPI score ≤ 25. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted on patients with a MPI score > 25.
- Neutropenic vs non-neutropenic patients. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted on neutropenic patients.

We will use Chi-square test to assess statistical heterogeneity between studies (test-of-interaction) with a p-value of 0.10 considered statistically significant.

Sensitivity analysis

In the zero event trials, empirical continuity correction will be applied.[20]

Summary of findings

The quality of evidence for each outcome will be assessed according to GRADE.[16] The domains assessed include risk of bias, inconsistency, indirectness, imprecision and publication bias.[16]

Ethics and dissemination

Ethical approval is not required as this systematic review only includes previously published data. We aim to publish the systematic review in an international peer-reviewed journal.

Author contributions: MW, FS, AP and MH drafted the protocol. MH and FS

developed the idea for the review and is the guarantor of the review.

Funding statement: This research project received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None

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APPENDIX

Example of search strategy performed in MEDLINE

(("peritonitis"[MeSH Terms] OR "peritonitis"[All Fields]) OR ("intraabdominal infections"[MeSH Terms] OR ("intraabdominal"[All Fields] AND "infections"[All Fields]) OR "intraabdominal infections"
[All Fields] OR ("intra"[All Fields] AND "abdominal"[All Fields] AND "infection"[All Fields]) OR "intra abdominal infection"[All Fields])) AND (("antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR ("antifungal"[All Fields] AND "agents"[All Fields]) OR "antifungal agents"[All Fields] OR "antifungal"[All Fields]) OR antimycotic[All Fields] OR ("azoles"[MeSH Terms] OR "azoles"[All Fields] OR "azole"[All Fields]) OR ("echinocandins"[MeSH Terms] OR "echinocandins"[All Fields] OR "echinocandin"[All Fields]) OR ("polyenes"[MeSH Terms] OR "polyenes"[All Fields] OR "polyene"[All Fields]) OR ("allylamine"[MeSH Terms] OR "allylamine"[All Fields]) OR ("caspofungin"[Supplementary Concept] OR "caspofungin"[All Fields]) OR ("anidulafungin"[Supplementary Concept] OR "anidulafungin"[All Fields]) OR ("micafungin"[Supplementary Concept] OR "micafungin"[All Fields]) OR ("amphotericin b"[MeSH Terms] OR "amphotericin b"[All Fields]) OR ("nystatin"[MeSH Terms] OR "nystatin"[All Fields]) OR ("itraconazole"[MeSH Terms] OR "itraconazole"[All Fields]) OR ("posaconazole"[Supplementary Concept] OR "posaconazole"[All Fields]) OR ("fluconazole"[MeSH Terms] OR "fluconazole"[All Fields]) OR ("ketoconazole"[MeSH Terms] OR "ketoconazole"[All Fields]) OR ("clotrimazole"[MeSH Terms] OR "clotrimazole"[All Fields]) OR isavuconazonium[All Fields] OR ("miconazole"[MeSH Terms] OR "miconazole"[All Fields]) OR ("voriconazole"[MeSH Terms] OR "voriconazole"[All Fields]) OR ("terbinafine"[Supplementary Concept] OR "terbinafine"[All Fields]) OR ("flucytosine"[MeSH Terms] OR "flucytosine"[All Fields]) OR ("griseofulvin"[MeSH Terms] OR "griseofulvin"[All Fields])

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
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	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
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	6-7
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	7
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	13
Study records:			
Data	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8

management			
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)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
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	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	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 I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9-10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Untargeted antifungal therapy in adult patients with complicated intra-abdominal infection: protocol for a systematic review with meta-analysis

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Evidence based practice, Medical management
Keywords:	Intra-abdominal infection, Peritonitis, Antifungal therapy, Human

TITLE

Untargeted antifungal therapy in adult patients with complicated intra-abdominal infection: protocol for a systematic review with meta-analysis

PROSPERO registration number: CRD42016053508

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- MD PhD Fredrik Sjövall, Department of Perioperative Medicine, Skane University Hospital, Malmö, Sweden, fredrik.sjovall@med.lu.se
- Associate Professor, MD PhD Morten Hylander, Department of Intensive Care 4131, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, mortenhylander@gmail.com

Timescale:

The anticipated start date is the 1st of February 2017, and the anticipated completion date is the 1st of November 2017.

Word count:

1.979 words

ABSTRACT

Introduction

Intra-abdominal infections are the second most frequent cause of sepsis. In a recent cohort, fungal specimens were found in 51.9% of all septic patients with peritonitis. Current systematic reviews comparing untargeted antifungal treatment with placebo or no treatment in critically ill patients have provided conflicting results, and clinical equipoise exists. Accordingly, we aim to assess patient-important benefits and harms of untargeted antifungal therapy versus placebo or no treatment in adult patients with complicated intra-abdominal infection.

Methods and analysis

We will conduct a systematic review with meta-analysis and trial sequential analysis of randomised clinical trials assessing any untargeted antifungal therapy compared to placebo or no treatment in adult patients with complicated intra-abdominal infections. The primary outcome is all-cause mortality, and secondary outcomes include adverse events, duration of mechanical ventilation and inotropic support, need for renal replacement therapy, emergence of antibiotic resistance and ICU and hospital length-of-stay. Conventional meta-analysis, including sensitivity and subgroup analyses, and assessment of the risk of systematic (bias) and random errors will be conducted. The review will be prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, the Cochrane methodology, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Ethics and dissemination

Ethical approval is not required as this systematic review only includes previously published data. We aim to publish the review in an international peer-reviewed journal.

PROSPERO registration number: CRD42016053508

STRENGHTS AND LIMITATIONS OF THIS STUDY

Strenghts

- The protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement.
- The systematic review will be conducted in accordance with recommendations from the Cochrane Collaboration, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines.
- Exclusively patient-important outcome measures, including mortality, adverse events, use of life support, and quality of life will be evaluated.

Limitations

- The included trials may be heterogeneous.
- Different antifungal treatment strategies (i.e. prophylaxis, pre-emptive and empirical therapy) will be assessed.
- New as well as older antifungal agents will be assessed.

BACKGROUND

Description of the condition

Intra-abdominal infections are the second most frequent cause of sepsis in critically ill patients.[1] Complicated intra-abdominal infection or peritonitis is characterised by inflammation of the peritoneum, most often caused by bacteria or fungi. Primary or spontaneous bacterial peritonitis occurs due to hematogenous dissemination of bacteria or translocation of bacteria through the enteric wall and is managed without surgical intervention.[2] Secondary peritonitis is the most common form. It develops in relation to disease or injury due to breach of the intestinal wall and requires immediate source control.[2] Tertiary peritonitis is defined as persistent or reoccurring peritonitis within 48 hours of adequate surgical source control.[2] All forms are associated with high morbidity and mortality despite administration of relevant antibiotics and/or surgical interventions.[1-3]

In a recent retrospective cohort of critically ill patients with sepsis due to peritonitis, fungal specimens were found in 52% of all patients.[4] Candida spp. constituted the majority of isolates, in particular C. albicans (60%), C. glabrata (24%) and C. tropicalis (9%).[4] Patients with fungal infection had a significantly higher rate of tertiary peritonitis and a higher overall mortality compared to patients without fungal infection.[4]

Description of the intervention

Untargeted antifungal treatment is defined as any antifungal intervention initiated before definitive microbiological evidence of fungi exists.[5-8] Currently, three different untargeted treatment strategies have been defined, namely prophylaxis, pre-emptive and empirical therapy.[5-8] Antifungal prophylaxis is used in patients with high risk of developing invasive fungal infections, including critical illness, recent abdominal surgery, hematologic malignancy, organ transplantation and treatment with glucocorticoids or broad-spectrum antibiotics.[5-9] Pre-emptive antifungal treatment is administered in response to direct or indirect microbiological evidence of fungi without clinical suspicion of invasive fungal infection.[5-8] Lastly, empirical antifungal treatment is used in

patients with known risk factors and suspicion of fungal infection.[5-8] In daily clinical practice, it is often difficult to distinguish the different untargeted antifungal treatment strategies.

How the intervention might work

Diagnosing fungal infection is challenging, as symptoms and signs are non-specific and mimic bacterial infections.[9] Also, the time to acquire definite diagnosis takes several days as it is still largely based on cultures. Thus, untargeted therapy strategies appear intuitively attractive.

In a prospective, population-based surveillance study of patients with Candida bloodstream infection, early administration of untargeted antifungal treatment was associated with reduced mortality.[10 11] Similarly, two previous systematic reviews investigating prophylactic antifungal treatment with fluconazole or ketoconazole in non-neutropenic critically ill patients demonstrated a reduction in both invasive fungal infection and all-cause mortality compared to placebo or no treatment.[12 13] However, in a recently updated Cochrane review including a total of 2761 non-neutropenic critically ill adults and children, untargeted antifungal treatment did not significantly reduce mortality (moderate quality of evidence). The results did indicate a reduction in rates of invasive fungal infections (low quality of evidence).[5] In conclusion, existing evidence have provided conflicting results regarding the use of untargeted antifungal therapy.[5 12 13]

Why it is important to do this review

Several disadvantages of antifungal treatment exist, including drug interactions, side effects, and economical expenses. In addition, resistance is increasing, in particular to fluconazole, highlighting the need for balancing benefits and harms of untargeted antifungal therapy.[1] Existing systematic reviews and meta-analysis on the matter are confined to critically ill patients. It remains to be elucidated if all or certain subgroups of adult patients with complicated intra-abdominal infection would benefit from treatment with untargeted antifungal therapy.

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Exclusively patient-important outcome measures will be evaluated.[17] The primary outcome measure is all-cause short-term mortality (≤ 90 days, including in-ICU and in-hospital mortality). Secondary outcomes include 1) long-term mortality (>90 days), 2) adverse events (as defined by the original trials) at longest follow-up, 3) duration of mechanical ventilation, 4) days free of mechanical ventilation, 5) need for renal replacement therapy at longest follow-up, 6) days free of renal replacement therapy, 7) duration of vasopressor/inotropic support, 8) days free of vasopressors/inotropes, 9) emergence of antibiotic resistance at longest follow-up, 10) emergence of fungi not susceptible to given antifungal agent, 11) ICU length-of-stay (LOS), 12) hospital LOS and 13) quality of life (as defined by the original trials) at longest follow-up. If multiple time points are reported, we will use and report the outcome with longest follow-up.

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We will assess the risk of small trial bias (publication bias) if ten or more trials are included by visually examining the funnel plots for asymmetry.[20]

Data synthesis

Review Manager (RevMan 5.3) will be used as statistical software to conduct the meta-analyses, including subgroup analyses (summary estimates). For the trial sequential analyses we will use the TSA software available from Copenhagen Trial Unit, Denmark.

Subgroup analysis

We will perform the following subgroup analyses by comparing estimates of the pooled intervention effect in each subgroup, if two of more trials exist:

- Overall low risk of bias versus overall high risk of bias. Hypothesised direction of subgroup effect: increased intervention effect in trials with high risk of bias.
- Prophylactic versus pre-emptive versus empirical treatment strategies. Hypothesised direction of subgroup effect: increased intervention effect

in trials assessing empirical antifungal treatment.

- Non-ICU trials versus ICU trials. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted in the ICU.
- Trials published before the year 2000 versus in and after the year 2000. Hypothesised direction of subgroup: increased intervention effect in trials published before the year 2000.
- Patients with primary versus secondary versus tertiary peritonitis. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted in patients with tertiary peritonitis.
- Patients with versus without septic shock. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted in patients with septic shock.
- Median/mean Mannheim Peritonitis Index (MPI) score > 25 versus trials with a median/mean baseline MPI score ≤ 25. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted on patients with a MPI score > 25.
- Neutropenic vs non-neutropenic patients. Hypothesised direction of subgroup effect: increased intervention effect in trials conducted on neutropenic patients.

We will use Chi-square test to assess statistical heterogeneity between studies (test-of-interaction) with a p-value of 0.10 considered statistically significant.

Sensitivity analysis

In the zero event trials, empirical continuity correction will be applied.[21]

Summary of findings

The quality of evidence for each outcome will be assessed according to GRADE.[16] The domains assessed include risk of bias, inconsistency, indirectness, imprecision and publication bias.[16]

Ethics and dissemination

Ethical approval is not required as this systematic review only includes

previously published data. We aim to publish the systematic review in an international peer-reviewed journal.

Author contributions: MW, FS, AP and MH drafted the protocol. MH and FS developed the idea for the review and is the guarantor of the review.

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Competing interests: None

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APPENDIX

Example of search strategy performed in MEDLINE

(("peritonitis"[MeSH Terms] OR "peritonitis"[All Fields]) OR ("intraabdominal infections"[MeSH Terms] OR ("intraabdominal"[All Fields] AND "infections"[All Fields]) OR "intraabdominal infections"
[All Fields] OR ("intra"[All Fields] AND "abdominal"[All Fields] AND "infection"[All Fields]) OR "intra abdominal infection"[All Fields])) AND (("antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR ("antifungal"[All Fields] AND "agents"[All Fields]) OR "antifungal agents"[All Fields] OR "antifungal"[All Fields]) OR antimycotic[All Fields] OR ("azoles"[MeSH Terms] OR "azoles"[All Fields] OR "azole"[All Fields]) OR ("echinocandins"[MeSH Terms] OR "echinocandins"[All Fields] OR "echinocandin"[All Fields]) OR ("polyenes"[MeSH Terms] OR "polyenes"[All Fields] OR "polyene"[All Fields]) OR ("allylamine"[MeSH Terms] OR "allylamine"[All Fields]) OR ("caspofungin"[Supplementary Concept] OR "caspofungin"[All Fields]) OR ("anidulafungin"[Supplementary Concept] OR "anidulafungin"[All Fields]) OR ("micafungin"[Supplementary Concept] OR "micafungin"[All Fields]) OR ("amphotericin b"[MeSH Terms] OR "amphotericin b"[All Fields]) OR ("nystatin"[MeSH Terms] OR "nystatin"[All Fields]) OR ("itraconazole"[MeSH Terms] OR "itraconazole"[All Fields]) OR ("posaconazole"[Supplementary Concept] OR "posaconazole"[All Fields]) OR ("fluconazole"[MeSH Terms] OR "fluconazole"[All Fields]) OR ("ketoconazole"[MeSH Terms] OR "ketoconazole"[All Fields]) OR ("clotrimazole"[MeSH Terms] OR "clotrimazole"[All Fields]) OR isavuconazonium[All Fields] OR ("miconazole"[MeSH Terms] OR "miconazole"[All Fields]) OR ("voriconazole"[MeSH Terms] OR "voriconazole"[All Fields]) OR ("terbinafine"[Supplementary Concept] OR "terbinafine"[All Fields]) OR ("flucytosine"[MeSH Terms] OR "flucytosine"[All Fields]) OR ("griseofulvin"[MeSH Terms] OR "griseofulvin"[All Fields])

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
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	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
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	6-7
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	7
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	13
Study records:			
Data	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8

management			
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)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
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	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	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 I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9-10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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