Antifungal prophylaxis against invasive *Candida* and *Aspergillus* infection in adult heart transplant recipients : Protocol for a systematic review and meta-analysis

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Abstract

Introduction

Invasive fungal infections (IFI) can contribute to increased mortality and morbidity rates after heart transplant in adults. The most common causes are *Aspergillus* and *Candida* species. There is uncertainty on how effective antifungal prophylaxis is against *Candida* spp infections, and limited guidance on the prevention of *Aspergillus* spp infections. This systematic review and meta analysis will assess the literature to see if antifungal prophylaxis reduces the incidence of IFI after heart transplant in adults.

Methods and analysis

This systematic review protocol follows the Preferred Reporting Items for Systematic reviews and Meta Analysis guidelines. A systematic search of the Cochrane Library,

Web of Science, Scopus, Embase, MEDLINE, and Proquest databases will be undertaken. Reference lists of retrieved publications and conference abstracts will also be searched.

Title, abstract, and full text screening will be undertaken by two reviewers. Discrepancies will be resolved by a third reviewer. Studies with paediatric patients, multi-organ transplants, or patients with a second heart transplant will be excluded, along with those that do not have clear definitions and diagnostic criteria for IFI.

Risk of bias will be assessed using the Cochrane Risk of Bias 2 tool and the Risk of Bias in Non-randomised Studies of Interventions tool.

A meta-analysis will be carried out, though if studies are not deemed to be sufficiently similar, only a narrative synthesis will be undertaken.

Ethics and dissemination

Ethical approval is not required for this systematic review as primary data will not be collected. The results of the review will be disseminated through publication in an academic journal and scientific conferences.

Prospero registration number CRD42024516588

What is already known on the topic

There is little guidance available on the prevention of *Aspergillus* and *Candida* infections after heart transplant due to insufficient evidence.

What this study adds

The last systematic review was undertaken 10 years ago. The proposed review and meta-analysis of the literature will provide a comprehensive overview of all relevant studies.

How this study might affect research, practice or policy

The results will be used to alter local practice, and to provide evidence to the International Society of Heart and Lung Transplantation for the creation of guidelines.

Background

Solid organ transplant (SOT) recipients are vulnerable to developing opportunistic fungal infections due to the immunosuppression required to maintain their transplanted organ.[1] The most common sources of IFI after heart transplantation are *Candida* and *Aspergillus* spp.[2] The risk varies between the organ transplanted, with small bowel and lung transplants at the highest risk of developing an invasive fungal infection (IFI), whilst kidney transplants have the lowest.[3,4] The patient's underlying disease state, co-morbidities, surgical techniques used, and immunosuppression strategy also contribute to overall risk for developing an IFI.[4,5] Patients with lung transplants are most likely to develop invasive *Aspergillus* infections, whilst those with abdominal organ transplants such as a liver, are more likely to develop *Candida* infections.[4,6] Due to the large number of variables contributing to the development of an IFI, results from studies are non-transferable between different SOT populations.

Infections in SOT recipients increase the duration of inpatient stay and escalate the financial impact on the healthcare system. Invasive fungal disease in haematology patients (a group of patients similarly immunosuppressed to SOT recipients) resulted in attributable costs greater than £50,000; 70% of which accounted for inpatient stay.[7,8] Infections also have the potential to raise morbidity and mortality with the presence of an invasive fungal infection (IFI) after organ transplantation resulting in a 1-year mortality of between 19-48%.[9] The incidence of IFI after heart transplant ranges from 3-8% within the first year of transplantation, though it may be as high as 26% in some series.[2,10,11]

To minimise the risk of infection, SOT recipients may be given medication to prevent fungal infection. Preventative strategies include 'prophylactic' – patients at high risk of developing an infection are given medication to decrease this risk, or 'pre-emptive' – there is evidence of infection (e.g. presence of a fungal species in a bronchial aspirate

sample) but no clinical manifestation yet and medication is given to prevent the progression of the infection.[12] Some transplant centres will opt for universal prophylaxis where all transplant recipients will receive prophylactic medication, whilst others will take a more targeted approach depending on factors affecting their patients.[10]

Known risk factors for IFI after heart transplant include hospitalisation prior to transplant, the use of induction immunosuppression, presence of antibody mediated rejection or cytomegalovirus disease, use of renal replacement therapy or extracorporeal membrane oxygenation after transplant, or reopening of the chest cavity.[2,10]

The International Society for Heart and Lung Transplantation (ISHLT) 2023 consensus guidelines and The American Society of Transplantation are unable to recommend the use of prophylactic antifungals against *Candida* spp infections after heart transplant due to insufficient evidence.[13,14] Both transplant societies suggest that prophylaxis against *Aspergillus* spp may be used in patients with known-risk factors, though The American Society of Transplantation is more specific in its recommendations, suggesting a drug, dose, and duration in patients with at least one or more specified risk factors.[2,13]

Whilst justifications can be made for using antifungal prophylaxis, there are also reasons to limit its use. Drug interactions between antifungals (e.g azoles) and some immunosuppressants (e.g. calcineurin inhibitors) can result in unpredictable plasma

levels of the immunosuppressant, increasing the likelihood of adverse effects such as transplant rejection.[15] Additionally antifungal use can contribute to adverse effects such as hepatic impairment.[16]

There is a drive to ensure antifungal usage meets the criteria of antifungal stewardship programmes that ensure antifungals are used within recommended guidelines, monitored correctly, and that treatment is commenced and stopped in a timely manner.[17] Uncontrolled use of antifungals goes against the principle of antifungal stewardship, and can add to the risk of antifungal resistance, potentially making treatment of an IFI more challenging.[18]

The systematic review undertaken by Uribe *et al.* (2014) is the most recent systematic review to look at the evidence supporting antifungal prophylaxis against *Aspergillus* spp infection post heart transplant.[19] The authors of the review stated there is "some evidence of a highly probable benefit of prophylaxis use", but admitted that better studies with standardised comparators were required.[19] The review was not able to find any randomised controlled trials in its search, and was primarily based on the results of retrospective analysis using historical controls.

Another limitation of the review is that it focused only on *Aspergillus* infection. The authors rationalised that this was due to a higher mortality rate of *Aspergillus* infections compared with *Candida* infections, and that most prophylactic antifungals protected against *Aspergillus* and *Candida* spp.[19] However as the systematic review only focused

on *Aspergillus* infection, the findings cannot automatically be applied to *Candida* infections. By analysing studies involving both *Candida* and *Aspergillus* spp, this latest review will be able to provide evidence that can contribute to future guidance on the prevention of IFI after heart transplantation.

The review by Uribe *et al.* was only able to assess a few antifungals; amphotericin B, itraconazole, caspofungin, anidulafungin and micafungin (the search strategy involved eight antifungal agents).[19] This protocol proposes to include thirteen known antifungal agents in the search strategy some of which were not in use at the time of the previous review. These include fluconazole, isavuconazonium, miconazole, posaconazole, voriconazole, rezafungin, flucytosine, and nystatin, in addition to those included in the initial review.

We will undertake a systematic review and meta-analyses of the available studies to assess whether antifungal prophylaxis reduces the incidence of IFI after heart transplant. As a secondary outcome the review will aim to look at mortality attributed to IFI, and to identify which antifungal, dose, and duration of use provides the most effective prophylactic cover against IFI. This review will provide evidence-based guidance in order to direct clinical practice.

Review question

Does antifungal prophylaxis reduce the incidence of an invasive *Candida* spp or *Aspergillus* spp fungal infection in adult heart transplant recipients?

Method

This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for protocols PRISMA-P.[20] (See supplemental material).

The search will be undertaken and reported as per the PRISMA-S (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.[21] SwiM (Synthesis Without Meta-analysis) guidelines will also be used as an extension to the PRISMA should a meta-analysis not be appropriate (if data is not sufficiently similar – see 'Data Synthesis' section).[22]

The overall quality of evidence will be evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[23]

The review will be undertaken as according to this protocol. Any deviations from the protocol will be reported in the systematic review / meta-analysis.

Study criteria

Randomised control trials and non-randomised studies of intervention (such as quasi-randomised trials, prospective cohort studies and case-control studies) that evaluate the

use of antifungals in the prevention of IFI will be included. Case reports, case series, cross sectional studies, and retrospective cohort studies will be excluded.

Inclusion

Studies will be eligible for review if they meet the following criteria:

Participants

Adult (age ≥ 18 years) heart transplant recipients within one year of transplantation who received antifungal prophylaxis.

Interventions

The intervention group will have received any prophylaxis against *Candida* spp or *Aspergillus* spp infection with a known antifungal agent (i.e. fluconazole, itraconazole, isavuconazonium, miconazole, posaconazole, voriconazole, anidulafungin, caspofungin, micafungin, rezafungin, amphotericin b, flucytosine, nystatin). The dose and duration of treatment with the antifungal agent will be analysed as a secondary outcome of the review.

Comparators

No antifungal agent, or different antifungal agents, dosing regimens and duration of prophylaxis.

Outcomes

The primary outcome will be to identify the incidence of IFI. The secondary outcomes will be mortality attributed to IFI, any adverse effects related to antifungal use, and which is

the preferred antifungal agent, dose and duration of use based on effectiveness. Studies will need to have clear definitions and diagnostic criteria for IFI, and transparent outcomes related to IFI.

Exclusion

The following will be excluded from the review:

- Studies that include only paediatric populations (age < 18 years) (due to variations in risk factors, and altered antifungal dosing requirements)
- Studies with patients that have multi-organ transplants, or patients with a second heart transplant (due to a difference in risk factors contributing to heterogeneity)
- Studies looking at *Pneumocystis jiroveci* (PJP) infection as there are clear recommendations available on its prevention.[13]
- Studies looking primarily at alternative fungal infections (i.e. *Cryptococcosis* spp, *Coccidioides* spp) as they are not common causes of IFI after heart transplantation.
- Studies looking at topical antifungals (as they are not used to treat IFI).
- Studies that have not provided clear definitions and diagnostic criteria for IFI

Search methods

Only English language papers will be included in the study due to limited resources.

Electronic searches

We will systematically search the following databases: Cochrane Library, Web of Science, Scopus, Embase, MEDLINE and Proquest. All databases will be searched from their inception to the present day.

Other resources

Reference lists of retrieved publications will be analysed to identify studies that are missing from the initial search. Conference abstract lists will be searched. An equivalent search strategy will be used to identify any ongoing, or completed clinical trials at ClinicalTrials.gov, The Turning Research into Practice (TRIP) database, euclinicaltrials.eu, and The World Health Organisation (WHO) International Clinical Trials Registry (ICTRP) search portal. If any relevant studies are found, the principal investigator will be contacted to see whether findings can be included in the review.

Duplicate reports of the same study will be excluded. If a complete paper or study data cannot be obtained through the search, the authors will be contacted a maximum of two times to request the paper. If they are unable to provide the required information, the study will be included in the review but excluded from the meta-analysis of the data. All searches will be rerun prior to publication of the systematic review.

Search strategy

Key search terms will be *heart transplantation*, *antifungal*, *Candida* and *Aspergillus*. Table 1 lists all the relevant search terms. Search terms will be linked by Boolean

operatives “AND” or “OR”. Synonyms and variations in spelling between UK and US English will be taken into account. If additional keywords are detected during the search, the search strategy will be updated to include these terms. This deviation from the protocol will be documented in the final review. The search strategy for Ovid MEDLINE and all the search terms used can be found in the appendix. The strategy will be adapted for all selected databases.

Table 1: List of search terms

Terms relating to *heart transplantation*
Heart Transplant(ation) or cardiac transplant(ation)
Terms relating to *antifungal*
anti-fungal or antifungal
mold or mould
mycoses or mycosis
fluconazole or itraconazole or isavuconazonium or miconazole or posaconazole or voriconazole or anidulafungin or caspofungin or micafungin or rezafungin or amphotericin b or flucytosine or nystatin
prophylaxis or prevent* or pre-emptive
Terms relating to *Candida and Aspergillus*
Candida or Candidaemia or Candidiasis
Aspergillus or Aspergillosis

Data collection and analysis

The review will be undertaken based on recommendations by Cochrane.[24]

Study reviews and selection will be undertaken by all authors using Rayyan. Screening will be undertaken by two reviewers, with any disagreements being resolved initially by discussion, and if necessary by a third reviewer.

Selection of studies

Study selection will be undertaken firstly by screening of titles and abstracts, and secondly the full paper. Studies will be screened by two authors and discrepancies will be resolved by a third reviewer. An abstract screening tool will be created to identify and record suitable studies for review, and to document the reasons for why a study is being rejected. The number of studies selected for the systematic review will be presented using the PRISMA 2020 flow diagram.[25]

Data extraction

Prior to data extraction, the data extraction form will be piloted on at least one study to ensure it is suitable. If necessary, the form will be amended prior to starting the systematic review. We will aim to gather the following information from each study eligible for review as per the recommendations of The Cochrane Handbook.[26]

Trial characteristics: name of authors and dates of study, study type, method of statistical analysis, biases in reporting results, sources of funding for study and/or

conflicts of interest, country in which study took place, length of follow up, and the diagnostic criteria used to define IFI.

Participant characteristics: gender, age, ethnicity, co-morbidities, reason for transplant, and the presence of any risk factors for IFI.

Outcomes: Antifungal use (name, dose, and duration if used), the definition of IFI used, the incidence of IFI, the severity of IFI (where possible), mortality related to IFI, and the timings of IFI detection in relation to heart transplantation.

Results: number of participants in study, number of participants excluded or lost to follow up, summary of data for each group of participants, effect of intervention on outcome (risk ratio, confidence interval, statistical significance), and the key conclusions of study authors.

Risk of bias assessment

Two reviewers will separately evaluate the risk of bias (ROB) in the studies selected for review, with any disagreements being resolved initially by discussion, and if necessary by a third reviewer. Randomised control trials will be assessed using the Cochrane ROB 2 tool, and non-randomised control trials will be assessed using the 'Risk Of Bias In Non-randomized Studies of Interventions' (ROBINS-I) tool.[27,28]

The risk of bias judgements made will be presented using the 'robvis' visualisation tool to create weighted bar plots to show the distribution of risk of bias judgements.[29] If one

or domains in each study is judges to have a ‘high’, ‘serious’, or unclear risk of bias, the trial will be classified as having a high risk of bias.

Data synthesis

A narrative synthesis will be undertaken. If studies clearly define the diagnostic criteria for used to determine IFI, and if studies are sufficiently similar (e.g. study populations and methods are similar and data is homoegenous) , a meta-analysis of the data will be undertaken by a statistician.

Dichotomous data will be analysed by calculating the risk ratio with a 95% confidence interval. Continuous data will be analysed by calculating the mean difference with corresponding standard deviation, and 95% confidence interval. All statistical analyses will be performed using RevMan software.

Clinical heterogeneity and risk of bias will be described and considered in the narrative synthesis. Statistical heterogeneity will be quantified using the Chi^2 test to see if observed differences are due to chance alone.[30] The I^2 test will be used to estimate the variance between studies, with a p-value of 0.10 considered statistically significant in this instance.[30] If a meta-analysis is appropriate, then a random effects model with be used to analyse the data. If meta-analysis is not appropriate due to heterogeneity then a narrative synthesis will be undertaken.

The quality of evidence and strength of recommendation for each outcome will be assessed according to the GRADE system, and present the findings in a 'summary of findings' table.[23]

Discussion

IFI after heart transplantation can increase mortality rates, the amount of time spent as an inpatient, and costs for healthcare providers.[7] The most common sources of IFI after heart transplantation are *Candida* and *Aspergillus* spp.[13] There is limited guidance available for the prevention of *Aspergillus* infection in adult patients at high risk of IFI, and there is insufficient evidence to recommend any preventative measures against *Candida* infection. The systematic review undertaken ten years ago, is the latest studying antifungal prophylaxis after heart transplantation and it concluded that better studies were required.[19]

This proposed review will enable analysis of all data available to make recommendations to direct current clinical practice. Recommendations will be made to the relevant working groups within the European Society for Organ Transplantation (ESOT) and the International Society for Heart and Lung Transplantation (ISHLT). The number of antifungals available for use has increased and it is anticipated that studies involving new and old agents will help to create a stronger evidence base regarding the need for antifungal prophylaxis, and the optimal agent. Review findings will be limited if participant

numbers in studies are low and if data is too heterogeneous to undertake a meta-analysis. The clinical application of the recommendations will be limited to the adult population only, thus excluding children who have received heart transplants. A separate systematic review and meta-analysis will be required to analyse IFI and antifungal prophylaxis requirements in child heart transplant recipients. By only including English language papers (due to time constraints) there is a risk of publication bias in the proposed review.

Review findings will be presented at relevant scientific conferences and will be submitted for publication to a peer reviewed journal. It is anticipated that this review will highlight areas that require further research, such as the use of antifungal propylaxis in paediatric heart transplant recipients, risk factors that contribute to IFI afer heart transplantation, and potentially studies looking at optimal duration of prophylaxis, pending the findings of this review.

Conclusion

A systematic review and meta-analysis looking at antifungal use after heart transplant will be able to provide guidance on antifungal need, choice and duration to complement antifungal stewardship programmes. The review will also highlight potential areas of further research such as the risk factors contributing to IFI after heart transplantation.

Patient and Public involvement has not been required as this systematic review is based on published studies.

Ethical approval is not required for this systematic review as primary data will not be collected. The results of the review will be disseminated through publication in an academic journal and scientific conferences.

Contributions ZI and HSL designed the research question. ZI drafted the manuscript with AJ, HSL, and IM providing guidance on all aspects of the manuscript. ZI is the guarantor.

Funding Not applicable

Competing interest None declared

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