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# Antifungal prophylaxis following heart transplantation: systematic review

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## Summary

Patients with heart transplantation have a high incidence of infectious complications, especially fungal infections. The aim of the systematic review was to determine the best pharmacological strategy to prevent fungal infections among patients with heart transplant. We searched the PubMed and Embase databases for studies reporting the effectivenesss of pharmacologic strategies to prevent fungal infections in adult patient with a heart transplant. Our search yielded five studies (1176 patients), four of them with historical controls. Two studies used inhaled amphotericin B deoxycholate, three used itraconazole and one used targeted echinocandin. All studies showed significant reduction in the prophylaxis arm. Different products, doses and outcomes were noted. There is a highly probable benefit of prophylaxis use, however, better studies with standardised doses and comparators should be performed.

**Key words:** Antifungal agents, antifungal agents/therapeutic use, *Aspergillus*, heart trasplantation, heart transplantation.

## Introduction

Invasive fungal infections (IFI) are a leading cause of death among heart transplant recipients and have a cumulative incidence of 3.4% in the first year following transplantation.[1] Invasive candidiasis remains the most common IFI in these patients accounting for 49% of cases, followed by invasive aspergillosis (IA) 23%, cryptococcosis 10%, non-*Aspergillus* moulds 7.1% and the endemic fungi 3%. The majority of the invasive candidiasis and aspergillosis cases occur in the first 180 days following transplantation. However, their onset following transplantation can be widely variable among different transplant centres due to differences in prophylactic antifungal measures, changes in surgical techniques, posttransplant care and CMV prophylaxis strategies.[2] Although the incidence of fungal infections in this group of patients have steadily declined over the past 30 years due to use of more selective immunosuppression and use of antifungal prophylaxis,[3] the high mortality caused by IFI is still a concern, reaching 75–100% in non-aspergillus mould IFI of the central nervous system.[4] Antifungal prophylaxis is a common practice used worldwide in various heart transplant centres, but questions about the specific antifungal, appropriate strategy (e.g. universal vs. targeted) and duration, continues to be controversial. It has centred on invasive aspergillosis due to the high mortality, high frequency, clinical and economical impact[5] and the fact that it covers *Candida* as well. Currently, there is no recommendation for the routine use of prophylaxis against *Candida* in heart transplant patients.[6] The goal of this study was to perform a systematic review of the literature to evaluate the evidence supporting the use of primary antifungal prophylaxis against aspergillosis following heart transplantation.

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## Material and methods

The following databases were searched using the search terms detailed in Data S1: Medline (1966–October 2013), EMBASE (1980 to October 2013), Cochrane Library (Issue 11 2013), LILACS (1980 to October 2013) and ISI Web of knowledge. This search included randomised controlled, controlled, not controlled, prospective or retrospective studies. All relevant studies regardless of language were included. Participants were limited to adults with heart transplants who received primary antifungal prophylaxis (antifungal medication before any fungal infection diagnosed). Studies were eligible if they included participants with and without antifungal prophylaxis, diagnostic criteria of IFI were clearly defined and information about outcomes related to IFI could be extracted. Antifungal prophylaxis intervention could include any known antifungal (i.e. amphotericin B, including lipid formulations, fluconazole, itraconazole, voriconazole, posaconazole, caspofungin, anidulafungin and micafungin). Primary outcomes included total (all cause) mortality, mortality attributable to IFI and incidence of IFI. Serious adverse events (those leading to hospitalisations and/or death), other adverse events (gastrointestinal, allergic/cutaneous, fever, neurological, haematological, hepatic among others) and non-compliance to treatment, if stated, were compared. Case reports or series of cases with insufficient data and outcome were excluded as well as trials using pre-emptive therapy. Duplicate reports of the same trial were also excluded *P. jirovecci* pneumonia, an important IFI in heart transplant patients, was excluded from this study because it is prevented by a separate class of drugs (e.g. trimethoprim-sulphamethoxazole) and the antimicrobial prophylaxis of choice is less controversial.

### Selection of studies

Three authors (LGU, CEG and JAC) screened the article titles and abstracts identified from the literature search to identify relevant studies. In cases of doubt, we obtained the full text for assessment. JAC and LGU obtained the full text of each citation and they were individually assessed. In case of disagreement between the reviewers, a third author (CEG) was invited to comment.

### Data extraction and management

Data were extracted from each article and a consensus was reached by all authors regarding the information to be analysed. Data regarding outcomes and number of participants for which outcomes were measured in treatment arms were extracted and tabulated. Internal validity including selection of subjects, risk of bias or confounding variables, measures of treatment effect, reporting bias and overall quality of evidence was performed and discussed for each study.

## Results

Using the search strategy delineated in 'Materials and Methods', 262 references were identified (see Data S1) and 20 duplicate references eliminated. The remaining 242 references were screened by analysing the information provided in the abstract. This systematic review yielded 15 potential studies for inclusion. The full text articles of these 15 studies were reviewed yielding only five studies that met the inclusion criteria for a total of 1176 patients (Fig. 1). These five studies were retrospective; four of the five used

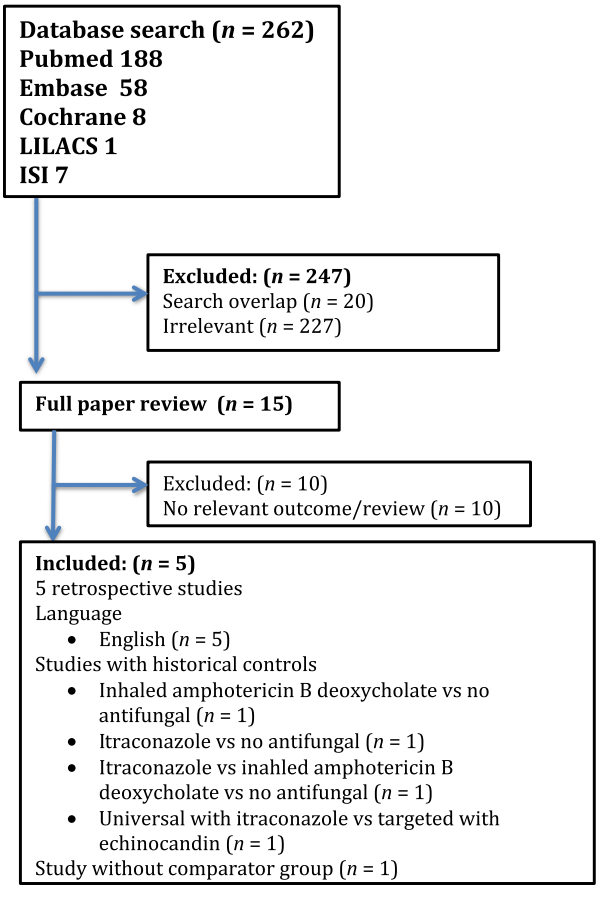


**Figure 1** Flow diagram showing the study selection process.

historical controls and one study did not have a comparator group. Of note, no randomised controlled trial was found in this systematic review. A qualitative analysis of the impact of antifungal prophylactic interventions in these four studies was performed by comparing amphotericin vs. no antifungal, itraconazole vs. no antifungal, itraconazole vs. amphotericin vs. no antifungal, itraconazole vs. targeted echinocandins and itraconazole use without comparator group (Table 1).

#### Inhaled amphotericin vs. no antifungal (historical controls)

In 1997 Reichenspurner *et al.* [7] reported their findings on a retrospective analysis of 126 cardiothoracic transplant patients from 1993 to 1996 who received inhaled amphotericin B throughout the hospital stay (at a dose of 5 mg TID to be increased up to 20 mg TID within the first 5 days after surgery). Of these, 75 patients were heart transplants. The incidence and spectrum of fungal infections were compared to a historical control group of 77 heart transplant patients before this period of time when no prophylaxis was given. Both groups received the same immunosuppressive protocol. Authors did not report their criteria used for the diagnosis of IFI (total numbers of IFI, aspergillosis and candidiasis). The incidence of total fungal infections, IA and candidiasis had a significant reduction in the amphotericin group at both 3 and 12 months post transplant. Known risk factors or important variables for IFI were not detailed for their two groups of patients. The administration of inhaled amphotericin was deemed to be safe. The only side effect was nausea which led to the discontinuation of inhaled amphotericin B in two patients. In a subsequent report from the same institution, the protective effect of inhaled amphotericin B for IA was confirmed using a model of longitudinal trends of actuarial incidence of IA ($P < 0.35$).[8]

#### Itraconazole vs. no antifungal (historical controls)

In 2004 Muñoz *et al.* [9] reported findings on a retrospective comparative study using historical controls with the aim to evaluate the efficacy of itraconazole capsules (PO) as universal antifungal prophylaxis and to potentially identify high-risk patients who could benefit from targeted antifungal prophylaxis. Only proven or probable IA cases were included in their analysis as defined by the National Institute of Allergy and Infectious Diseases Mycoses Study Group.[10] Of the 278 patients enrolled in their study, the first 185 patients included (1988 to September 1994 period) did not receive any kind of antifungal prophylaxis (cohort 1). The remaining 93 patients (October 1994–2002) received itraconazole 400 mg per day since day 5 post trasplant, for a period of 110 ± 49 days (cohort 2). Patients in cohort 2 underwent routine monitoring of itraconazole levels and were prescribed 3 or 6 months of itraconazole in the absence or presence of rejection respectively. Immunosuppressive regimens and CMV prophylaxis protocols used in both cohorts varied over time. In this study, a broad and detailed list of possible risk factors for IA was analysed with the aim to identify variables that could independently influence outcomes and identify patients at high risk of IA. Although it was a worthwhile task, the authors acknowledge the limitations inherent to studies comparing historical cohorts given variations over time in the use of immunosuppression drugs, diagnostic technology, other opportunistic and nosocomial infections and availability of antimicrobials.[11] Through a multivariate analysis (regression logistic model) independent risk factors for IA were obtained: reoperation (RR 5.8%; 95% CI 1.8–18 $P = 0.002$), CMV disease (RR 5.2%; 95% CI 2–13.9 $P = 0.001$), posttransplant haemodialysis (RR 4; 95% CI 1.2–18 $P = 0.02$) and other cases of IA in the HT programme 2 months before or after transplant date (RR 4.6; 95% CI 1.5–14.4 $P = 0.007$). IA was diagnosed in 24 of a total of 278 patients (8.6%) in the first year after transplant (media of 50 ± 63 days after HT). All cultures grew *Aspergillus fumigatus*. Use of universal prophylactic itraconazole had a protective role with a calculated RR of 0.2 IC 95%(0.07–0.9) $P = 0.03$. Previous studies have suggested that prophylaxis against CMV and specific immunosuppressive regimens have an important impact on the incidence of invasive fungal disease.[8] In this study, CMV disease was shown to be a risk factor, but although immunosuppression agents from induction and maintenance changed from both periods of time, neither the univariate analysis nor the multivariate analysis showed these differences in immunosuppression as a risk factor.

#### Itraconazole vs. amphotericin vs. no antifungal (historical controls)

In 2010 Paniagua *et al.* reported findings on a single-centre, retrospective study that included 571 adult heart transplant patients (from 1991 to 2009) with the aim to determine the impact of universal antifungal prophylaxis in the incidence of IA during the first 3 months following heart transplantation.[12] Three prophylactic regimens were compared: no prophylaxis – 1991–1994

**Table 1** Studies on primary antifungal prophylaxis in heart transplant patients.

| Study | Population | Methodological aspects | Intervention | Doses of antifungal used & presentation & Intervals | Drug levels of antifungal | Outcomes & adverse events | Results |
|---|---|---|---|---|---|---|---|
| Reichenspurner H, *et al.* 1997 USA [7] | 152 | Retrospective analysis using historical cohorts<br>No definition of the invasive fungal infections studied (total numbers of invasive fungal infections, aspergillosis, and candidiasis) was provided | No prophylaxis 77 patients<br>Universal prophylaxis with inhaled amphotericin 75 patients for in hospital stay | Amphotericin B deoxicholate (5 mg TID to be increased up to 20 mg TID within 5 days after surgery) and during posttransplant hospital stay | No | Incidence of invasive fungal infections at 3 and 12 months | Incidence of invasive fungal infections was lower in the intervention cohort |
| Muñoz P, *et al.* 2004 Spain [9] | 278 | Retrospective analysis using historical cohorts<br>Definition of invasive aspergillosis according to the National Institute of Allergy and Infectious Diseases Mycoses Study Group | No antifungal prophylaxis for 185 patients<br>Universal prophylaxis with itraconazole was administered to 93 patients for 3–6 months | From day 5 after HT oral Itraconazole 600 mg for the first 3 days then 400 mg oral day$^{-1}$<br>Itraconazole capsules were administered with food and cola drink. Duration was 3 months for patients without rejection 6 months for patients with rejection | Yes | Incidence of invasive aspergillosis<br>1-year survival | Itraconazole showed independent protective value against developing invasive aspergillosis RR of 0.2 CI 95% (0.07–0.9) $P = 0.03$.<br>Prolonged 1 year survival RR 0.5 CI 95% (0.3–0.8) $P = 0.01$ |
| Paniagua Martin MJ, *et al.* 2010 Spain [12] | 571 | Retrospective analysis using historical controls<br>No definition of *Aspergillus* infection, aspergillus tracheobronchitis, invasive or disseminated aspergillosis, was provided | No prophylaxis to 99 patients<br>Universal prophylaxis with itraconazole to 352 patients for 3 months<br>Universal prophylaxis with inhaled amphotericin B to 120 patients for 3 months | Itraconazole oral capsules 200 mg day$^{-1}$ for 3 months<br>Inhaled amphotericin B deoxycholate 7.5 mg every 8 h during mechanical ventilation then liposomal amphotericin B 50 mg weekly for 3 months | No | Incidence of aspergillosis, | Incidence of aspergillosis was lower in the two periods of prophylaxis compared to period of no prophylaxis (5% with no intervention vs. 1.4% with itraconazole and 0% with inhaled amphotericin) |

**Table 1** Continued.

| Study | Population | Methodological aspects | Intervention | Doses of antifungal used & presentation & Intervals | Drug levels of antifungal | Outcomes & adverse events | Results |
|---|---|---|---|---|---|---|---|
| Hayes DJ, *et al.* 2011 USA [13] | 42 | Retrospective analysis of a single cohort receiving itraconazole. No comparator group.<br>Definition of invasive fungal infections according to the National Institute of Allergy and Infectious Diseases Mycoses Study Group | Universal prophylaxis with itraconazole for 12 months | From day 3.2 ± 3.8 days of surgery oral itraconazole 200 mg $day^{-1}$<br>Mean duration of 12 months | No | Incidence of invasive fungal infections | Five out of 42 patients developed fungal invasive disease (incidence 11.9%) |
| Muñoz P, *et al.* 2013 Spain [16] | 226 | Retrospective analysis using historical controls.<br>Definition of invasive aspergillosis according to the National Institute of Allergy and Infectious Diseases Mycoses Study Group | Universal prophylaxis with itraconazole to 93 patients for 3–6 months (from Muñoz *et al.* 2004 reference)<br>Targeted prophylaxis with echinocandins to 13 of 133 (9.8%) eligible patients that presented at least one risk factor for invasive aspergillosis | Itraconazole dose according to Muñoz *et al.* 2004.<br>Antifungal agent (caspofungin, anidulafungin or micafungin) was selected by the attending physician and the infectious diseases consultant. Targeted prophylaxis was maintained for approximately 1 month after resolution of all risk factors | Yes (Muñoz *et al.* 2004)<br>Not applicable | Incidence of invasive aspergillosis, *Aspergillus* – related mortality. | In the historical prophylaxis group, IA was present in 8.6% of the patients and had an attributable mortality of 5.75%.<br>In the targeted prophylaxis group, IA was present in 2.25% of the patients and had an attributable mortality of 1.5%. |

($n = 99$), itraconazole capsule 200 mg day for 3 months – 1995–2004 ($n = 352$) and inhaled amphotericin deoxycholate while the patient was on mechanical ventilation followed by liposomal amphotericin B for 3 months; liposomal amphotericin was administered at a 50 mg weekly dose – 2004 to 2009 ($n = 120$). Authors did not report the criteria used for the diagnosis of IA but the disease was divided in aspergillus tracheobronchitis and invasive/disseminated aspergillosis. Itraconazole serum levels were not monitored. Known risk factors or dependent variables highly associated with progression of IA were not reported. The incidence of aspergillosis was 5% in the first group, 1.4% in the second group and 0% in the third group. No adverse effects were associated with use of itraconazole but in three of 120 patients (2.5%) using inhaled amphotericin had to be discontinued because of repeated atelectasis and orotracheal tube blockade. Differences in severity of the disease were observed among the three groups of prophylaxis. Eighty per cent (4/5) of the invasive/disseminated aspergillosis cases were diagnosed in the group without prophylaxis, whereas 80% (4/5) of the tracheobronchitis cases in the group with itraconazole prophylaxis. Patients in this study received the following immunosuppressive regimen: for induction: OKT3 (5 mg $day^{-1}$ for 3–10 doses, which was substituted with basiliximab in 2000); for maintenance: cyclosporine or tacrolimus, azathioprine (replaced by mycophenolate mofetil in 1998) and steroids.

Authors concluded that universal prophylaxis with itraconazole or amphotericin significantly impacted the incidence of aspergillosis (from 5% to 1.4% and 0%). The interaction of immunosuppressive drugs (calcineurin inhibitors and proliferation signal inhibitors) with itraconazole led them to change the prophylactic regimen to amphotericin in the last period (2004–2009).

#### Itraconazole without comparator group

In 2011, Hayes *et al.* [13] reported findings on a retrospective study including 42 heart transplant patients who received itraconazole (PO) prophylaxis at a dose of 200 mg day for a period of 12 months starting from day 3.2 ± 3.8 days post transplant. The form of itraconazole (solution vs. capsules) used in their study was not specified and serum itraconazole levels were not monitored. Authors decided not to use historical controls since, in their judgement, surgical techniques, antimicrobial and antifungal prophylaxis strategies and other infectious complications at their institution had change sufficiently over time making comparisons unfeasible. Proven, probable or possible IFI cases were included as defined by the National Institute of Allergy and Infectious Diseases Mycoses Study Group.[10] Their overall incidence of IFI was reported at 11.9% (4 patients, five cases of 42 patients), which is relatively high compared with incidence of IFI at other transplant centres.[14,15] Unfortunately, known risk factors for IFI and other dependent variables were not detailed. No significant adverse effect was identified with the use of itraconazole. Of interest, a weak relationship (without statistical significance) between a recent episode of rejection and subsequent development of IFI was noted during the first 6 months following transplantation (three of four patients who developed IFI had received treatment for rejection).

#### Universal itraconazole vs. targeted echinocandin prophylaxis

Recently, in 2013 Muñoz *et al* [16] reported findings on a retrospective study using historical controls comparing the efficacy of universal prophylaxis with oral itraconazole vs. targeted prophylaxis with echinocandins. The historical control group using universal prophylaxis with oral itraconazole ($n = 93$) was the same cohort reported in their 2004 publication.[9] The targeted prophylaxis with echinocandin group included a new cohort of 133 heart transplant patients who received caspofungin, anidulafungin or micafungin only if they had at least one risk factor for IA ($n = 13$; thus, 120 patients did not qualify to receive echinocandin targeted prophylaxis). Only proven or probable invasive aspergillosis cases were included in their analysis as defined by the National Institute of Allergy and Infectious Diseases Mycoses Study Group. Risk factors for invasive aspergillosis that had been identified in their 2004 study were reoperation, CMV disease, posttransplantation haemodialysis and the existence of another patient with IA in their heart transplant programme 2 months before or after the procedure. The duration of each risk factor was established as follows: haemodialysis was considered a risk factor while it was ongoing; CMV disease was considered a risk factor while the patient was receiving antiviral therapy; and reoperation was considered a risk factor for 7 days. Echinocandin prophylaxis was started from the beginning of the risk factor and continued for 3–4 weeks after their resolution. Caspofungin was administered at a loading dose of 70 mg for one dose, followed by 50 mg per day; caspofungin dose was adjusted in cases of Child B score for liver failure (50 mg $day^{-1}$ as the loading dose followed by 35 mg $day^{-1}$). Anidulafungin

at a loading dose of 200 mg for one dose, followed by 100 mg per day. Micafungin was administered at 100 mg per day without a preceding loading dose. As reported in their 2004 study, in the universal prophyaxis with itraconazole group, IA had an incidence of 8.6% and an attributable mortality of 5.75%. In their 2013 study, in the targeted prophylaxis with echinocandin group, IA had an incidence of 2.25% ($P = 0.01$ when compared to the 2004 study) and attributable mortality of 1.5% ($P = 0.06$ when compared to the 2006 study). Using their targeted approach only 13 (9.8%) of 133 patients required echinocandin prophylaxis. Of the patients on prophylaxis, 1 of 13 (7.7%) developed IA. This patient was receiving caspofungin because of two risk factors were present (haemodialysis and reoperation). In addition, a reduced dose (35 mg $day^{-1}$) of caspofungin had being used because of liver failure despite his high body mass index of 35 kg $m^{-2}$ and that apparently the patient had been exposed to an extremely high environmental load of *Aspergillus* while in the intensive care unit. Of the remaining 120 patients who were not eligible to receive prophylaxis, two (1.6%) developed very early IA (mean of 26 days following heart transplantation) within a period of an ongoing outbreak of IA. One potential bias in favour of the echinocandin protective effect is that in patients whose prophylaxis was initiated due to the presence of a previous IA case, the protective effect of introducing HEPA filters cannot be separated from the protective effect of echinocandin.

## Discussion

A systematic review of the literature did not yield a single randomised controlled trial assessing the utility of primary antifungal prophylaxis following heart transplantation. However, five studies were identified using retrospective designs and historical controls (i.e. quasi-experimental study design).[7,9,12,13,16] With the exception of one study,[13] these studies used historical controls as their comparator group (Table 1). Using this methodology, each of the four studies reported a reduction in the incidence of IFI and attributable mortality to IFI. Three of the studies used widely accepted definitions of IFI (i.e. those of the National Institute of Allergy and Infectious Diseases Mycoses Study Group), one study used their own definitions[12] and the remaining study took place before definitions such as the National Institute of Allergy and Infectious Diseases Mycoses Study Group were available.[7]

The antifungal agents used in the five studies included inhaled amphotericin B deoxicholate, inhaled amphotericin B lipid complex, itraconazole and the three clinically available echinocandins. Other antifungals commonly used for primary prophylaxis in other transplant settings such as a voriconazole[17] and posaconazole[18] had not been studied in the context of heart transplantation. Future studies could assess the role of these newer antifungal agents for primary prophylaxis in the setting of heart transplantation. Doses, formulations, drug level monitoring and protocols of the antifungals used in these studies varied significantly among studies and continue to be a source of confusion and debate for transplant programmes in need to initiate protocols for primary antifungal prophylaxis.

Among azole drugs, only itraconazole has been studied as primary antifungal prophylaxis following heart transplantation despite that it carries a 'black box warning' in its label regarding a risk of negative cardiac inotropic effect.[19] However, it appears that the negative effect on left ventricular contractility produced by itraconazole either is not clinically significant in patients receiving a new heart and/or it is outweighed by beneficial effect of itraconazole in lowering the incidence of IFI. The negative inotropic effect of itraconazole should provide the impetus to further study alternative antifungal drugs for primary prophylaxis following heart transplantation such as other oral azoles (e.g. voriconazole, posaconazole), inhaled formulations of amphotericin B or echinocandins. It also supports the study of strategies such as targeted prophylaxis that significantly decrease the number of heart transplant patients receiving the antifungal drug.[16]

It is difficult to agree on the threshold in IFI incidence that should trigger primary antifungal prophylaxis at a given heart transplant programme. Based on the study by Muñoz *et al.* [9] it appears reasonable to adopt primary antifungal prophylaxis in centres when the incidence of aspergillosis is ≥5%. However, a sudden increase in the incidence of IFI considered to constitute an outbreak or epidemic should also prompt the programme to consider initiation or change in their primary antifungal prophylaxis strategy. In transplant centres where the incidence of IFI is <5% targeted prophylaxis as outlined by Muñoz *et al.* [9] should be considered assuming that the risk factors are the same as those described in this study.

Although randomised controlled trials to determine the efficacy of primary fungal prophylaxis following heart transplantation have not been performed, it appears that the evidence provided by studies using historical controls is sufficient to avoid the need of *placebo* controlled trials in the future. Studies should use widely accepted definitions of IFI (i.e. those provided by the

European Organisation for the Research and Treatment of Cancer/National Institute of Allergy and Infectious Diseases Mycoses Study Group).[10] It will be important to perform prospective clinical trials to avoid biases inherent to the use of historical controls using itraconazole in the comparator group since it has been the most frequently studied antifungal drug in this setting. An endpoint evaluating the impact of itraconazole on left ventricular function should be included because of its potential to cause a negative inotropic effect in heart transplant patients. Formulation (capsules vs. suspension), dose and results of itraconazole serum levels should be reported in those trials. Itraconazole suspension formulation (including a loading dose) is suggested in future trials since it has greater bioavailability than the capsule formulation.[20] Therapeutic drug monitoring (TDM) is crucial because itraconazole is notable for having significant patient-to-patient variability in its pharmacokinetic and pharmacodynamics properties and for major drug–drug interactions. Although there is no agreement on what constitutes an optimal level of itraconazole, it is now widely accepted that TDM should be instituted for prophylaxis or treatment purposes to detect patients with extreme low (e.g. itraconazole $<1$ mcg ml$^{-1}$) or high (e.g. $>10$ mcg ml$^{-1}$) levels. Itraconazole levels should be obtained every week until the desired prophylactic level is reached. Once this is obtained levels could be measured every month for the duration of the prophylaxis. Alternative options for the comparator group in future studies include inhaled amphotericin B formulations and echinocandins.

In conclusion, our systematic review showed some evidence of a highly probable benefit of prophylaxis use, in terms of a lower incidence of invasive aspergillosis and prolonged survival; however, better studies with standardised doses and comparators should be performed.

## Financial disclosure

None.

## Conflict of interests

None.

## References

1 Muñoz P, Fernandez NS, Farinas MC. Epidemiology and risk factors of infections after solid organ transplantation. *Enferm Infecc Microbiol Clin* 2012; **30**(Suppl 2): 10–18.
2 van Hal SJ, Marriott DJ, Chen SC *et al.* Candidemia following solid organ transplantation in the era of antifungal prophylaxis: the Australian experience. *Transpl Infect Dis* 2009; **11**: 122–7.
3 Haddad F, Deuse T, Pham M *et al.* Changing trends in infectious disease in heart transplantation. *J Heart Lung Transplant* 2010; **29**: 306–15.
4 Playford EG, Webster AC, Sorell TC, Craig JC. Antifungal agents for preventing fungal infections in solid organ transplant recipients. *Cochrane Database Syst Rev* 2004; **3**: CD004291.
5 Baddley JW, Andes DR, Marr KA *et al.* Antifungal therapy and length of hospitalization in transplant patients with invasive aspergillosis. *Med Mycol* 2013; **51**: 128–35.
6 Silveira FP, Kusne S. A.S.T. infectious diseases coumminty of practice. Candida infections in solid organ transplantation. *Am J Transplant* 2013; **13**(Suppl 4): 220–7.
7 Reichenspurner H, Gamberg P, Nitschke M *et al.* Significant reduction in the number of fungal infections after lung-, heart-lung, and heart transplantation using aerosolized amphotericin B prophylaxis. *Transplant Proc* 1997; **29**: 627–8.
8 Montoya JG, Giraldo LF, Efron B *et al.* Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. *Clin Infect Dis* 2001; **33**: 629–40.
9 Muñoz P, Rodriguez C, Bouza E *et al.* Risk factors of invasive aspergillosis after heart transplantation: protective role of oral itraconazole prophylaxis. *Am J Transplant* 2004; **4**: 636–43.
10 De Pauw B, Walsh TJ, Donnelly JP *et al.* Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46**: 1813–21.
11 Patterson TF, Kirkpatrick WR, White M *et al.* Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 *Aspergillus* study group. *Medicine (Baltimore)* 2000; **79**: 250–60.
12 Paniagua Martin MJ, Marzoa Rivas R, Barge Caballero E *et al.* Efficacy and tolerance of different types of prophylaxis for prevention of early aspergillosis after heart transplantation. *Transplant Proc* 2010; **42**: 3014–16.
13 Hayes D Jr, Ball AM, Mansour HM, Martin CA, Flynn JD. Fungal infection in heart-lung transplant recipients receiving single-agent prophylaxis with itraconazole. *Exp Clin Transplant* 2011; **9**: 399–404.
14 Montoya JG, Chaparro SV, Celis D *et al.* Invasive aspergillosis in the setting of cardiac transplantation. *Clin Infect Dis* 2003; **37**(Suppl 3): S281–92.
15 Pappas PG, Alexander BD, Andes DR *et al.* Invasive fungal infections among organ transplant recipients: results of the transplant-associated infection surveillance network (TRANSNET). *Clin Infect Dis* 2010; **50**: 1101–11.
16 Muñoz P, Valerio M, Palomo J *et al.* Targeted antifungal prophylaxis in heart transplant recipients. *Transplantation* 2013; **96**: 664–9.
17 Wingard JR, Carter SL, Walsh TJ *et al.* Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood* 2010; **116**: 5111–18.
18 Cornely OA, Maertens J, Winston DJ *et al.* Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356**: 348–59.
19 Ahmad SR, Singer SJ, Leissa BG. Congestive heart failure associated with itraconazole. *Lancet* 2001; **357**: 1766–7.
20 Prentice AG, Glasmacher A. Making sense of itraconazole pharmacokinetics. *J Antimicrob Chemother* 2005; **56**(Suppl 1): i17–22.

## Supporting information

Additional supporting information may be found in the online version of this article.

**Data S1.** Systematic search strategy.