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Fungal infection in cardiothoracic transplant recipients: outcome without systemic amphotericin therapy

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Summary

Transplant recipients require immunosuppression to prevent allograft rejection, placing them at risk of opportunistic infections including fungal infection. Difficulties in managing fungal infections include: establishing diagnosis, poor treatment response, drug interactions and toxicity. We report our single centre experience of treating fungal infections using systemic non-Amphotericin current generation antifungals. Patients receiving inpatient antifungal therapy from September 2005 to December 2010 were identified from pharmacy records. Fungal infections were retrospectively classified according to European Organization for Research and Treatment of Cancer (EORTC) criteria. Treatment outcomes were classified in a manner similar to those used in clinical trials. Two hundred and forty-nine recipients received antifungal treatment, 204 lungs and 45 hearts. One hundred and one patients received Voriconazole, 82 Caspofungin and 65 received both agents. One patient was unsuccessfully treated with additional Amphotericin. Treatment duration varied from 1.5 to 12 weeks. One hundred and sixty-five patients had a complete response, 24 had a partial response and in 60 patients treatment was unsuccessful. The response to systemic non-Amphotericin based antifungal therapy was high. We propose that diagnostic criteria without positive identification of a fungus allow treatment to be started early with few clinically relevant side effects.

Introduction

Pharmacological immunosuppression predisposes to opportunistic infection. Fungal infections are common in transplant recipients and cause significant morbidity and mortality. The reported annual incidence of fungal infections lies between 5% in kidney transplant recipients and 40% in liver transplant recipients [1]. In lung and heart transplant recipients the reported annual incidence of invasive fungal infections lies between 15% and 35% [2]. Mortality rates in transplant recipients with *Aspergillus* infections have been reported between 68% and 92% [3].

The management of fungal infections in thoracic organ transplant recipients is complicated by difficultly in diagnosis, drug interactions [4] and the potential nephrotoxicity of antifungal drugs combined with pharmacological immunosuppressant [5]. A response was seen in 57.3% of patients in a study of 572 patients with invasive fungal infections treated with colloidal amphotericin in an attempt to limit the toxicity of conventional amphotericin treatment [6].

We report our single centre experience of treating fungal infections in cardiothoracic transplant recipients using Voriconazole and Caspofungin in a protocol that avoided the use of systemic amphotericin, the agent that had previously been regarded as the gold standard for antifungal treatment.

Patients and methods

Patients receiving inpatient antifungal therapy at our hospital from September 2005 to December 2010 were identified from pharmacy records. Age at presentation, gender, underlying disease and diabetic status were recorded (Table 1). We then identified immunosuppressive regimen, site of infection, symptoms and spirometry before and after treatment together with, fungal isolates (Table 2), radiological findings and antifungal therapy.

Table 1. Patient characteristics at time of presentation.

Characteristic	Value
Mean age, years (range), *n* = 249	46.7 (18–73)
Sex (%), M = 140/249, F = 109/249	Male = 140 (56.2%) Female = 109 (43.8%)
Preoperative fungal colonization	8/249 (3.2%)
Underlying disease (lung transplant recipients, *n* = 118)	
Cystic fibrosis	83
Emphysema (non-A1ATD)	46
A1ATD (alpha 1 antitrypsin deficiency)	18
Pulmonary fibrosis	14
Pulmonary hypertension	10
Sarcoidosis	4
Other (bronchiectasis/CFA/pulmonary vasculitis/LAM/GVHD)	31
Underlying disease (heart Tx recipients, *n* = 23)	
DCM	38
ICM	5
Postpartum DCM	1
Giant cell myocarditis	1
Diabetes (total 89)	
Diabetes (Type I and type II)	Lung Tx: 161/204 Heart Tx: 28/45

Table 2. Source of fungal isolate.

Source of fungal isolate	Lung	Heart
Sputum (excluding *Candida*)	23	7
Urine	18	6
BAL	40	2
Blood	0	1
Surgical wound swab	10	7
Tissue (donor lung/bronchus, Bx, explanted lungs)	13	0
LVAD site pre-Tx.	0	2
Other (nasal aspirate)	1	1

This information was recorded from a review of the patient case records.

Full blood count (FBC) and C-reactive protein (CRP) were recorded at presentation. Changes in serum creatinine (SCr), bilirubin, alanine transaminase (ALT) and alkaline phosphatase (ALP) were recorded at their peak during treatment to determine the prevalence and severity of toxicity of the antifungal agents used. Hepatotoxicity was defined as a rise in serum ALT/ALP of three times baseline level and severe toxicity as five times baseline level or a rise in bilirubin of one and a half times baseline and three times baseline. Nephrotoxicity was defined as a rise in SCr over one and a half times baseline level and severe nephrotoxicity was a rise of over twice baseline level. These levels were set in accordance with the definition of acute kidney injury as defined in Clinical practice guidelines for acute kidney injury [7] (SCr increase by one and a half times baseline is stage one acute kidney injury and twice baseline level stage two acute kidney injury). They have also been set at this level to maintain comparability to previous studies including that by Walsh *et al.* [8]. Calcineurin inhibitor levels were monitored during treatment to assess drug interactions. Radiological abnormalities included intracavitary masses with or without halos, nodules, tree in bud opacities, diffuse or focal ground glass opacities. Regression or worsening of lesions could be determined on serial HRCT. Fungal isolates were recorded from microbiology records with the exclusion of *candida* isolated from sputum culture.

Fungal infections were retrospectively classified into proven, probable or possible infection according to revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [9]. The criteria for these definitions are outlined in Table 3.

The predefined protocol for starting antifungal therapy was as follows; Voriconazole to be used as first line therapy. Caspofungin was used as second line therapy in refractory cases or when the patient was (i) intolerant to Voriconazole, (ii) had a creatinine clearance <50 ml/min (a contraindication to the intravenous formulation of Voriconazole), (iii) unable to absorb oral medication, (iv) being treated with Rifampicin (in this case, dose of Caspofungin was administered at the increased dose of 70 mg daily) or (v) receiving Sirolimus. Antifungal prophylaxis was provided at the time of transplantation with nebulized amphotericin for all patients until hospital discharge. Secondary prophylaxis was also given for 6 weeks using Voriconazole or Caspofungin as above in those patients with previous fungal isolates from respiratory specimens. CMV prophylaxis was given as standard for 3 months following

Table 3. Diagnostic criteria for invasive fungal infection.

Class of infection	Diagnostic criteria
Proven	Hyphae or yeasts seen on tissue biopsy from site of infection OR Blood culture yielding fungi or yeasts
Probable	Patient on long-term immunosuppression + Positive fungal culture from sputum, bronchial washings or urine + Symptoms of infection and persistent fever* + Radiological abnormalities consistent with infection
Possible	Patient on long-term immunosuppression + Symptoms of infection and persistent fever* despite broad-spectrum antibiotic therapy ± Radiological abnormalities consistent with infection

*Temperature >38 °C for 72 h.

transplantation using Valganciclovir with weekly monitoring for CMV antigenaemia.

Immunosuppression following heart transplantation consists of RATG and Methyl-prednisolone induction, Mycophenolate mofetil 1.5 g twice daily if used with Ciclosporin, and 1 g twice daily if used with Tacrolimus and Prednisolone 0.1 mg/kg maintenance. Prior to August 2007, Ciclosporin was given with a target level of 250 ng/ml, reducing to 175 ng/ml after 1 year. After August 2007, Tacrolimus was given with an initial target level of 8–13 ng/ml reducing to a target of 5–10 ng/ml during the course of the first post-transplant year. Immunosuppression following lung transplantation consists of Methyl-prednisolone at the time of surgery reducing to Prednisolone 0.1 mg/kg maintenance. Prior to October 2010, this was with Ciclosporin with a target level of 300 ng/ml reducing to 150 ng/ml during the course of the first post-operative year and azathioprine 2 mg/kg. After October 2010, Prednisolone was given with Tacrolimus with target levels of 8–13 ng/ml reducing to 5–10 ng/ml during the first postoperative year and Mycophenolate mofetil 1 g twice daily. Mycophenolate levels are not measured. Sirolimus (5–10 ng/ml) with Mycophenolate (1 g twice daily) and Prednisolone are used as a renal sparing immunosuppressive strategy in some transplant recipients.

Treatment outcomes were classified as successful or unsuccessful. A successful outcome was further divided into a complete response or partial response to antifungal therapy. These classifications are further detailed in Table 4. These classifications are similar to those used in a large prospective trial of antifungal therapy by Herbrecht *et al.* [10]. Cause of death was taken from death certificates, clinical records and postmortem examination findings.

Table 4. Classification of treatment outcomes.

Successful	Complete response	Resolution of clinical symptoms and signs + Resolution of radiological changes
	Partial response	Improvement of clinical symptoms and signs + Improvement of radiological changes
Unsuccessful		Death

Results

Two hundred and forty-nine patients received antifungal therapy during the study period; 204 lung and 45 heart transplant recipients. The patient characteristics are shown in Table 1. The total number of patients under follow-up during the study period was 1,205; 750 heart and 455 lung recipients (102 with Cystic Fibrosis). In our study population 89/249 (35.7%) patients were diabetic; 67/205 (32.7%) lung recipients and 22/45 (48.9%) heart recipients. The total number of diabetic patients under cardiothoracic transplant follow-up is 139/1205 (11.5%). This shows a significantly higher rate of IFI in diabetic transplant patients when compared with nondiabetic patients ($P < 0.0001$). Pretransplant sputum microbiology showed that all the patients with Cystic Fibrosis were colonized with *Pseudomonas aeruginosa*. Of the study population six had previous isolates of *Aspergillus* spp. and two had previous isolates of *Candida* spp. Candida isolated from respiratory specimens or routine swabs in otherwise asymptomatic and apyrexial patients were not considered to be pathological, these were not treated and were not included in this analysis. Fifty-five per cent of the fungal infections occurred within 6 months of transplantation, 108 in lung and 28 in heart transplant recipients. The annual incidence of fungal infections was 7.5% in the lung transplant recipients and 1.0% in the heart transplant recipients.

Immunosuppressive medication was prescribed in accordance with the predefined protocol outlined in the methods section. Amongst all the patients under follow-up at our centre 45% (546) were receiving Ciclosporin, 45% (543) Tacrolimus and 10% (116) Sirolimus. Of those treated for fungal infection immunosuppression at the time of diagnosis consisted of Ciclosporin 25.7% (64), Tacrolimus 65.0% (162) and Sirolimus 9.2% (23), together with Mycophenolate Mofetil ($n = 138$; Welwyn Garden City, UK) or Azathioprine ($n = 67$) and

corticosteroids ($n = 245$). Mycophenolate and Azathioprine were stopped during treatment for fungal infections. A greater risk of invasive fungal infection (IFI) was seen in those patients taking Tacrolimus (29.8%) and Sirolimus (19.8%) when compared with those patients taking Ciclosporin (11.7%) in both cases $P < 0.0001$. Almost all patients 245/249 were taking corticosteroids and either Mycophenolate or Azathioprine at diagnosis. Dose adjustment of Calcineurin inhibitors was undertaken in view of drug interaction with Voriconazole with no adjustment of the target level.

One hundred and thirty fungal isolates were found; *Aspergillus* (57), *Candida* (66), *Paecilomyces* (3), *Penecillium* (1), *Rhizopus arrhizus* (1) and *Scedosporium* (2). Isolates of *Candida* in sputum were excluded from analysis. Radiological evidence of fungal infection was seen in 178 (71.5%) cases. In 71 (28.5%) cases, no radiological abnormalities were detected. There were two cases classed as probable infections in the absence of radiological abnormalities. This was based on high eosinophil counts (0.9 and 1.3×10^9/l) at the time of diagnosis despite long-term steroid therapy.

Laboratory investigations showed the total white cell count was raised ($>11.0 \times 10^9$/l) in 70/204 (34.3%) lung transplant recipients and in 10/45 (22.2%) heart transplant recipients. The mean WCC of both groups was $9.8 \pm 5.8 \times 10^9$/l. Fourteen cases (5.6%) had eosinophilia ($>0.04 \times 10^9$/l) at diagnosis, however, the overall mean eosinophil count was $0.15 \pm 0.01 \times 10^9$/l. C-reactive protein (normal range 0–10 mg/l) was raised to >50 mg/l in 150/249 (60.2%) patients, moderately raised (10–50) in 63/249 (25.3%) and normal (<10) in 36/249 (14.5%). Mean CRP was 44 ± 9 mg/l with a range of 0–460 mg/dl.

Symptoms recorded included breathlessness in 94, cough in 62, sputum purulence in 95 and fever in 214. Frequently, more than one symptom was present. All lung transplant recipients monitor their FEV_1 at home and report a decline of more than 10% from their baseline readings; a decline of FEV1 was a presenting feature in 49/204 (24%).

Treatment was provided according to a predefined protocol which is described in the methods section. As per protocol, 101 Patients were treated with Voriconazole only, 82 with Caspofungin only and 46 with Caspofungin followed by oral Voriconazole as continuation therapy. Nineteen patients who were initially on Voriconazole required additional Caspofungin during treatment. Attempted salvage therapy with amphotericin in one patient with a resistant *Paecilomyces lilacinus* infection was unsuccessful. The cost of drugs for a 6-week course of treatment at our centre is £3672 for oral Voriconazole (200 mg BD), £13,910 for intravenous Voriconazole (4 mg/kg bd) and £14,880 for intravenous Caspofungin (50 mg od) compared with £8862 or £17,724 for AmBisome (Gilead, Great Abbingdon, UK) given at a dose of 1 mg/kg od or 3 mg/kg od respectively.

Hepatotoxicity and nephrotoxicity were assessed by elevations in ALP, ALT, serum bilirubin and SCr during therapy [8]. The liver function tests showed an elevated ALP greater than three times the baseline value in 19 (7.6%) patients and greater than five times baseline values in 13 (5.2%) patients. Similarly ALT values of greater than three times the baseline value were recorded in 20 (8.3%) patients and greater than five times baseline values in 15 (6%) patients. Bilirubin rose by greater than one and a half times the baseline during therapy in 22 (8.8%) patients and three times the baseline in 14 (5.6%) patients. After successful therapy ALP returned to baseline in 24/32 patients, ALT in 27/35 patients and bilirubin in 28/36 patients on discharge from hospital. The SCr was raised one and a half times baseline value in 15 (6.0%) and twice the baseline value in a further 15 (6.0%) during therapy. Serum creatinine returned to baseline in 48/50 (96%) patients on hospital discharge. Raised liver function tests and serum creatinine were seen in all patient groups including those taking Voriconazole only, Caspofungin only and both Voriconazole and Caspofungin. In all patients taking Caspofungin only, raised liver function and SCr had returned to baseline at the time of discharge. There were 10 patients with persistently deranged liver function and 5 patients with persistently raised SCr. These results were all seen in patients who subsequently died on that admission.

Of 151 (60.6%) patients who received Voriconazole; 98 were receiving concomitant Tacrolimus, the levels of which went up by 77.6% on day 2 of the antifungal treatment. In the presence of Voriconazole, levels of Ciclosporin increased by 67% over 4 days. This required a dose reduction of 50%, which is similar to results from studies done by Romero *et al.* in renal transplant recipients [11]. Caspofungin did not require any alteration in the dose of Tacrolimus or Ciclosporin.

The outcomes of treatment according to the classification of the fungal infections are shown in Table 5. Of the 249 patients treated, 189 had a successful outcome (165 had a complete response, 24 a partial response), whereas

Table 5. Treatment outcome results.

	Treatment outcome		
Category of IFI	Complete response (165)	Partial response (24)	Treatment failure (60)
Proven (36)	19 (52.9%)	5 (13.8%)	12 (33.3%)
Probable (77)	51 (66.2%)	4 (5.1%)	22 (28.7%)
Possible (136)	95 (69.8%)	15 (11%)	26 (19.2%)

in 60 patients the outcome was unsuccessful. There was complete response in 141/204 (69.1%) lung transplants and 24/45 (53.3%) heart transplants, and partial response in 20/204 lung transplants and 4/45 heart transplants. There was no significant difference in response rate between patients with proven or probable infections (all with fungal isolates), or those with possible fungal infections ($P = 0.35$.)

Of the 49 lung transplant patients who presented with a decline in FEV_1, 39 experienced a recovery in their lung function after therapy back to their baseline level. In the 67 deaths that occurred, the cause of death (CoD) in 41 patients following treatment was directly attributed to the fungal infection. This can be divided into 37 of 50 lung transplant recipients and 4 of 17 heart transplant recipients. In the remaining 13 lung transplant recipients, the primary CoD was multiorgan failure, bronchiolitis obliterans, pseudomembranous colitis and CMV pneumonitis. In the remaining 13 heart transplant recipients the cause of death was primarily cardiac allograft failure.

Discussion

Prior to the availability of echinocandins and second-generation triazole antifungal drugs, amphotericin was considered to be the gold standard for treatment of IFI because of its broad-spectrum and potent fungicidal activity [12]. However, IFI have been associated with a high rate of morbidity and mortality attributable to both the infection and toxicity of the antifungal drug therapy. In this study, treatment of IFI was successful without systemic amphotericin and was associated with few clinically relevant side effects. This strategy resulted in low levels of nephrotoxicity (3.2%) compared with nephrotoxicity in 30% when treated with amphotericin with 18% requiring dialysis [13].

The incidence of fungal infection observed here was lower than that reported in previous studies, supporting the view that the diagnostic criteria used were discriminatory. The response rate to nonamphotericin therapy was high 66.7% in proven invasive infection, 71.4% in probable infection and 80.8% in possible infection. This study is not powered to demonstrate a difference in treatment outcomes between groups. There was no significant difference in treatment failure between groups; 33.3% in proven invasive infections, 22% in probable infections and 19.2% in possible infections. However, the trend towards less treatment failure in possible IFI may indicate that these patients had less severe disease. The overall mortality of patients with IFI at hospital discharge was 16.4%; 37/204 (18.1%) in the lung transplant group and 4/45 (8.9%) in the heart transplant group. When comparing this with previously reported mortality rates, 60% in lung transplant recipients [14] and 35.3% in heart transplant recipients [15]. Figure 1 shows the longer term survival of patients from the time of diagnosis, which also demonstrated no significant difference in outcomes between diagnostic groups. In a large study by Guo LS of patients with systemic fungal infections secondary to severe underlying disease (not specifically transplant patients), patients were treated with Amphotericin with a response seen in 57.3% [6]. Our study has shown an overall response rate of 75.9% comprising of 161/204 (78.9%) lung recipients and 4/45 (8.9%) heart recipients.

The annual incidence of IFI was higher in lung (18.8%) than heart (3.4%) transplant recipients; this is likely to be owing to the combination of pharmacological immunosuppression, exposure of the lung to inhaled pathogens and local immune dysregulation within the allograft. All lung transplant recipients were given nebulized Amphotericin from time of transplant until hospital discharge as prophylaxis which may reflect the low annual incidence of IFI when comparing to other studies. Three heart transplant recipients received mechanical circulatory support with Heart Mate II prior to transplantation. No lung transplant recipients received ventilator support or ECMO immediately prior to transplantation. Most IFI occurred within the first 6 months following transplantation (55.0%) and 81.9% within the first year; the frequency of infection tailed off sharply thereafter. A greater risk of IFI was seen in those patients taking Tacrolimus (29.8%) and Sirolimus (19.8%) when compared with Ciclosporin (11.7%) $P < 0.0001$. This would indicate that the use of either Tacrolimus or Sirolimus for

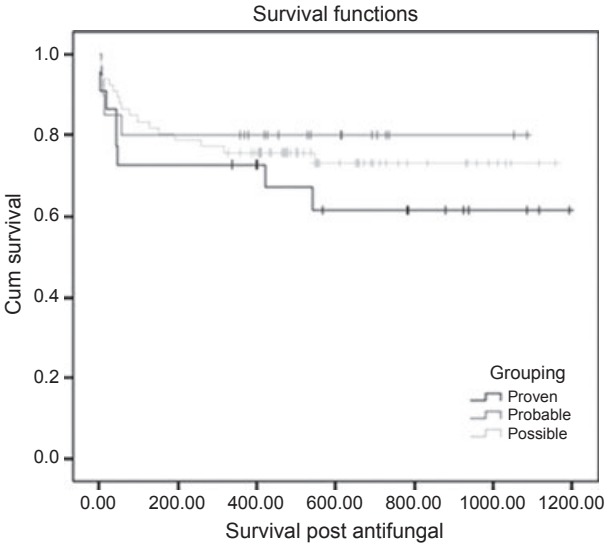

Figure 1 Survival Kaplan–Meier plot.

immunosuppression is an independent risk factor for developing IFI. A greater risk of IFI was also seen in those patients who are diabetic compared with nondiabetic transplant patients ($P < 0.0001$), highlighting this again as a known risk factor.

One hundred and one patients who received Voriconazole developed abnormalities of their liver function tests. This led to discontinuation of therapy in 10/101 (9.9%). The remainder of patients of hepatotoxicity returned to baseline prior to discharge demonstrating that Voriconazole can be given safely in the majority of patients without significant long-term hepatotoxicity. Significant nephrotoxicity (doubling of baseline creatinine level) occurred in only 15 patients, all of whom were receiving Voriconazole treatment. In these cases, nephrotoxicity was associated with increased Ciclosporin or Tacrolimus levels implicating drug–drug interactions and raised calcineurin inhibitor (CNI) levels as the cause. To avoid such interactions a pre-emptive 50% reduction in the Tacrolimus dose was made when starting Voriconazole therapy. No pre-emptive changes were made to Ciclosporin therapy; however, the dose did need to be halved over a 4-day period as a result of daily therapeutic drug monitoring. Caspofungin therapy was not found to cause any hepatotoxicity, nephrotoxicity or drug interactions.

The relatively low mortality in our study may be owing to early initiation of therapy based on clinical criteria, not dependent upon identification of a fungal pathogen. At the outpatient review, 2 weeks after hospital discharge following successful treatment, the FEV_1 returned to baseline in 39 of 49 lung transplant patients who had presented with a decline in FEV_1. This implies that full recovery of lung function is possible in the majority of lung transplant recipients after treatment for a pulmonary fungal infection. The purulent sputum and dyspnoea improved after starting antifungal therapy empirically indicating that a response to treatment may also support a presumptive diagnosis of fungal infection. Immunosuppression with Mycophenolate or Azathioprine was stopped during antifungal treatment. In accordance with our hospital protocol, this was reintroduced when antifungal therapy was stopped and clinical stability achieved in outpatient clinic. The effects on progression of bronchiolitis obliterans were not analysed; however, we have accounted for deaths not relating to IFI in the follow-up period, and shown long-term mortality in Fig. 1.

Positive identification of a fungus had often not been made at the start of treatment because laboratory tests are insensitive for the diagnosis of invasive fungal infection. The low toxicity and broad spectrum of action of Voriconazole and Caspofungin facilitated this approach. Radiological diagnosis of fungal infection was based on the presence of suggestive features including nodules, halos and tree-in-bud opacities in CT scans. Such findings prompted immediate antifungal therapy and subsequent changes assisted in determining the duration of therapy. Nonamphotericin therapy is significantly more expensive than the low dose intravenous amphotericin but not high dose intravenous amphotericin. There is little information about the optimal length of treatment of fungal infections. Most often, the clinical response is monitored along with resolution of radiological features of infection to guide treatment [16].

This was an observational cohort study and so there were no internal comparators of outcome. Concomitant antibiotic therapy was not always discontinued when starting the antifungal treatment and so determining whether and when individual patients responded to antifungal therapy was not always possible.

We found that the response to systemic nonamphotericin therapy was high in possible, probable and proven invasive fungal infection. This reflected the high efficacy and low toxicity of the antifungal agents used which enabled treatment to be started early. Close monitoring allowed drug interactions to be detected and toxicity minimized. We propose that nonamphotericin antifungal treatment should be started early in cardiothoracic organ transplant recipients with infection that does not respond to antibacterial therapy, and who meet the diagnostic criteria for a potential fungal infection without waiting for a positive culture or tissue diagnosis.

Authorship

DD: Data collection, analysis and interpretation. Manuscript writing and revision. JLD: Data collection, analysis and interpretation. Manuscript writing and revision. MRC: Study initiation, design and analysis. Drafting and revision of the manuscript. HSL: Immunosuppression protocols, data collection, analysis and interpretation. AVH: Providing data, analysis and interpretation of data. NRB: Study design and analysis. Drafting and revision of the manuscript.

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