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Intravenous Therapy for Chronic Pulmonary Aspergillosis: A Systematic Review and Meta-analysis

Running head: IV therapy for CPA

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Summary

Chronic pulmonary aspergillosis (CPA) is a potentially life-threatening debilitating lung disease necessitating long-term oral antifungal treatment. However, development of antifungal resistant isolates of *Aspergillus* and major toxicities requiring discontinuation of treatment limit their use. Intravenous (IV) antifungals are an option in this group of patients. We comprehensively evaluate the response rates to IV antifungals in the management of CPA. We searched Medline and Embase databases to select clinical studies providing information about IV amphotericin B or an echinocandin for the treatment of CPA from inception to May 2020. Reviews, single case reports and case series reporting less than 10 patients were excluded. We evaluated 12 eligible studies. A total of 380 patients received amphotericin B (n =143) or an echinocandin (n=237) and were included in the meta-analysis. In a pooled analysis, overall response to IV antifungals was 61% ((95% confidence interval (CI): 52-70%; I^2=73.3%; p<0.001), to amphotericin B was 58% (95% CI: 36-80%; I^2=86.6%; p<0.001) and to echinocandins was 62% (95% CI: 53-72%; I^2=63.6%; p<0.001). Amphotericin B courses were usually doses at slightly less that 1mg/Kg (deoxycholate) or 3mg/Kg (liposomal) for 2-3 weeks. Micafungin doses varied from 12.5 to 300mg (frequently, 150mg) daily for at least 3 weeks, and sometimes much longer. Liposomal amphotericin B was well tolerated, but led to renal function loss in 25% of patients. Adverse events were observed in 5 – 35.3% of patients receiving echinocandins, none of which was considered major. Intravenous antifungals have a place in the management of CPA. A head-to-head comparison of amphotericin B and echinocandins is lacking, and future studies should look at evaluating short and longer-term outcomes of these agents.

Keywords: chronic pulmonary aspergillosis, amphotericin, micafungin, caspofungin, anidulafungin, *Aspergillus*, resistance,

Introduction

Chronic pulmonary aspergillosis (CPA) describes a diverse clinical and radiological spectrum of a progressive and destructive parenchymal lung disease occurring in patients with structural lung diseases, with or without subtle immunodeficiency [1,2]. CPA manifests with prominent respiratory and systemic symptoms occurring over several months to years, with an annual mortality rate of approximately 15% and a 5-year mortality rate ranging from 15% to 82.5% [3–8].

Long-term oral antifungal agents, typically itraconazole or voriconazole, given for a minimum of 6 months is the mainstay of treatment for symptomatic patients with CPA, with associated modest response rates and improvement in overall health status [9–11]. Emerging issues due to prolonged use of the oral triazoles are major adverse events warranting discontinuation of therapy, and multi- or pan-azole resistant strains of *Aspergillus*, render these agents of no use [12,13]. Antifungal treatment is discontinued in up to 30% of CPA patients due to adverse events and about 5 to 15% of patients develop resistant *Aspergillus* isolates during the course of their treatment [8,14].

Current strategies for managing CPA patients with pan-azole resistance or pan-azole cross-intolerance include surgical resection [15,16], short- or long- courses of an echinocandin [17] or amphotericin B, [18] and/or supplemental gamma interferon injections [19].

However, the outcomes from these strategies are not well documented in the literature. In the present study, therefore, we aimed at evaluating response rates to IV antifungals in the management of CPA based on published literature.

Methods

Using the following MeSH terms: “chronic pulmonary aspergillosis,” “CPA,” “simple aspergilloma,” “chronic cavitary pulmonary aspergillosis,” “CCPA,” “chronic fibrosing pulmonary aspergillosis,” “CFPA,” “amphotericin B,” “echinocandins,” “micafungin,” “anidulafungin,” “caspofungin,” “adverse events,” “side-effects,” and “toxicities”, we searched all studies published from inception to May 2020 in Embase and Medline databases. This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20]. (Supplementary 1, PRISMA Checklist).

In addition, manual literature search of all the references of the included articles were performed to find relevant studies. The search was limited to human studies and only studies written in English were selected.

The studies found through databases that were duplicates were removed using the HDSA program. Records were initially screened by title and abstract by two independent reviewers (F.B and L.G.A.) to exclude those not related to the current study. The full text of potentially eligible records was retrieved and examined. Any discrepancies were resolved by consensus.

Risk of bias was assessed using Critical Appraisal Skills Programme (CASP) Qualitative Checklist. Risk of bias was graded as low, moderate and high. Studies with high risk of bias were excluded. (Supplementary 2, completed CASP Assessment tool).

We excluded studies on oral triazoles, amphotericin B administered by other means such as aerosols or intracavitary instillations, other forms of aspergillosis, single case reports, and case studies of <10 patients.

We used the PICO (patient/population, intervention, comparator/control, outcome) criteria to extract data from the eligible studies. The study outcomes were antifungal response and the cumulative incidence of adverse events. Radiological, microbiological, serological, and clinical factors, or a combination of these factors were used as a composite for measuring response rate.

A pooled, random effect meta-analysis was performed using STATA (version 15.1, StataCorp, College Station, TX). Heterogeneity across studies was assessed using Q statistics and I^2 value. A two-sided P value of <0.05 was considered indicative of statistical significance.

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as the research in this article relates to review of the literature.

Results

Study characteristics

We evaluated full texts of 12 eligible studies from the 544 studies identified by both electronic and manual searches: A total of 380 patients received either amphotericin B

(143 patients) or an echinocandin (237 patients) and were included in the quantitative synthesis, **Table 1**.

Overall antifungal response

Considering all the antifungal agents used (all amphotericin B formulations and the echinocandins), in a pooled analysis, overall response to IV antifungals was 61% ((95% confidence interval (CI): 52-70%; I^2=73.3%; p<0.001), irrespective of the IV antifungal administered, and the patient population was similarly heterogeneous (p= 0.694), **Figure 1**.

Amphotericin B courses were usually doses at slightly less that 1mg/Kg (deoxycholate) or 3mg/Kg (liposomal) for 2-3 weeks. Micafungin doses varied from 12.5 to 300mg with most experience at 150mg daily, again usually given for at least 3 weeks, and sometimes much longer. Caspofungin was usually given at 150mg daily for 5weeks, sometimes in repeating cycles with azole therapy, Table 1.

Response to amphotericin B

Response could be analysed for 4 studies [1,21–23]; two studies reported the use of amphotericin B deoxycholate (AmBD) [1,21] and the remaining 2, liposomal amphotericin B (LAmB) [22,23]. Response rate to AmBD was 23.5% [21] and 80% [1]. On the other hand, response to LAmB was reported at 74% for short-term usage and 100% long-term therapy [18]. In another study, response rate to LAmB was 49.0% after 2 weeks and 52.9% at the end of treatment [23]. In a pooled analysis, overall response to amphotericin B was 58% ((95% confidence interval (CI): 36-80%; I^2=86.6%; p<0.001), **Figure 1**.

Adverse events to amphotericin B

Three studies reported adverse events [1,22,23]. Adverse events were observed in 70% of patients who received AmBD, [1] as compared to 25% [22] and 54.2% [23] among those who received LAmB.

Echinocandins

Response to the echinocandins

Seven studies [24–30] reported response rates to micafungin and 2 studies [25,31] reported response rates to caspofungin for the treatment of CPA. Reported response rates to micafungin were 78% [24], 68.4% [27], 55% [26], 58.8% [28], 68.0% [17], and 57.7% [29].

A double-blinded RCT comparing micafungin with caspofungin showed that caspofungin (response rate, 46.7%) and micafungin (response rate, 42.4%) had similar efficacy in the treatment of CPA. Among CPA patients with sarcoidosis, response to caspofungin was observed in 90% of the patients [31].

In a pooled analysis, overall response to the echinocandins was 62% (95% CI: 53-72%; I^2=63.3%; p<0.001), **Figure 1**.

Adverse events to echinocandins

Adverse events were reported in 7 studies [24–28,30]. Adverse events attributable to micafungin ranged between 10% and 35.3%, Table 1. In one study, abnormal liver functions were observed among 6 (15.8%) patients and none were considered severe [27]. In another study, 5.0% and 10.0% of patients experienced adverse events to caspofungin and micafungin, respectively [32].

Discussion

With the increasing incidence of azole-resistant *A. fumigatus* isolates, clinical failure, high mortality, intolerance and /or adverse events to first and second line antifungal agents, intravenous agents, including amphotericin B and echinocandins, may be used in the treatment of CPA [33]. In one study, about 10% of the patients required IV antifungals after failing or developing pan-azole resistant isolates of *Aspergillus* spp.[8]. One option involves the use of injectable antifungals such as echinocandins and polyenes or potentially synergistic combination of polyene, azole-, and echinocandin-based therapies to improve efficacy and minimise adverse events [33,34]. The utility of these antifungals, however, has not been well evaluated and remains controversial because the drugs are expensive and require patients to be admitted to the hospital for their use, at least initially [35]**.** Although, administration as outpatient parenteral antimicrobial therapy (OPAT) has been shown to be possible at a CPA centre of excellence [24].

Amphotericin B is a broad spectrum antifungal agent that was first used in the treatment of any form of aspergillosis since the 1950s [36], followed by several case series and clinical studies thereafter [21,23,37]. Amphotericin B binds to ergosterol in the fungal cell membrane leading to the formation of pores, ion leakage and eventually fungal cell death [38]. Amphotericin B has various formulations to increase its efficacy and reduce toxicities.

Conventional formulations of amphotericin B penetrate lung tissues 3 times more efficiently than LAmB. However, lung inflammation improves LAmB penetration [39]. Thus all formulations of amphotericin B may be used for the treatment of pulmonary mycoses, including CPA [40,41]. Following intravenous administration, amphotericin B is highly protein binding (95%) and undergoes urinary and biliary excretion, unchanged. Dose-dependent adverse effects like nephrotoxicity, anaphylaxis, high fevers, hepatotoxicity and potentially, death, can occur following administration of amphotericin B [38].

We observed a variable response rate, between 36 and 80% using pooled data from several studies. LAmB is preferred because of its associated fewer adverse effects as compared to the other formulations, especially AmBD [42]. However, permanent loss of renal function has been reported in up to 25% of patients on LAmB [22]. Also long-term therapy may be associated with catheter infections.

Echinocandins consist of a class of semisynthetic lipopeptides with an N-linked acyl lipid side chain and include micafungin, caspofungin, anidulafungin [43]. Echinocandins are non-competitive inhibitors of β - (1, 3) - D-glucan synthase, an essential component of the fungal cell wall impeding ability of the organism to synthesize β - (1, 3) - D-glucan, leading to osmotic instability and cell death in *Candida* spp., but not so reliably in *Aspergillus* [44].

Echinocandins possess fungistatic activity against *Aspergillus* species and are better tolerated than amphotericin B [44]. Due to poor oral bioavailability and 90-99% protein binding; echinocandins are mainly administered by the intravenous route [45]. They undergo non-hepatic metabolism. Metabolites are excreted via urine and faeces. Infusion-related reactions (facial flushing, swelling, rash, pruritus, and fever) and derangement of hepatic transaminases have been reported with all the echinocandins following their administration [45]. Side effects may be related to the ability of the echinocandins to mediate release of glucans, which may have immunomodulatory effects.

Overall, this study found echinocandins to have a response rate of about 62% with few adverse effects. These side effects were seen in 5-16% of cases, most being mild, such as minor elevation in liver function tests. More recently, cyclical/pulsed caspofungin therapy has been shown to stabilize CPA patients with pan-resistance or intolerance to

azole therapy [46]. Most data are for micafungin; the data regarding use of caspofungin in treatment of CPA are still quite limited whereas there are none available for anidulafungin.

One of the significant limitations of these analyses is reliance on the authors' definition and interpretation of response. There are broadly 4 elements that can contribute to response: clinical improvement, radiological change, falling *Aspergillus* antibody titres and inflammatory markers, and turning *Aspergillus* culture in sputum from positive to negative. However CPA manifests great heterogeneity in symptomatology, markedly variable radiological findings, hugely variable antibody tires at baseline of therapy (and often normal inflammatory markers), and sputum cultures, which frequently do not grow *Aspergillus* spp. Also most IV therapy is short term whereas radiological and serological change takes weeks or months. Newton *et al* split the symptoms of CPA into 2 categories, respiratory and constitutional, and assessed response in each separately [22]. So while 55% had a response in respiratory symptoms after L-AmB therapy, 51% had a constitutional symptom improvement, 32% improvement in both and 23% had no improvement in either. This illustrates the challenge of summarising all outcomes in a patient as a response or not. Improved and agreed means of doing this is required, as called for by others [47].

Resistance in *A. fumigatus* has recently been described after long-term micafungin use [48]. The new formulation of echinocandin, rezafungin, can be administered once a week due to its very long half-life and may be an option for patients with drug-resistant CPA [49].

Conclusions

Intravenous antifungals have a place in the management of CPA. Amphotericin B probably has superior efficacy compared to the echinocandins, although head-to-head comparisons are lacking. Micafungin and probably caspofungin administered as a monotherapy or in a combination therapy with an azole or a polyene appear to be safe and efficacious agents for CPA. Future studies evaluating short and longer-term outcomes of injectable antifungals are therefore welcome.

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Author contributions: F.B. and D.W.D. conceived the manuscript. F.B., L.G.A., R.O. and D.W.D. participated in initial manuscript drafting. R.O and F.B did formal data analysis. All authors participated in critical revisions for intellectual content and material support, and approved of the final manuscript.

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Conflict of interest:

Dr Denning and family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company. He acts or has recently acted as a consultant to Scynexis, Pulmatrix, Pulmocide, Zambon, iCo Therapeutics, Mayne Pharma, Biosergen, and Fujifilm. In the last 3 years, he has been paid for talks on behalf of Hikma, Gilead, Merck, Mylan and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group. FB, LGA, and RO declare no conflict of interest.

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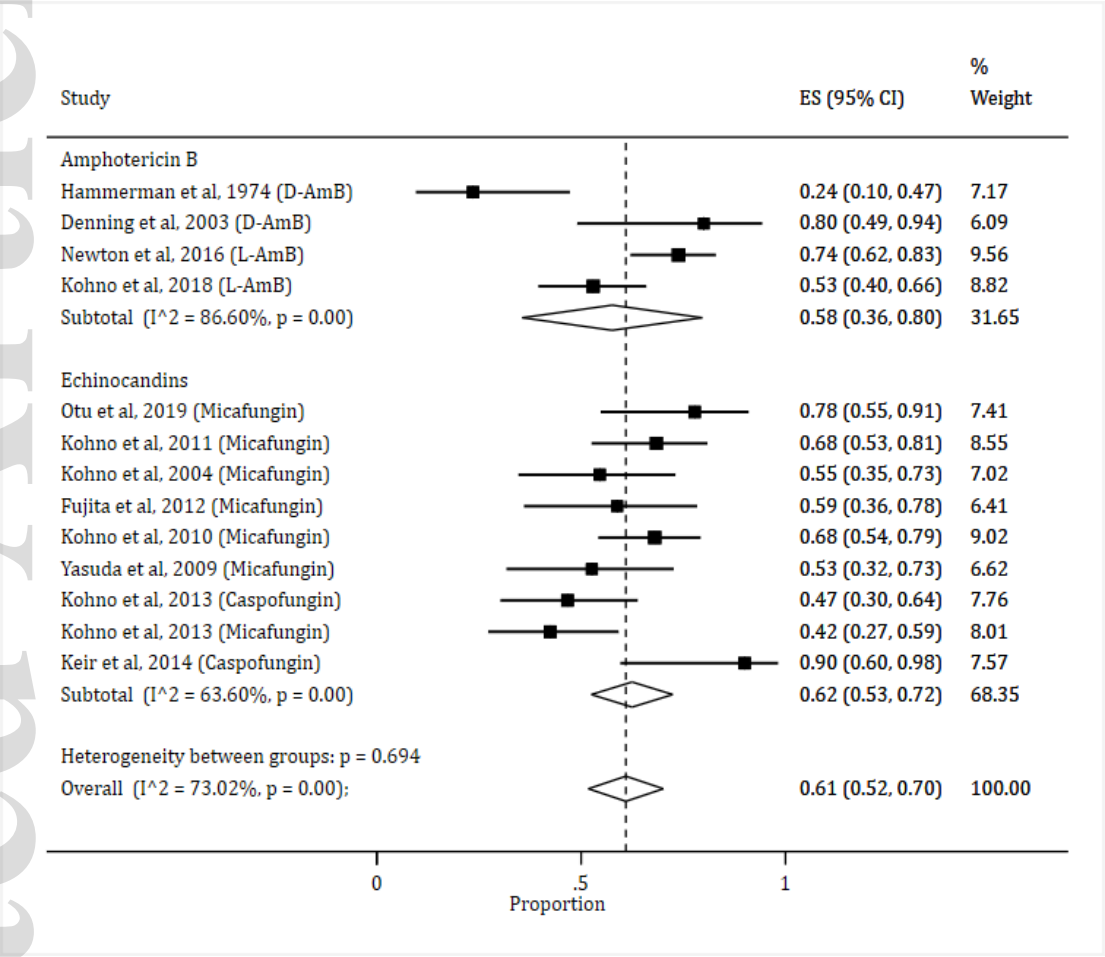
Table 1: Characteristics of included studies

Author (ref)	Year	Country	Study design	Population	Intervention	Duration of treatment	Measure of response	Response rate (%)	Adverse events rate (%)
Hammerman et al [21]	1974	USA	Observational, retrospective	17	AmBD, 25.6mg/kg	-	Radiology and microbiology	24	-
Denning et al [1]	2003	UK	Observational, retrospective	10	AmBD, 0.5 – 1mg/kg/day, IV	-	Clinical	80	70
Newton et al [22]	2016	UK	Observational, retrospective	65	LAmB, 2.5-5.0mg/kg/day	< 6 weeks	Clinical	74	25
Kohno et al [23]	2018	Japan	Clinical trial	51	LAmB, 2.5-5.0mg/kg/day	2-4 weeks	Clinical, Radiology	53	54.2
Otu et al [24]	2019	UK	Observational, retrospective	18	Micafungin 150mg/dose	4-248 days Mean: 21 days	Clinical	78	14.3
Kohno et al [27]	2011	Japan	Observational, prospective	38	Micafungin, 50-300mg/day	4-84 days Mean: 33.7±19.9 days	Clinical	68.4	15.8
Kohno et al [26]	2004	Japan	Clinical trial	22	Micafungin, 12.5-150mg/day	7-56 days	Clinical, radiology	55	30
Kohno et al [30]	2010	Japan	Clinical trial	50	Micafungin, 150-300mg/day	2-4 weeks Mean: 23.6 days	Clinical, microbiology, serology and	68	26.4

							radiology		
Kohno et al [25]	2013	Japan	Clinical trial	30	Caspofungin, 150mg/day	2-84 days Mean: 37.1 days	Clinical, Radiology	46.7	5
Kohno et al [25]	2013	Japan	Clinical trial	33	Micafungin, 70mg/day loading, then 50mg/day	1-84 days Mean: 42.1 days	Clinical, Radiology	42.4	10
Fujita et al [28]	2012	Japan	Observational, prospective	17	Micafungin 150mg + itraconazole 200mg/day	28 days	Clinical, microbiology, serology and radiology	58.8	35.3
Yasuda et al [29]	2009	Japan	Observational, retrospective	19	Micafungin	-	Clinical	52.6	-
Keir et al [31]	2014	UK	Observational, retrospective	10	Caspofungin + itraconazole (n=5) or voriconazole (n=4)	1-32 months	Clinical, Radiology	90	-

UK, United Kingdom; USA, United States of America; LAmB- liposomal amphotericin B; AmbD, Amphotericin B deoxycholate

Figure 1: Meta-analysis for antifungal response among patients treated with amphotericin B and the echinocandins.



Abbreviations: D-AmB, Amphotericin B deoxycholate; L-AmB, Liposomal amphotericin B