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CLINICAL AND EPIDEMIOLOGICAL STUDY

The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis

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Abstract
Purpose The efficacy of voriconazole against fungal central nervous system (CNS) infections was examined retrospectively.
Methods Voriconazole-treated patients with proven (137) or probable (55) CNS infections were identified in the voriconazole database (114) and the literature (78). Investigator-determined success was a complete or partial response. Survival was calculated from the start of voriconazole therapy.
Results The patients' age range was <1–81 years (median 43) and 127 (66%) were male. *Aspergillus* spp. (63%) and *Scedosporium* spp. (18%) predominated, but 12 other genera were recorded. Underlying conditions were haematopoietic stem cell transplantation (HSCT, 35), haematologic malignancy (HM, 35), solid-organ transplantation (SOT, 25), chronic immunosuppression (CI, 40) and other conditions (OC, 57). The median voriconazole therapy duration was 93 days (range 1–1,128), with success in 93 patients (48%). Only 35 patients received primary therapy, with success in 63% versus 45% for salvage ($p = 0.06$ NS). Underlying conditions influenced success; HSCT 14%, HM 54%, SOT 40%, CI 45% and OC 72% ($p < 0.001$). Additional antifungal combination therapy (37 patients) gave a trend towards an improved response rate ($p = 0.09$) and superior survival ($p = 0.0149$), while patients receiving neurosurgical interventions (72) showed superior responses ($p = 0.0174$) and survival ($p = 0.0399$). In all, 49% of patients died, 71% (67/94) due to fungal infection. The overall median survival was 297 days (range 3 to >2,000). Paediatric ($p = 0.014$) and literature patients ($p < 0.001$) exhibited superior survival compared with adults and voriconazole database patients, respectively.
Conclusions Voriconazole shows encouraging efficacy against various CNS fungal infections. Combination therapy and/or CNS surgery may improve outcomes.

Keywords Voriconazole · Aspergillosis · Scedosporiosis · Central nervous system · Mycoses

Introduction

Invasive fungal infections (IFI) of the central nervous system (CNS) are notoriously difficult to treat and mostly affect immunocompromised patients [1, 2]. Major factors impacting the outcome include the severity of immunosuppression, the susceptibility pattern of the infecting fungus and, importantly, the ability of antifungal agents to cross the blood–brain barrier [3]. Amphotericin B, the echinocandins, itraconazole and posaconazole are large molecules (>700 Da) with limited CNS penetration. Fluconazole and 5-fluorocytosine penetrate well into the CNS, but exhibit a narrow spectrum of activity. In contrast, voriconazole displays broad antifungal activity and enhanced CNS penetration. Peak voriconazole cerebrospinal fluid levels >1 μg/mL and concentrations in human brain tissue or brain abscess material exceeding 1 μg/g have been repeatedly reported [4].

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In a retrospective analysis of 81 patients with cerebral aspergillosis, an improved rate (35%) of complete and partial responses with voriconazole treatment was recorded and 31% of patients survived the infection for a median time of 390 days [5]. Interestingly, there was a significant trend towards improved survival in patients who had neurosurgical interventions.

A growing number of publications indicate that voriconazole has substantial clinical activity in other, non-*Aspergillus* CNS fungal diseases, including those caused by *Scedosporium* spp. [6], various yeasts and rare or emerging fungi, but most published data are limited to case reports and small case series. Thus, we systematically reviewed the cases from the voriconazole clinical trials database and literature data to evaluate the clinical efficacy of voriconazole against various CNS fungal infections.

Patients and methods

The Pfizer voriconazole clinical trials database (plus supplementary data for *Scedosporium*, see Troke et al. [6]) was queried for CNS IFI. Database patients came from those enrolled in a Phase III, comparative invasive aspergillosis study [7], a Phase III non-comparative salvage therapy study of IFI [8], a Phase II study of acute invasive aspergillosis [9], a Phase II study of chronic IFI [10] and unpublished compassionate studies. In addition, published data (all were individual case reports or small case series), in English, from 1st January 2002 (the year voriconazole was marketed) to 31st December 2008, inclusive, were identified via Medline and using the search terms as follows: voriconazole, brain, CNS, cerebral, cerebrospinal fluid and *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Fusarium*, *Histoplasma*, hyalohyphomycetes, phaeohyphomycetes, *Pseudallescheria*, *Scedosporium* and zygomycetes.

All cases were reviewed individually (by S.S. and P.F.T.) and only those that we classed as satisfying the recent EORTC/MSG criteria for proven or probable CNS infections were included [11]. Efficacy was based on the investigator's assessment at the end of therapy and, in line with current practice [12], a complete or partial response was classed as success, while all other responses were classed as failure.

For the purposes of this analysis, salvage therapy patients were defined as those receiving at least one day of appropriate antifungal therapy (i.e. not fluconazole in cases of aspergillosis) prior to commencing voriconazole.

Survival is defined throughout as from the first day of voriconazole therapy until death or the last day that the patient was known to be alive.

For statistical analyses, the distributions of categorical variables were compared using the Chi-square or Fisher's exact tests, as appropriate. All-cause mortality and survival was assessed using the Kaplan–Meier curves and the log-rank test was used to detect statistically significant differences. There was no adjustment for multiplicity of statistical testing. Analyses were conducted in SAS, version 8.2.

Results

Baseline characteristics and microbiology

Patients with confirmed proven or probable infection were included in this analysis after a review of over 200 cases. The 192 selected patients (database $n = 114$ and published cases $n = 78$) included 127 males and 65 females, and 41 (21%) were less than 18 years of age (Table 1). There were 137 proven and 55 probable infections. One probable CNS aspergillosis infection from the previously published dataset [5] was downgraded to possible infection and excluded.

The majority of patients were infected with *Aspergillus* species ($n = 120$) and the 53 infections speciated were predominantly *A. fumigatus* (89%), including one triple infection with *A. fumigatus*, *A. fischeri* and *A. nidulans*. In addition, there were 34 infections caused by *Scedosporium* species and 38 caused by various yeasts and rare or emerging fungi (Table 1).

Most patients were salvage therapy cases (157/192, 82%) and had, thus, received prior antifungal therapy. A single patient with aspergillosis received only prior fluconazole and was considered to be receiving voriconazole as the primary therapy. Known prior therapies were predominantly amphotericin B (either deoxycholate; $n = 86$ or a lipid formulation; $n = 73$). However, azoles (itraconazole or fluconazole; $n = 68$), 5-fluorocytosine ($n = 19$), echinocandins (caspofungin or anidulafungin; $n = 9$) and a few other treatments (rifampicin or interferon or granulocyte colony-stimulating factor [G-CSF]; $n = 6$) were also used. A total of 91/157 (58%) salvage therapy patients were known to have received multiple therapies either sequentially or as combinations.

For all Phase III database cases, and the published cases where this was clearly recorded, the initial voriconazole dose regimen was 6 mg/kg i.v. × 2 on Day 1, followed by 4 mg/kg i.v. q12 h. Patients might then switch to 200 mg p.o. b.i.d. The two Phase II aspergillosis studies used different initial regimens (either 6 mg/kg × 2 on day 1, then 3 mg/kg i.v. q12 h., then 200 mg p.o. b.i.d. [9] or 200 mg b.i.d. p.o. [10]).

Table 1 Baseline and clinical characteristics of 192 patients with central nervous system (CNS) fungal infections and voriconazole therapy

	Aspergillus		*Scedosporium*		Other fungi[a]	
	Database ($n = 80$)	Published data ($n = 40$) [13–49]	Database ($n = 21$)	Published data ($n = 13$) [50–61]	Database ($n = 13$)	Published data ($n = 25$) [62–84]
Age in years (median)	0.75–81 (44)	2–69 (46)	2–62 (42)	1–65 (39)	13–66 (36)	0.33–76 (39)
Gender (male/female)	46/34	27/13	11/10	11/2	10/3	22/3
Underlying conditions						
HSCT ($n = 35$)	32	–	–	–	2	1
Haem malig ($n = 35$)	13	11	7	–	1	3
SOT ($n = 25$)	11	5	5	2	–	2
Chronic ($n = 40$)	10	10	4	1	10	5
Other ($n = 57$)	14	14	5	10	–	14
Proven infection	47	23	17	13	13	24
Probable infection	33	17	4	–	–	1
Prior antifungal Rx	77 (96%)	22 (55%)	19 (90%)	6 (46%)	13 (100%)	20 (80%)
Voriconazole Rx in days (median)	1–1,128 (48)	5–810 (144)[b]	4–600 (115)	25–670 (365)[c]	3–148 (71)	7–900 (155)[d]
Combination or sequential Rx	–	26 (65%)	–	4 (31%)	–	7 (28%)
CNS surgery	31 (39%)	22 (55%)	–	4 (31%)	–	15 (60%)

The numbers of patients are given, if not stated otherwise; medians are given in parentheses for continuous variables

HSCT haematopoietic stem cell transplantation, *Haem malig* haematological malignancies, *SOT* solid organ transplantation, *Chronic* disease or drug-induced immunosuppression, *Rx* therapy

[a] Other fungi were: *Blastomyces dermatitidis*, 5; *Cryptococcus neoformans*, 11; *C. gattii*, 1; *Coccidioides immitis*, 3; *Cladophialophora bantiana*, 5; *Candida* spp., 3 (*C. albicans*, 1; *C. krusei*, 1; *Candida* spp., 1), *Chrysosporium* spp., 1; *Curvularia geniculata*, 1; *Fonsecaea monophora*, 1; *Fusarium* spp., 3 (*F. dimerum*, 1; *F. solani*, 1; *Fusarium* spp., 1), *Histoplasma capsulatum*, 2; *Ochroconis gallopavum*, 1; *Ramichloridium mackenziei*, 1

[b] Five patients without data, one patient with cerebral infection despite prior voriconazole; [c] one and [d] three patients without data

Response to therapy

A successful response was recorded in 93/192 (48%) patients (Table 2), with a median duration of voriconazole therapy of 93 days (range 1–1,128). Patients receiving at least 5 days of voriconazole therapy exhibited a 51% (88/174) response rate. There was no significant difference in the rates of complete response for patients with proven versus probable infections (13/34, 38% vs. 6/23, 26%; $p = 0.4$). However, 36/93 (39%) of patients with a successful response had insufficient information (generally, imaging data) for a clear assignment to complete or partial responders, thereby, precluding this analysis.

Paediatric patients showed a somewhat better response rate than adults (63 vs. 44%, $p = 0.06$, NS) (Table 2). The median duration of voriconazole therapy was 231 days (range 3–1,128 days) and 86 days (range 1–900 days) for paediatric and adult patients ($p = 0.004$), respectively. Slightly fewer paediatric patients than adults received primary voriconazole therapy (7/41, 17% vs. 28/151, 19%; $p = 1$ NS) or suffered from aspergillosis (22/41, 54% vs. 98/151, 65%; $p = 0.2$ NS), while more paediatric patients than adults underwent HSCT or suffered from haematologic malignancies (17/41, 41% vs. 53/151, 35%; $p = 0.47$ NS), received combination therapy (11/41, 27% vs. 26/151, 17%; $p = 0.18$ NS) or underwent neurosurgical interventions (17/41, 41% vs. 55/151, 36%; $p = 0.59$ NS). The response rates of paediatric patients from the clinical trials database or the literature were better than the responses for their corresponding adult populations (12/23, 52% vs. 25/91, 27%; $p = 0.04$ and 14/18, 78% vs. 42/60, 70%; $p = 0.77$, respectively). However, the 78 patients from the literature had larger median voriconazole therapy durations (Table 1) and also exhibited significantly better response rates compared with the 114 patients from the database (56/78, 72% vs. 37/114, 32%, $p < 0.001$) (Table 2).

Response by pathogen and underlying condition

Responses were seen in 56% (19/34) of patients with scedosporiosis, 47% (56/120) of patients with aspergillosis and 47% (18/38) of patients infected with other fungi (Table 2). Amongst the 38 patients infected with other fungi were 12 with cryptococcosis, nine of whom had acquired immune deficiency syndrome (AIDS) as their

Table 2 Outcome by various efficacy groups

	Clinical response (%)		*p*-value
Overall response rate	93/192 (48)		–
Paediatric versus adult patients	26/41 (63)	67/151 (44)	0.06 NS
Proven versus probable infection	69/137 (50)	24/55 (44)	0.39 NS
Primary versus salvage therapy	22/35 (63)	71/157 (45)	0.06 NS
CNS surgery versus no known CNS surgery	43/72 (60)	50/120 (42)	0.0174
Additional therapy versus voriconazole monotherapy	23/37 (62)	70/155 (45)	0.09 NS
Database versus published cases	37/114 (32)	56/78 (72)	<0.001
Aspergillus spp.	56/120 (47)		0.63 NS
Scedosporium spp.	19/34 (56)		
Other 12 genera[a]	18/38 (47)		

NS not significant

[a] See legend of Table 1

underlying condition. The three non-AIDS cases were all treated successfully. The nine AIDS patients had durations of voriconazole therapy ranging from 7 to 148 days, but 8/9 eventually failed therapy. These therapy failures were all salvage cases and were known to have previously received fluconazole (5), amphotericin formulations (7), 5-fluorocytosine (4) or itraconazole (1). However, most were not receiving triple therapy for their AIDS infection.

The response rates also varied across risk groups, from 14% (5/35) in patients with HSCT to 72% (41/57) in patients with other underlying conditions and absent or a less severe immunosuppression (Table 3). The clinical response rate of patients with HSCT was significantly less than all of the other groups ($p < 0.001$), while patients with other underlying conditions had significantly better response rates compared to all of the others combined ($p < 0.001$) (Table 3). There was no difference in response rates between patients with probable or proven infections (69/137, 50% vs. 24/55, 44%; $p = 0.39$ NS) (Table 2).

Adjunctive treatments

In 37 patients, caspofungin ($n = 18$), amphotericin B lipid formulations (L-AMB, $n = 17$), amphotericin B deoxycholate ($n = 6$), 5-fluorocytosine ($n = 5$), terbinafine ($n = 4$), itraconazole ($n = 2$), γ-interferon ($n = 2$), G-CSF ($n = 1$) or posaconazole ($n = 1$) were given in addition to voriconazole or as sequential therapy (termination of voriconazole and continuation of alternate therapy). A slight, but not significant, trend towards an improved response in favour of patients with these additional treatments versus voriconazole monotherapy was detected (23/37, 62% vs. 70/155, 45%, $p = 0.09$ NS) (Table 2). However, only a single patient with adjunctive treatment had previously received HSCT.

Table 3 Outcome by underlying conditions

Underlying condition (*n* patients)	Median voriconazole Rx (range) days[a]	Clinical response *n*/*N* (%)	Known median survival (range) days[b]	Died/total (due to IFI)
HSCT (35)	18 (3–390)	5/35 (14)[e]	25 (3–689)	28/35 (21)
Haem malign (35)	112 (5–810)	19/35 (54)	150 (5–810)	23/35 (12)
SOT (25)	42 (7–857)	10/25 (40)	78 (8–1,245)	17/25 (15)
Chronic[c] (40)	115 (4–1,128)	18/40 (45)	147 (8–1,260)	10/40 (7)
Other[d] (57)	155 (1–946)	41/57 (72)[f]	365 (11–2,000)	16/57 (12)
Total (192)	93 (1–1,128)	93/192 (48)	130 (3–2,000)	94/192 (67)

IFI invasive fungal infection; *HSCT* haematopoietic stem cell transplantation; *Haem malign* haematological malignancy; *SOT* solid organ transplantation

[a] Nine patients without data, one patient with cerebral infection despite prior voriconazole

[b] Survival duration unknown in four patients

[c] Chronic immunosuppression: acquired immune deficiency syndrome (AIDS), 13; chronic granulomatous disease (CGD), 7; steroids/other immunosuppression, 5; arthritic conditions, 3; immunodeficiency, 3 (agranulocytosis, 1; bone marrow aplasia, 1; undefined, 1), renal conditions, 3; hepatic conditions, 2; sarcoidosis, 1; lupus, 1; cancer, 1; unknown, 1

[d] No immunodeficiency, 15; near-drowning, 8; diabetes mellitus, 7; surgery/trauma, 5; other infection, 5; alcohol/drug abuse, 2; other, 6 (medulloblastoma, multiple sclerosis, renal failure, cerebrovascular disease, prematurity, polyradiculopathy); unknown, 9

[e] Clinical response worse than all other conditions ($p < 0.001$)

[f] Clinical response better than all other conditions ($p < 0.001$)

Treatments which included L-AMB appeared to show a somewhat better response rate than those which did not (12/17, 71% vs. 11/20, 55%; $p = 0.5$ NS), but none of the 17 L-AMB patients underwent HSCT and only three suffered from a haematologic malignancy. Treatments with or without caspofungin showed similar response rates (11/18, 61% vs. 12/19, 63%; $p = 0.15$ NS).

In addition, 72 patients underwent various neurosurgical interventions, including ventricular drainage/shunt (7), abscess biopsy/drainage (28) and other (mostly craniotomy or abscess resection, 37). Patients receiving these neurosurgical interventions showed significantly higher response rates compared with those without/unknown neurosurgery (43/72, 60% vs. 50/120, 42%; $p = 0.017$). In all, 74% (53/72) of the patients who underwent neurosurgery were receiving voriconazole as salvage therapy (salvage therapy success 30/53, 57%; primary therapy success 13/19, 68%).

Survival

A total of 112/188 (60%) patients were known to have survived for 90 days or more from the start of voriconazole therapy and 54/188 (29%) survived for at least 365 days (four patients had missing survival times). Only 10/54 (19%) of these long-term survivors had HSCT or a haematological malignancy as their predisposing underlying condition. The median survival time for all 188 patients was 297 days (range 3 to >2,000, Table 4). There was a trend towards shorter survival in patients with aspergillosis, although this was not significant (Table 4).

When survival by underlying condition was examined, there was a significant difference between the groups ($p < 0.001$), and patients with HSCT also had a significantly poorer survival than all of the other groups ($p < 0.001$) (Fig. 1). There was also a significant difference in survival between those patients with chronic immunosuppression or other underlying conditions and the remaining patients ($p < 0.001$).

Paediatric patients ($p = 0.014$), patients with neurosurgical interventions ($p = 0.0399$) or those from the publications ($p < 0.0001$) exhibited significantly better survival compared to adults, those without/unknown neurosurgery or database patients, respectively (Table 4; Fig. 2). There was also evidence for improved survival in those patients who received voriconazole with other antifungal agents over those that did not ($p = 0.0149$) (Table 4).

Discussion

In a previous retrospective study of 81 voriconazole-treated patients with CNS aspergillosis from the voriconazole clinical trials database, an encouraging efficacy rate of 35% was observed, despite most patients in this series suffering from profound immunosuppression [5]. Voriconazole has since become the drug of choice for treating this devastating infection [85, 86]. However, apart from case studies, there is no substantive examination of the role of voriconazole for the therapy of other fungal infections of the CNS. In this second, larger retrospective analysis,

Table 4 Known survival

	n/*N* (%)	Median survival in days (range)[a]	*p*-value
Overall survival	98/192 (51)	297 (3 to >2,000)	–
Survived ≥365 days	54/192 (28)	638 (365 to >2,000)	–
Paediatric survival	28/41 (68)	Not reached (8 to >2,000)	0.014
Adult survival	70/151 (46)	232 (3 to 1,260)	
Aspergillus spp.	51/120 (43)	159 (3 to 1,260)	0.076 NS
Scedosporium spp.	20/34 (59)	Not reached (8 to >2,000)	
Other 12 genera[b]	27/38 (71)	Not reached (8 to >900)	
Neurosurgery	41/72 (57)	Not reached (4 to >1,460)	0.0399
No known neurosurgery	57/120 (48)	190 (3 to >2,000)	
Database	45/114 (39)	22 (3 to >2,000)	<0.0001
Publications	53/78 (68)	Not reached (5 to >1,460)	
Combination therapy	24/37 (65)	Not reached (5 to 1,260)	0.0149
Voriconazole monotherapy	74/155 (48)	190 (3 to >2,000)	
HSCT	7/35 (20)	31 (3 to 689)	<0.001
Haematologic malignancy	12/35 (34)	190 (5 to 810)	
SOT	8/25 (32)	78 (8 to 1,245)	
Chronic immunosuppression	30/40 (75)	Not reached (8 to 1,260)	
Other	41/57 (72)	Not reached (11 to >2,000)	

NS not significant, *HSCT* haematopoietic stem cell transplantation, *SOT* solid organ transplantation

[a] Survival duration unknown in four patients

[b] See legend of Table 1

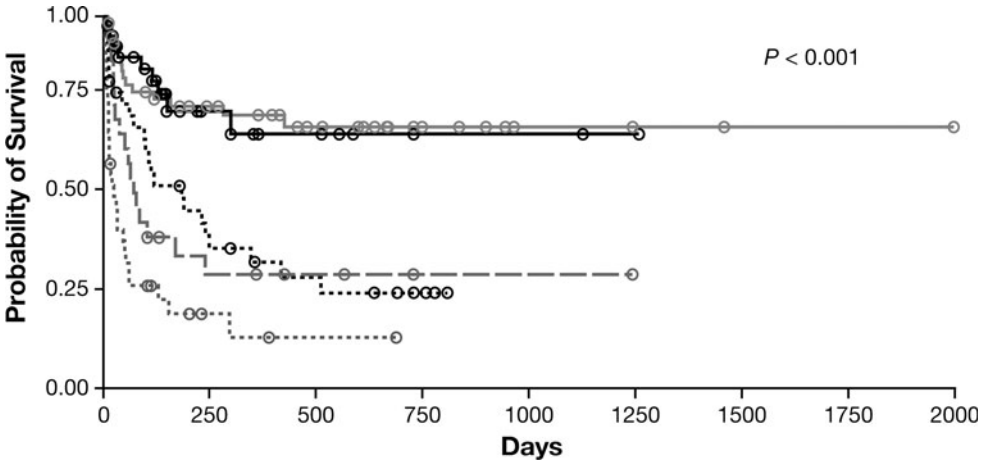

Fig. 1 Kaplan–Meier curves of survival by underlying condition: *grey dotted line* haematopoietic stem cell transplant; *black dotted line* haematologic malignancy; *grey dashed line* solid organ transplant; *black line* chronic immune suppression; *grey line* other; *circles* censored patients

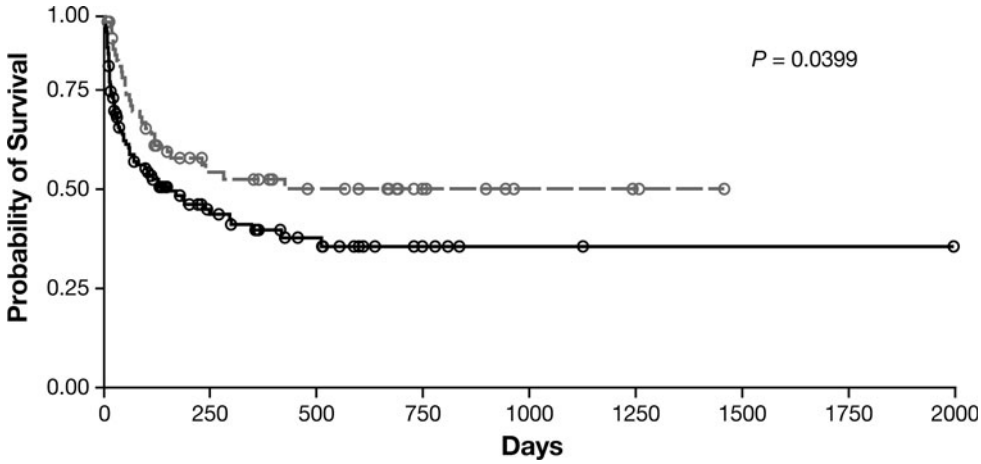

Fig. 2 Kaplan–Meier curves of survival by neurosurgical intervention: *grey dashed line* neurosurgery; *black line* no/unknown; *circles* censored patients

we update the efficacy of voriconazole against CNS aspergillosis and summarise the available data for other fungal CNS infections. The analysis utilises the voriconazole database until the drug was launched in 2002 and includes additional cases from publications spanning January 2002 to December 2008. Over 200 patients were identified and reviewed using the current definitions of proven and probable fungal infections [11]. The result was 192 cases for final analysis. The 47% response rate for the 120 patients with CNS aspergillosis is an improvement over that previously recorded [5], and this encouraging response rate is maintained for all 192 patients (48%). However, comparison of the database cases with those from the literature revealed highly significant response and survival differences in favour of the published cases, which is likely due to a publication bias (only one patient with HSCT among all literature cases), possibly skewed, at least in part, by an underrepresentation of unsuccessfully treated patients in the literature and improvements in patient management over the 6 years of the literature survey.

Despite this concern, the analysis also revealed some interesting findings. Both response and survival of the 41 paediatric cases were better than those for the 151 adults, with statistically significant differences in survival. These differences were maintained when the database and literature subsets were analysed separately, suggesting a real effect. The fact that fewer paediatric cases than adults suffered from aspergillosis while more received combination therapy and neurosurgical interventions may account, at least in part, for the improvements. It has been suggested that early diagnosis and aggressive intervention in paediatric patients with CNS aspergillosis results in improved outcome [87, 88].

Neurosurgical interventions did seem to favour an improved response rate and survival in these patients, which is consistent with the published data [5, 46]. However, there was no predefined algorithm for selecting an adjunct neurosurgical approach and patients with lesions localised to CNS regions more suitable for surgery might have carried a lower risk of deterioration and, therefore, have received a neurosurgical intervention more frequently. Interestingly, neurosurgical cases with primary voriconazole therapy responded slightly better than those with salvage therapy (68 vs. 57%) and, possibly, were more

likely having received an effective "pre-operative antifungal therapy". However, we were unable to analyse the sequence of medical and surgical therapies due to limitations of the available data. Recently published data, mostly in immunocompetent patients with cerebral aspergillosis, indicate that antifungal treatment prior to neurosurgery is associated with an improved outcome [89].

There was also limited, but not statistically significant, evidence for improved response and survival amongst the 37 patients who received both voriconazole and other antifungal agents, particularly for treatments that included L-AMB (but not caspofungin) with voriconazole. However, these 37 patients formed less than 20% of the dataset and appeared to be somewhat less severely immunocompromised (only 27% with HSCT or haematologic malignancy) than the remaining patients (36% with HSCT or haematologic malignancy). Not surprisingly, patients with the least severe immune compromisation (other underlying conditions) responded the best to therapy (72%) and HSCT the worst (14%). Thus, the benefits of combination therapies in this analysis are unclear and require further study in formal trials.

Except in cryptococcosis, where an amphotericin B formulation combined with 5-fluorocytosine or fluconazole is the therapy of choice [90, 91], meaningful clinical data supporting a combination therapy in CNS fungal infections are lacking. However, two small comparative studies suggest that caspofungin combined with L-AMB may be better than L-AMB alone in invasive aspergillosis or mucormycosis, including a few patients with rhinocerebral mucormycosis [92, 93].

Indeed, there are few substantive studies of the efficacy of any antifungal agent in CNS infections other than cryptococcosis. Conventional amphotericin B as monotherapy for CNS aspergillosis or mono- and combination therapy with 5-fluorocytosine for phaeohyphomycosis gives poor outcomes [94, 95]. However, conventional or lipid formulations of amphotericin B followed by an oral azole are effective in CNS blastomycosis [96], while fluconazole monotherapy of CNS coccidioidomycosis is often effective [97]. Consequently, the data presented in this retrospective study are the most comprehensive by far for any antifungal agent and suggest that voriconazole not only shows promise for CNS fungal infections due to *Aspergillus* spp., but also those caused by a variety of other, non- *Aspergillus* fungi. A neurosurgical management was associated with improved outcomes and should always be considered in individual patients with CNS fungal infections, whereas the impact of combination therapies is less clear and these should be assessed in future trials.

We also detected a publication bias and evaluated patients from a study database, which is a clear limitation of this analysis. Other limitations include the wide heterogeneity of the reported cases due to the retrospective analysis, differences in design of the different data sources (prospective clinical trials with well-standardised therapy, case reports), missing information on neutropenic status, the relative severity and initial stage of disease and, in some instances, the reason for switching to voriconazole (non-response vs. toxicity).

However, this approach appears to be currently the best way to gain a deeper insight into the effects of more refined treatment options in patients with CNS fungal infections. The analysis also supports the use of voriconazole for these life-threatening fungal infections.

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References

1. Black KE, Baden LR. Fungal infections of the CNS: treatment strategies for the immunocompromised patient. CNS Drugs. 2007;21:293–318.
2. Schwartz S, Ruhnke, M. *Aspergillus* sinusitis and cerebral aspergillosis. In: Latgé J-P, Steinbach WJ, editors. *Aspergillus fumigatus* and aspergillosis. 1st ed. Washington, DC: ASM Press; 2008, p. 301–17.
3. Kethireddy S, Andes D. CNS pharmacokinetics of antifungal agents. Expert Opin Drug Metab Toxicol. 2007;3:573–81.
4. Schwartz S, Thiel E. Cerebral aspergillosis: tissue penetration is the key. Med Mycol. 2009;47:S387–93.
5. Schwartz S, Ruhnke M, Ribaud P, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood. 2005;106:2641–5.
6. Troke P, Aguirrebengoa K, Arteaga C, et al. Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. Antimicrob Agents Chemother. 2008;52:1743–50.
7. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Eng J Med. 2002;347:408–15.
8. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis. 2003;36:1122–31.
9. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis. 2002;34:563–71.

10. Sambatakou H, Dupont B, Lode H, et al. Voriconazole treatment for subacute invasive and chronic pulmonary aspergillosis. Am J Med. 2006;119:527.e17–24.
11. De Pauw BE, 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.
12. Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria. Clin Infect Dis. 2008;47:674–83.
13. Ehrmann S, Bastides F, Gissot V, et al. Cerebral aspergillosis in the critically ill: two cases of successful medical treatment. Intensive Care Med. 2005;31:738–42.
14. Elter T, Sieniawski M, Gossmann A, et al. Voriconazole brain tissue levels in rhinocerebral aspergillosis in a successfully treated young woman. Int J Antimicrob Agents. 2006;28:262–5.
15. Gottfredsson M, Steingrimsdóttir H. Disseminated invasive aspergillosis in a patient with acute leukaemia. Acta Biomed. 2006;77:10–3.
16. Saitoh T, Matsushima T, Shimizu H, et al. Successful treatment with voriconazole of *Aspergillus* meningitis in a patient with acute myeloid leukemia. Ann Hematol. 2007;86:697–8.
17. Wandroo F, Stableforth P, Hasan Y. *Aspergillus* brain abscess in a patient with acute myeloid leukaemia successfully treated with voriconazole. Clin Lab Haematol. 2006;28:130–3.
18. Athanassiadou F, Tragiannidis A, Kourti M, et al. Treatment of disseminated aspergillosis with voriconazole/liposomal amphotericin B in a child with leukemia. Pediatr Blood Cancer. 2005;45:1003–4.
19. Balasubramaniam P, Madakira PB, Ninan A, et al. Response of central nervous system aspergillosis to voriconazole. Neurol India. 2007;55:301–3.
20. Damaj G, Ivanov V, Le Brigand B, et al. Rapid improvement of disseminated aspergillosis with caspofungin/voriconazole combination in an adult leukemic patient. Ann Hematol. 2004;83:390–3.
21. Marbello L, Nosari A, Carrafiello G, et al. Successful treatment with voriconazole of cerebral aspergillosis in an hematologic patient. Haematologica. 2003;88:e16–8.
22. Denes E, Pichon N, Debette-Gratien M, et al. Pharmacokinetics of voriconazole in the cerebrospinal fluid of an immunocompromised patient with a brain abscess due to *Aspergillus fumigatus*. Clin Infect Dis. 2004;39:603–4.
23. Eloy JA, Bederson JB, Smouha EE. Petrous apex aspergillosis as a long-term complication of cholesterol granuloma. Laryngoscope. 2007;117:1199–201.
24. Eslick GD, Casikar V. Ring lesions of the brain. Mayo Clin Proc. 2006;81:1145.
25. Freudenstein D, Koerbel A, Beschorner R, et al. Successful treatment of *Aspergillus* granuloma involving the cavernous sinus and the middle fossa by using surgery and voriconazole. Case illustration. J Neurosurg. 2007;106:511.
26. Gubler C, Wildi SM, Imhof A, et al. Disseminated invasive aspergillosis with cerebral involvement successfully treated with caspofungin and voriconazole. Infection. 2007;35:364–6.
27. Hot A, Mazighi M, Lecuit M, et al. Fungal internal carotid artery aneurysms: successful embolization of an *Aspergillus*-associated case and review. Clin Infect Dis. 2007;45:e156–61.
28. Hummel M, Spiess B, Kentouche K, et al. Detection of *Aspergillus* DNA in cerebrospinal fluid from patients with cerebral aspergillosis by a nested PCR assay. J Clin Microbiol. 2006;44:3989–93.
29. Alsultan A, Williams MS, Lubner S, et al. Chronic granulomatous disease presenting with disseminated intracranial aspergillosis. Pediatric Blood Cancer. 2006;47:107–10.
30. Bethell D, Hall G, Goodman TR, et al. Resolution of orbitocerebral aspergillosis during combination treatment with voriconazole and amphotericin plus adjunctive cytokine therapy. J Pediatric Hematol Oncol. 2004;26:304–7.
31. Giacchino M, Chiapello N, Riva C, et al. Intracranial aspergillosis in children successfully treated with antifungal therapy and surgical intervention. Pediatr Infect Dis J. 2006;25:379–81.
32. Sood S, Sharma R, Gupta S, et al. Neuroaspergillosis in an immunocompetent patient. Indian J Med Microbiol. 2007;25:67–9.
33. Gunaratne PS, Wijeyaratne CN, Seneviratne HR. *Aspergillus* meningitis in Sri Lanka—a post-tsunami effect? N Engl J Med. 2007;356:754–6.
34. Moling O, Lass-Floerl C, Verweij PE, et al. Case reports. Chronic and acute *Aspergillus* meningitis. Mycoses. 2002;45:504–11.
35. van Hal SJ, Clezy K. Emergence of invasive cerebral aspergillosis in an HIV-positive patient on voriconazole therapy. HIV Med. 2005;6:45–6.
36. Vianna R, Misra V, Fridell JA, et al. Survival after disseminated invasive aspergillosis in a multivisceral transplant recipient. Transplant Proc. 2007;39:305–7.
37. Reis LJ, Barton TD, Pochettino A, et al. Successful treatment of *Aspergillus* prosthetic valve endocarditis with oral voriconazole. Clin Infect Dis. 2005;41:752–3.
38. Akhaddar A, Gazzaz M, Albouzidi A, et al. Invasive *Aspergillus terreus* sinusitis with orbitocranial extension: case report. Surg Neurol. 2008;69:490–5.
39. Slusher JR, Maldonado ME, Mousavi F, et al. Central nervous system *Aspergillus fumigatus* presenting as cranial nerve palsy in a patient with ankylosing spondylitis on anti-TNF therapy. Rheumatology (Oxford). 2008;47:739–40.
40. Schelenz S, Goldsmith DJ. *Aspergillus* endophthalmitis: an unusual complication of disseminated infection in renal transplant patients. J Infect. 2003;47:336–43.
41. Stiefel M, Reiss T, Staege MS, et al. Successful treatment with voriconazole of *Aspergillus* brain abscess in a boy with medulloblastoma. Pediatr Blood Cancer. 2007;49:203–7.
42. Traboulsi RS, Kattar MM, Dbouni O, et al. Fatal brain infection caused by *Aspergillus glaucus* in an immunocompetent patient identified by sequencing of the ribosomal 18S–28S internal transcribed spacer. Eur J Clin Microbiol Infect Dis. 2007;26:747–50.
43. de Lastours V, Lefort A, Zappa M, et al. Two cases of cerebral aspergillosis successfully treated with voriconazole. Eur J Clin Microbiol Infect Dis. 2003;22:297–9.
44. Garcia RJ, Troya P, Edwards C. Invasive aspergillosis with central nervous system dissemination in a presumably immunocompetent, non-neutropenic patient: case report and review. South Med J. 2006;99:607–10.
45. Hafner V, Albermann N, Haefeli WE, et al. Inhibition of voriconazole metabolism by chloramphenicol in an adolescent with central nervous system aspergillosis. Antimicrob Agents Chemother. 2008;52:4172–4.
46. Kaffarnik M, Utzolino S, Blaich A, et al. Successful multimodal therapy of invasive pulmonary and central nervous system aspergillosis in a neutropenic surgical patient: case report and review of the literature. Mycoses. 2008;51:74–8.
47. Karakousis PC, Magill SS, Gupta A. Paraplegia caused by invasive spinal aspergillosis. Neurology. 2007;68:158.
48. van de Beek D, Patel R, Campeau NG, et al. Insidious sinusitis leading to catastrophic cerebral aspergillosis in transplant recipients. Neurology. 2008;70:2411–3.

49. Zwitserloot AM, Warris A, van't Hek LG, et al. Disseminated aspergillosis in an adolescent with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2008;51:423–6.
50. Buzina W, Feierl G, Haas D, et al. Lethal brain abscess due to the fungus *Scedosporium apiospermum* (teleomorph *Pseudallescheria boydii*) after a near-drowning incident: case report and review of the literature. Med Mycol. 2006;44:473–7.
51. Danaher PJ, Walter EA. Successful treatment of chronic meningitis caused by *Scedosporium apiospermum* with oral voriconazole. Mayo Clin Proc. 2004;79:707–8.
52. Apostolova LG, Johnson EK, Adams HP Jr. Disseminated *Pseudallescheria boydii* infection successfully treated with voriconazole. J Neurol Neurosurg Psychiatry. 2005;76:1741–2.
53. Husain S, Muñoz P, Forrest G, et al. Infections due to *Scedosporium apiospermum* and *Scedosporium prolificans* in transplant recipients: clinical characteristics and impact of antifungal agent therapy on outcome. Clin Infect Dis. 2005;40:89–99.
54. Katragkou A, Dotis J, Kotsiou M, et al. *Scedosporium apiospermum* infection after near-drowning. Mycoses. 2007;50:412–21.
55. Panichpisal K, Nugent K, Sarria JC. Central nervous system pseudallescheriasis after near-drowning. Clin Neurol Neurosurg. 2006;108:348–52.
56. Mursch K, Trnovec S, Ratz H, et al. Successful treatment of multiple *Pseudallescheria boydii* brain abscesses and ventriculitis/ependymitis in a 2-year-old child after a near-drowning episode. Childs Nerv Syst. 2006;22:189–92.
57. Garzoni C, Markham L, Bijlenga P, et al. *Cladophialophora bantiana*: a rare cause of fungal brain abscess. Clinical aspects and new therapeutic options. Med Mycol. 2008;46:481–6.
58. Leechawengwongs M, Milindankura S, Liengudom A, et al. Multiple *Scedosporium apiospermum* brain abscesses after near-drowning successfully treated with surgery and long-term voriconazole: a case report. Mycoses. 2007;50:512–6.
59. Chakraborty A, Workman MR, Bullock PR. *Scedosporium apiospermum* brain abscess treated with surgery and voriconazole. Case report. J Neurosurg. 2005;103:83–7.
60. Chaney S, Gopalan R, Berggren RE. Pulmonary *Pseudallescheria boydii* infection with cutaneous zygomycosis after near drowning. South Med J. 2004;97:683–7.
61. Bhat SV, Paterson DL, Rinaldi MG, et al. *Scedosporium prolificans* brain abscess in a patient with chronic granulomatous disease: successful combination therapy with voriconazole and terbinafine. Scand J Infect Dis. 2007;39:87–90.
62. Cortez KJ, Walsh TJ, Bennett JE. Successful treatment of coccidioidal meningitis with voriconazole. Clin Infect Dis. 2003;36:1619–22.
63. Sabbatani S, Manfredi R, Pavoni M, et al. Voriconazole proves effective in long-term treatment of a cerebral cryptococcoma in a chronic nephropathic HIV-negative patient, after fluconazole failure. Mycopathologia. 2004;158:165–71.
64. Srinivasan J, Ooi WW. Successful treatment of histoplasmosis brain abscess with voriconazole. Arch Neurol. 2008;65:666–7.
65. Pinto A, Chan RC. Lack of allergic cross-reactivity between fluconazole and voriconazole. Antimicrob Agents Chemother. 2009;53:1715–6.
66. Borgia SM, Fuller JD, Sarabia A, et al. Cerebral blastomycosis: a case series incorporating voriconazole in the treatment regimen. Med Mycol. 2006;44:659–64.
67. Lyons MK, Blair JE, Leslie KO. Successful treatment with voriconazole of fungal cerebral abscess due to *Cladophialophora bantiana*. Clin Neurol Neurosurg. 2005;107:532–4.
68. Steininger C, van Lunzen J, Sobottka I, et al. Mycotic brain abscess caused by opportunistic reptile pathogen. Emerg Infect Dis. 2005;11:349–50.
69. Garg N, Devi IB, Vajramani GV, et al. Central nervous system cladosporiosis: an account of ten culture-proven cases. Neurol India. 2007;55:282–8.
70. Singh H, Irwin S, Falowski S, et al. Curvularia fungi presenting as a large cranial base meningioma: case report. Neurosurgery. 2008;63:E177.
71. Panicker J, Walsh T, Kamani N. Recurrent central nervous system blastomycosis in an immunocompetent child treated successfully with sequential liposomal amphotericin B and voriconazole. Pediatr Infect Dis J. 2006;25:377–9.
72. Bakleh M, Aksamit AJ, Tleyjeh IM, et al. Successful treatment of cerebral blastomycosis with voriconazole. Clin Infect Dis. 2005;40:e69–71.
73. Hong XY, Chou YC, Lazareff JA. Brain stem candidiasis mimicking cerebellopontine angle tumor. Surg Neurol. 2008;70:87–91.
74. Trinh JV, Steinbach WJ, Schell WA, et al. Cerebral phaeohyphomycosis in an immunodeficient child treated medically with combination antifungal therapy. Med Mycol. 2003;41:339–45.
75. Fica A, Diaz MC, Luppi M, et al. Unsuccessful treatment with voriconazole of a brain abscess due to *Cladophialophora bantiana*. Scand J Infect Dis. 2003;35:892–3.
76. Tunuguntla A, Saad MM, Abdalla J, et al. Multiple brain abscesses caused by *Cladophialophora bantianum*: a challenging case. Tenn Med. 2005;98:227–8.
77. Antony SJ, Jurczyk P, Brumble L. Successful use of combination antifungal therapy in the treatment of *Coccidioides* meningitis. J Natl Med Assoc. 2006;98:940–2.
78. Proia LA, Tenorio AR. Successful use of voriconazole for treatment of *Coccidioides* meningitis. Antimicrob Agents Chemother. 2004;48:2341.
79. Surash S, Tyagi A, de Hoog GS, et al. Cerebral phaeohyphomycosis caused by *Fonsecaea monophora*. Med Mycol. 2005;43:465–72.
80. Vincent AL, Cabrero JE, Greene JN, et al. Successful voriconazole therapy of disseminated *Fusarium solani* in the brain of a neutropenic cancer patient. Cancer Control. 2003;10:414–9.
81. Wang TK, Chiu W, Chim S, et al. Disseminated *Ochroconis gallopavum* infection in a renal transplant recipient: the first reported case and a review of the literature. Clin Nephrol. 2003;60:415–23.
82. Amr SS, Al-Tawfiq JA. Aspiration cytology of brain abscess from a fatal case of cerebral phaeohyphomycosis due to *Ramichloridium mackenziei*. Diagn Cytopathol. 2007;35:695–9.
83. Shen YZ, Wang JR, Lu HZ. Voriconazole in an infant with cryptococcal meningitis. Chin Med J (Engl). 2008;121:286–8.
84. Sasakawa A, Yamamoto Y, Yajima K, et al. Liposomal amphotericin B for a case of intractable cryptococcal meningoencephalitis and immune reconstitution syndrome. J Med Invest. 2008;55:292–6.
85. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008;46:327–60.
86. British Committee for Standards in Haematology (BCSH). Guidelines on the management of invasive fungal infection during therapy for haematological malignancy. http://www.bcshguidelines.com. Accessed 1 Oct 2010.
87. Wright JA, Bradfield SM, Park JR, et al. Prolonged survival after invasive aspergillosis: a single-institution review of 11 cases. J Pediatr Hematol Oncol. 2003;25:286–91.
88. Sato T, Kaneda M, Ichikawa M, et al. Current approaches to management of cerebral fungal infection in pediatric patients with hematologic disorders. J Pediatr Hematol Oncol. 2008;30:249–53.

89. Wasay M, Patel J, Azam I, et al. Preoperative antifungal therapy may improve survival in patients with *Aspergillus* brain abscess. Clin Neurol Neurosurg. 2009;111:565–7.
90. Sun HY, Alexander BD, Lortholary O, et al. Lipid formulations of amphotericin B significantly improve outcome in solid organ transplant recipients with central nervous system cryptococcosis. Clin Infect Dis. 2009;49:1721–8.
91. Pappas PG, Chetchotisakd P, Larsen RA, et al. A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. Clin Infect Dis. 2009;48:1775–83.
92. Caillot D, Thiébaut A, Herbrecht R, et al. Liposomal amphotericin B in combination with caspofungin for invasive aspergillosis in patients with hematologic malignancies: a randomized pilot study (Combistrat trial). Cancer. 2007;110:2740–6.
93. Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis. 2008;47:364–71.
94. Schwartz S, Ruhnke M, Ribaud P, et al. Poor efficacy of amphotericin B-based therapy in CNS aspergillosis. Mycoses. 2007;50:196–200.
95. Revankar SG, Sutton DA, Rinaldi MG. Primary central nervous system phaeohyphomycosis: a review of 101 cases. Clin Infect Dis. 2004;38:206–16.
96. Bariola JR, Perry P, Pappas PG, et al. Blastomycosis of the central nervous system: a multicenter review of diagnosis and treatment in the modern era. Clin Infect Dis. 2010;50:797–804.
97. Drake KW, Adam RD. Coccidioidal meningitis and brain abscesses: analysis of 71 cases at a referral center. Neurology. 2009;73:1780–6.