Impact of Surgical and Medical Treatment on Survival of Patients with Cerebral Aspergillosis: Systematic Review of the Literature

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Key words
- Antifungal agents
- Aspergillosis
- Itraconazole
- Neurosurgery
- Voriconazole

Abbreviations and Acronyms
CI: Confidence interval
CNS: Central nervous system
IDSA: Infectious Diseases Society of America
OR: Odds ratio

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OBJECTIVE: **Cerebral aspergillosis carries a high mortality. Rapid diagnosis and treatment can increase survival, but symptoms and imaging findings are nonspecific. The literature on cerebral aspergillosis consists mostly of case reports and case series and lacks large-scale review of data.**

METHODS: **We performed a review of the literature using PubMed in March 2019. We recorded the year of publication, age and sex of patients, neurosurgical involvement, the antifungals administered, use of intrathecal antifungals, and the outcome of patients. The relationships among variables were tested using bivariant statics and linear regression.**

RESULTS: **A total of 324 studies met the eligibility criteria, and 198 studies including 248 patients were included. Surgical resection (odds ratio [OR], 0.45; 95% confidence interval [CI], 0.25—0.80; $P < 0.01$) and administration of voriconazole (OR, 0.32; 95% CI, 0.18—0.55; $P < 0.001$) or itraconazole (OR, 0.36; 95% CI, 0.16—0.72; $P < 0.001$) were shown to be significantly associated with survival.**

CONCLUSIONS: **Given the significant survival benefits for patients who received voriconazole and surgical intervention, we suggest early antifungal medical treatment and resection.**

INTRODUCTION

Fungal infections of the brain carry high rates of morbidity and mortality.[1] They are often associated with diabetic and immunocompromised patients.[1-3] They have various nonspecific presentations, with difficult and invasive diagnosis, and require pathogen-specific antifungal treatment.[1,4,5] Central nervous system (CNS) fungal infections are acquired through inhalation, inoculation, trauma, and cranial or sinus surgery.[1,5] *Aspergillus* species are an aggressive pathogen that can cause CNS infections even with proper prophylaxis.[2] Patients can present with headache, fever, irritability, proptosis, focal neurologic deficits, progressive weakness, and altered mental status.[3,6-8] Cerebral aspergillosis caused mortality of approximately 99% before the introduction of the antifungal agent voriconazole.[9,10]

Rapid diagnosis and treatment of CNS aspergillosis can increase rates of survival.[1] Treatment options for CNS fungal infections are limited by the blood-brain barrier. Antifungals such as voriconazole, fluconazole, and flucytosine have shown adequate CNS penetration and are therefore good candidates for treatment of cerebral fungal infections. Neurosurgical intervention has been shown to play a critical role in the management of cerebral aspergillosis[6] and is associated with improved outcomes compared with medical management alone.[11] The combination of voriconazole and surgical resection or aspiration shows better response and survival over any other therapy.[9,11,12] The literature on cerebral aspergillosis consists of case reports and series and lacks large-scale review of data.

With the increasing incidence of CNS fungal infections,[4] consensus regarding the most effective treatments is needed. We conducted a systematic review to compare outcomes of patients with cerebral aspergillosis who underwent neurosurgical intervention with those who did not. Furthermore, we sought to identify predictors of survival, including age, sex, specific antifungal agents used, and the number of antifungals used cumulatively.

METHODS

Search Selection

Using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic review, a search of PubMed was conducted in March 2019 by the first author of this study (H.B.P.) using the keyword "cerebral aspergillosis." The search included articles from inception to March 2019. No restrictions were placed on language, publication type, or publication date. After examination of each article, the author determined if it contained pertinent diagnostic or treatment information to be included. Duplicates were avoided through careful review by 2 authors, including review of other literature reviews against original articles to ensure that the same patient was not included in the study

twice. A detailed description of the strategy and selection criteria is provided in Figure 1.

Inclusion Criteria

Selected articles all included diagnoses of cerebral aspergillosis, inclusion of treatment course of the patient including specific antifungal treatment and surgical intervention, and outcome of the patient. Cases were classified using previously reported criteria.[9] Articles met inclusion criteria if the diagnosis of definitive cerebral aspergillosis was made through direct histologic or cytologic evidence from a CNS specimen. Furthermore, diagnosis of presumed and probable invasive aspergillosis through growth of *Aspergillus* from sterile site or bronchoalveolar lavage plus cerebral imaging was sufficient to be included in the review.

Exclusion Criteria

Articles were excluded if they included fungi other than *Aspergillus* species. Articles with patients with possible aspergillosis infections without any histologic, cytologic, or cultural evidence of aspergillosis were excluded. Other exclusions included articles with patients who had $\geq$2 concurrent fungal infections. Studies with large patient numbers without patient-level data were excluded because our goal was to analyze patient-level data. Patients with aspergillosis confined to the sinuses without invasion of the orbits or calvarium, or patients with aspergillosis with only vascular findings were also excluded.

Data Extraction

For included articles, we recorded the year of publication, age and sex of patients, neurosurgical involvement and their specific intervention, the antifungals administered and antifungal failure, use of intrathecal antifungals, and the outcome of the patient including whether or not mortality was attributable to aspergillosis.

Statistical Analysis

All statistical analyses were performed using R (R Core Team, 2014 [R Foundation for Statistical Computing, Vienna, Austria]). Mortality from aspergillosis was used as the primary outcome variable. Bivariate analysis was performed to determine baseline statistical correlations. Categorical variables (treatment modality) were analyzed using χ^2 testing to determine associations with primary outcome measures. Continuous variables (age and mean number of agents) were analyzed using an independent-sample Student *t* test. For independent variables reaching a significance level of 0.05, a univariate and multivariate linear regression was performed. Linear regression associations are reported as odds ratios (OR) with corresponding 95% confidence interval (CI). Significance was determined at a P value $\leq$0.05. For significant variables on multivariable linear regression analysis, a Cox proportional hazard model was performed, and associated Kaplan-Meier curves were generated. Mortality from aspergillosis was used as the primary censoring event.

RESULTS

Study Selection and Characteristics

The search identified 1169 articles, of which 324 met the eligibility criteria and were reviewed in full and used for data collection. A total of 198 studies including 248 patients were included in the analysis. Study selection methods are presented in Figure 1. Most studies included in the analysis were case reports and retrospective reviews. Some studies included review of the literature. Patient characteristics, treatments, and outcomes were extracted (see Supplementary Table 1, which shows clinical data collected).

Risk of Bias

Case reports carry the risk of publication bias, because ordinary, unremarkable cases have a reduced chance of being reported. Retrospective studies carry a high risk of bias because the investigator has no control over which data are collected or the quality of the data.

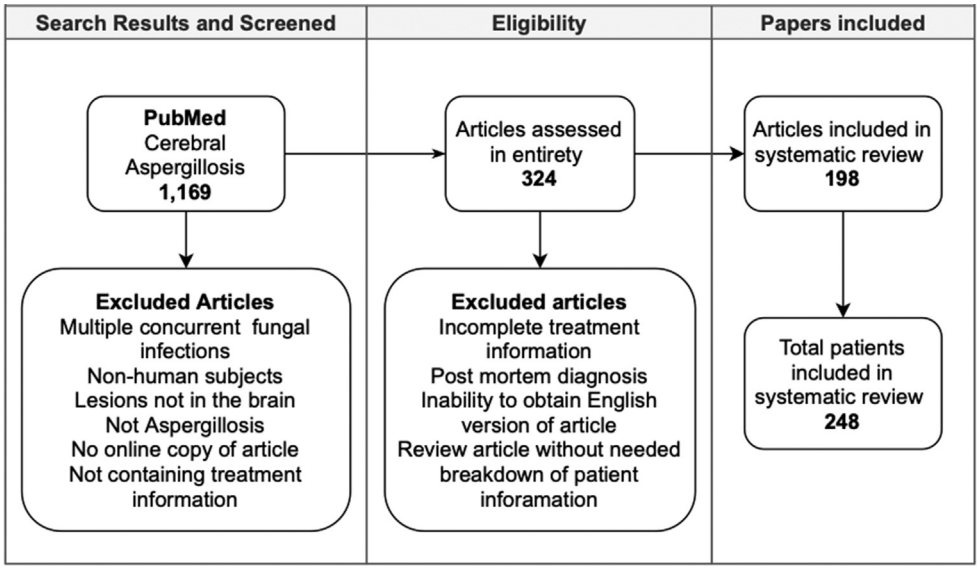

Figure 1. Search Strategy and Selection Criteria.

Table 1. Overall Descriptive Statistics and Bivariate Analysis for Patients Surviving and Dying of Aspergillosis by Treatment Type

Treatment*	Survived (%)	Died (%)	*P* Value†
All patients	168 (67.7)	80 (32.3)	Not available
Mean age (SD)	39.5 (22.4)	42.8 (21.1)	0.25
Mean number of agents (SD)	2.3 (1.2)	1.9 (1.0)	0.06
Sex			
Male	88 (66.7)	44 (33.3)	0.69
Female	76 (69.1)	34 (30.9)	
Surgery			
No	89 (61.0)	57 (39.0)	<0.05
Yes	79 (77.5)	23 (22.5)	
Surgery type			
None	89 (61.0)	57 (39.0)	<0.01
Biopsy	12 (80.0)	3 (20.0)	
Partial resection	20 (87.0)	3 (13.0)	
Complete resection	23 (88.5)	3 (11.5)	
Unknown	24 (63.2)	14 (36.8)	
Intrathecal			
None	151 (66.2)	77 (33.8)	0.09
AmpB	13 (81.2)	3 (18.8)	0.23
VCZ	1 (100.0)	0 (0.0)	0.49
L AmpB	2 (100.0)	0 (0.0)	0.33
Systemic			
VCZ	112 (78.3)	31 (21.7)	<0.001
Capsofungin	21 (61.8)	13 (38.2)	0.42
AmpB	66 (61.1)	42 (38.9)	0.05
L AmpB	62 (75.6)	20 (24.4)	0.06
Amphotericin B lipid complex	2 (66.7)	1 (33.3)	0.97
Amphotericin B colloidal dispersion	1 (100.0)	0 (0.0)	0.49
Itraconazole	48 (82.8)	10 (17.2)	<0.05
Isavuconazole	1 (100.0)	0 (0.0)	0.49
Posaconazole	4 (57.1)	3 (42.9)	0.54

SD, standard deviation; AmpB, amphotericin B deoxycholate; VCZ, voriconazole; L AmpB, liposomal amphotericin B.
*Data only shown for those patients receiving the listed treatment option.
†Statistical analysis performed in R Studio using χ^2 testing for categorical variables. Student *t* test for continuous variables to determine difference among survival based on treatment type. Significance determined at the $P < 0.05$ level. Those variables reaching significance on bivariate analysis were included in the subsequent regression analysis.

Overall Morbidity and Mortality Associated with Aspergillosis Infections

Of the 248 patients included in this study, 98 (40%) died during the duration of their respective studies. Eighteen of those patients died of other causes, and 80 (32%) died of aspergillosis. Sensitivity analysis was performed to account for changes in death as a function of study publication year. There was no difference in patient mortality based on year of treatment.

Patient age ranged from first day of life to 90 years, with an average age of 40.6 years. There was no significant difference in the mean age of patients who did and did not survive. There was a slight predominance of male patients; however, this finding was not significant, and sex was not associated with increased survival. Nineteen patients received intrathecal antifungals including amphotericin B, liposomal amphotericin B, and voriconazole, but the use of intrathecal antifungals did not significantly affect survival.

Morbidity and Mortality with and without Surgery

Surgical intervention was used in 102 patients to aid in diagnosis and/or treatment. Of these interventions, 23 were partial resections, 26 were complete resections, and in the remaining 38 patients, the extent of the resection was not specified (Table 1). A bivariate analysis of patients undergoing surgical resection (Table 1) showed a statistically significant ($P < 0.05$) increase in survival for patients who underwent surgery, regardless of surgery type, compared with those who did not.

Morbidity and Mortality Associated with Use of Various Antifungal Agents

Systemic antifungals were used in the treatment of 243 patients. The specific antifungals used in this review are listed in Table 1. We found the most commonly used antifungal to be voriconazole, followed by amphotericin B, liposomal amphotericin B, itraconazole, and caspofungin. Voriconazole had a failure rate of 5.5%, amphotericin B had a failure rate of 11.1%, liposomal amphotericin B had a failure rate of 7.3%, itraconazole had a failure rate of 8.6%, and caspofungin had a failure rate of 5.9%. Posaconazole was used in 7 cases and did not have a noted failure. A bivariate analysis of patient mortality from aspergillosis after systemic antifungals (Table 1) showed increased survival for patients who were treated with voriconazole (78.3%; $P < 0.001$), itraconazole (82.8%; $P < 0.05$), and amphotericin B (61.1%; $P = 0.05$).

There was no difference in the number of antifungals used in patients who died compared with those who survived ($P = 0.06$). Patients surviving received an average of 2.3 antifungals (standard

Table 2. Multivariate and Univariate Linear Regression Analysis for Variables Determined to Statistically Decrease Expiration on Bivariate Analysis

Treatment	Survived, n (%)	Died, n (%)	Univariable OR (95% CI)*	*P* Value	Multivariable OR (95% CI)*	*P* Value
Surgery	79 (77.5)	23 (22.5)	0.45 (0.25—0.80)	<0.01	0.40 (0.21—0.76)	<0.01
Surgery type						
None	89 (61.0)	57 (39.0)	—	—	—	—
Biopsy	12 (80.0)	3 (20.0)	0.39 (0.09—1.29)	0.16	0.38 (0.08—1.38)	0.17
Partial resection	20 (87.0)	3 (13.0)	0.23 (0.05—0.72)	0.02	0.20 (0.04—0.66)	0.02
Complete resection	23 (88.5)	3 (11.5)	0.20 (0.05—0.62)	0.01	0.15 (0.03—0.50)	<0.01
Unknown	24 (63.2)	14 (36.8)	0.91 (0.43—1.89)	0.8	0.88 (0.38—1.99)	0.76
Voriconazole	112 (78.3)	31 (21.7)	0.32 (0.18—0.55)	<0.001	0.19 (0.09— 0.39)	<0.001
Amphotericin B deoxycholate	66 (61.1)	42 (38.9)	1.71 (1.00— 2.93)	0.05	1.20 (0.62— 2.32)	0.59
Itraconazole	48 (82.8)	10 (17.2)	0.36 (0.16—0.72)	<0.01	0.18 (0.07—0.43)	<0.001

OR, odds ratio; CI, confidence interval.

*Statistical analysis performed in R Studio using a least-squares stepwise linear regression analysis. Significance determined at the $P < 0.05$ level. Number in model = 248; Akaike Information Criterion = 271.5; C-statistic = 0.758; Hosmer-Lemeshow test = 5.01 ($P = 0.757$).

deviation = 1.2), and patients who died received an average of 1.9 antifungals (standard deviation = 1.0). Furthermore, there was no difference in survival for patients who received intrathecal antifungal treatment compared with those who did not.

Linear Regression Results

Surgical intervention and use of systemic fungal agents were investigated to identify potential predictors of decreased mortality after treatment for CNS fungal infection. In univariate analysis (Table 2), there was a 55% reduction in mortality for those treated with surgery (OR, 0.45; 95% CI, 0.25—0.80; P < 0.01). The odds of mortality after treatment with systemic voriconazole and itraconazole were reduced by 68% and 64%, respectively (OR, 0.32, 95% CI, 0.18—0.55, P < 0.001; OR, 0.36, 95% CI, 0.16—0.72, P < 0.01).

In multivariable analysis (Table 2), the odds of mortality with surgery were independently reduced by 60% (OR, 0.40; 95% CI 0.21—0.75; P < 0.01). The odds of mortality after receiving voriconazole and itraconazole were independently reduced by 86% and 85%, respectively (OR, 0.14, 95% CI, 0.05—0.36, P < 0.001; OR, 0.15, 95% CI, 0.05—0.38, P < 0.001).

DISCUSSION

Summary of Evidence

Our study shows the importance of antifungal treatment and neurosurgical intervention as first-line treatment for cerebral aspergillosis.[9,11-13] Surgical resection and administration of voriconazole or itraconazole were all shown to be significantly associated with survival. Patient age, sex, intrathecal antifungals, and cumulative number of antifungals used did not predict survival.

We found a significant reduction in mortality in patients who underwent surgical resection compared with those patients who did not. To our knowledge, this is the first systematic review to show this finding regarding cerebral aspergillosis. Furthermore, both partial and complete resection seem to trend toward benefiting survival. Although this finding was statistically significant, both CIs are too large for any conclusion to be drawn. More data is required to differentiate if a specific type of surgery is superior. A retrospective study has reported similar findings regarding CNS aspergillosis with a relatively small number of patients.[9] These investigators retrospectively collected data from patients previously enrolled in a voriconazole clinical trial, subject to notable selection bias.[9] The Infectious Diseases Society of America (IDSA) guidelines recommend surgical intervention but advise providers to exercise caution when considering surgery for patients with cerebral aspergillosis because of the potential for significant neurologic disability.[13] The IDSA also suggests that improved survival with surgery in previous studies may be caused by selection bias, because patients who are healthy enough to undergo surgery may have improved chances of survival at baseline.[13] The results of the present study suggest that providers should consider lowering their threshold for surgery because of the synergistic effect of surgery and systemic antifungals on cerebral aspergillosis.

In our study, 15 patients underwent surgical biopsy. These biopsies were not without risk, because some patients developed hemorrhage requiring a craniotomy. Although tissue biopsy is required for definitive diagnosis of aspergillosis, guidelines recommend that providers proceed with treatment based on clinical suspicion or tissue collected outside the CNS.[13] Biopsy samples can be collected at the time of surgery, but definitive diagnosis should not delay prompt administration of antifungal therapy.

Voriconazole, isavuconazole, and amphotericin B are the only drugs approved by the U.S. Food and Drug Administration for first-line treatment of invasive aspergillosis.[14] Voriconazole,[9,15] lipid formulation of amphotericin B,[16] and itraconazole[17] have been successfully used in the treatment of CNS aspergillosis; however, voriconazole is the only antifungal recommended as first-line treatment by the IDSA.[13] In our study, patients who were treated with voriconazole or itraconazole were significantly more likely to survive than were patients who did not receive these treatments. Voriconazole was the most effective agent overall, with 78% of patients receiving this treatment surviving. Our study did not show treatment with amphotericin B as a factor in improved survival. This finding has been reported in other studies.[10] Furthermore, when comparing the outcomes of patients treated with amphotericin B and voriconazole, those treated with voriconazole showed improved responses, improved survival, and fewer side effects than did those treated with amphotericin B.[18] The IDSA also recommends against intrathecal and intralesional antifungals, because there are no data to suggest improved outcomes.[13] The present study affirms that intrathecal antifungals do not improve survival in cerebral aspergillosis.

The literature on mortality of patients with cerebral aspergillosis has been described in older data.[9,10] The mortality in this study attributable to aspergillosis of 32.3% is lower than that seen epidemiologically. This finding may be to the result of selection bias of publications with increased survivability, but nonetheless, the true mortality of patients should be reexamined because of improved treatment.

Limitations

We present this systematic review with expected limitations from retrospective review of the literature in this process. Information was missing from various studies including laboratory test values, dosing and mode of delivery for antifungals, and timing of the regimen. Further limitations include variation in treatment and unknown health status and comorbidities of patients. Systematic reviews, case reports, and retrospective studies are limited because they can report only the information documented in the patient's medical record, which affects downstream data analysis and reporting. The studies included in this review span a wide period, over which there have been significant advancements in the treatment of fungal infections, such as the availability of new antifungal agents.[9]

CONCLUSIONS

Cerebral aspergillosis is a rare but highly fatal infection. On suspicion of diagnosis, neurosurgical consultation should be rapidly initiated, because these patients decompensate beyond surgical stability rapidly. Given the significant survival benefits for patients who receive voriconazole and surgical intervention, we suggest early antifungal treatment and resection.

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SUPPLEMENTARY DATA

Supplementary Table 1. Patient Characteristics of Patients with Aspergillosis

Reference	Age*	Surgical Intervention	Antifungal	Intrathecal Antifungal	Outcome
Al Otaibi, 2018[1]	43	Complete resection	VCZ, capsofungin	None	Died—other cause
Danion et al., 2018[2]	75	None	L AmpB, VCZ → isavuconazole	None	Partial recovery
	39	None	L AmpB → VCZ, capsofungin	None	Complete recovery
Kural et al., 2018[3]	21	Complete resection	AmpB	AmpB	Died—other cause
	45	Complete resection	AmpB	AmpB	Complete recovery
Vázquez et al., 2017[4]	41	Complete resection	VCZ	None	Died—other cause
Wang et al., 2017[5]	11 months	None	VCZ	None	Complete recovery
Chavez et al., 2018[6]	48	Complete resection	VCZ → posaconazole	None	Complete recovery
Zhang et al., 2017[7]	72	Aspiration	VCZ	None	Partial recovery Refusal of further care
Turki et al., 2017[8]	52	Biopsy	VCZ →L AmpB → VCZ	None	Complete recovery
Hiraga et al., 2018[9]	21	None	VCZ	None	Complete recovery
Bennis et al., 2018[10]	14	None	VCZ, caspofungin → L AmpB, caspofungin	None	Complete recovery
Winterholler et al., 2017[11]	64	None	VCZ	None	Died
Salam et al., 2017[12]	47	None	L AmpB	None	Died
Lee et al., 2017[13]	59	Aspiration	VCZ	None	Complete recovery
Liapiset al., 2009[14]	54	None	VCZ, L AmpB	None	Died—other cause
Matas et al., 2015[15]	79	Partial resection	VCZ, caspofungin	None	Died
Roilides et al., 2003[16]	18 months	None	L AmpB	None	Died
Norlinah et al., 2007[17]	45	None	AmpB	None	Died
Imai et al.,1999[18]	47	Partial resection	FLCZ →ITZ	None	Complete recovery
Iemmolo et al., 1998[19]	52	Complete resection	ITZ → AmpB → L AmpB	None	Complete recovery
Florescu et al., 2009[20]	42	Aspiration	VCZ, caspofungin, L AmpB	None	Died
Sutton et al., 2009[21]	18	None	ABLC, VCZ, posaconazole	None	Refusal of further care → died
Ehrmann et al., 2005[22]	49	None	VCZ, L AmpB	None	Complete recovery
	54	None	VCZ, L AmpB, caspofungin	None	Complete recovery
Elgamal et al., 2000[23]	24	Complete resection	AmpB → ITZ → L AmpB	AmpB	Complete recovery
Camarata et al., 1992[24]	20	Aspiration, complete resection	AmpB, 5FC	AmpB	Complete recovery
Green et al., 1991[25]	3 months	Aspiration	AmpB, 5FC	AmpB	Complete recovery
Tsai et al., 2006[26]	48	Aspiration	ITZ, AmpB	None	Died—other cause
Gubler et al., 2007[27]	43	Partial resection	Caspofungin, VCZ	None	Complete recovery
Azarpira et al., 2008[28]	49	Unspecified resection	AmpB	None	Died

VCZ, voriconazole; L AmpB, liposomal amphotericin B; AmpB, amphotericin B; ABLC, amphotericin B lipid complex; ITZ, itraconazole; 5FC, flucytosine; FLCZ, fluconazole.
*Age is given in years unless specified otherwise.

Continues

Supplementary Table 1. Continued

Reference	Age*	Surgical Intervention	Antifungal	Intrathecal Antifungal	Outcome
Robinson et al., 2000[29]	13	Unspecified resection	ITZ → L AmpB → ITZ → VCZ	None	Died
	12	None	AmpB → ITZ	None	Died
	11	Unspecified resection	L AmpB →micafungin	None	Died
Schwartz et al., 1997[30]	18	Biopsy	AmpB → L AmpB → ITZ → VCZ	AmpB	Died—other cause
Machetti et al., 2000[31]	16	None	AmpB → VCZ	None	Died—other cause
Mollahoseini et al., 2011[32]	29	Biopsy	AmpB, ITZ	None	Complete recovery
Pagliano et al., 2004[33]	23	None	L AmpB, 5FC → ITZ	None	Complete recovery
Keven et al., 2008[34]	46	None	AmpB → L AmpB	None	Died
Antony et al., 2003[35]	7	Complete resection	AmpB → L AmpB → ITZ	None	Complete recovery
Narayan et al., 2009[36]	30's	Biopsy, partial resection	L AmpB → VCZ	None	Died
Khan et al., 2007[37]	62	Biopsy	L AmpB, caspofungin	None	Died
Thakar et al., 2012[38]	10 months	Partial resection	None	None	Complete recovery
Damaj et al., 2004[39]	57	None	AmpB, caspofungin → VCZ, caspofungin	None	Complete recovery
Pieroth et al., 2004[40]	79	Biopsy	L AmpB	None	Died—Other cause
de Lastours et al., 2003[41]	48	Biopsy	AmpB, ITZ → VCZ	None	Complete recovery
	48	Biopsy	AmpB → VCZ	None	Complete recovery
Zwitserloot et al., 2008[42]	16	None	VCZ, caspofungin	None	Partial recovery
Ho et al., 2007[43]	69	None	Caspofungin, VCZ	None	Died
Cocchi et al., 2005[44]	50	None	ABLC, VCZ	None	Complete recovery
Pavlina et al., 2018[45]	70	Biopsy	VCZ, micafungin	None	Died—other causes
van Hal et al., 2005[46]	40	Biopsy	VCZ → caspofungin, L AmpB	None	Died
Figueiredo et al., 2003[47]	42	Partial resection	AmpB	None	Unspecified recovery
Cuccia et al., 2000[48]	14	Unspecified resection	L AmpB, 5FC	None	Complete recovery
	12	Unspecified resection	AmpB, 5FC	None	Died
	5	Partial resection	L AmpB	None	Partial recovery
Neil et al., 2016[49]	69	Complete resection	ABLC → VCZ	None	Complete recovery
Buchheidt et al., 2004[50]	25	None	FLCZ → AmpB → L AmpB, 5FC	AmpB	Died
Middelhof et al., 2005[51]	6	Complete resection	L AmpB, micafungin → VCZ	None	Complete recovery
	6	Complete resection	FLCZ → L AmpB → VCZ	None	Complete recovery
	16	Partial resection	VCZ	None	Complete recovery
	7	Complete resection	VCZ	None	Complete recovery
Merseburger et al., 2004[52]	63	Complete resection	None	None	Complete recovery
Choi et al., 2002[53]	59	Unspecified resection	AmpB → ITZ	None	Partial recovery
Kohler et al., 2009[54]	34	Unspecified resection	L AmpB, caspofungin→ VCZ, caspofungin → L AmpB, 5FC	None	Complete recovery
Guermazi et al., 2002[55]	30	None	AmpB, 5FC	None	Died
Fuchs et al., 2006[56]	Pre-mature newborn (28+3/7 weeks)	Biopsy	AmpB → L AmpB	None	Died
Galassi et al., 1978[57]	59	Complete resection	AmpB	None	Died

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Supplementary Table 1. Continued

Reference	Age*	Surgical Intervention	Antifungal	Intrathecal Antifungal	Outcome
Baslar et al., 1998[58]	18	Aspiration	Fluconazole → L AmpB, ITZ	None	Complete recovery
Garcia et al., 2006[59]	45	None	VCZ	None	Partial recovery
Rodriguez et al. 1999[60]	16	Unspecified resection	AmpB, ITZ → L AmpB → ITZ → L AmpB	None	Complete recovery
Elter et al., 2006[61]	29	Aspiration	L AmpB → VCZ, caspofungin	None	Complete recovery
Verma et al., 2013[62]	45	Unspecified resection	VCZ	None	Died
Hidron et al., 2009[63]	28	Biopsy, aspiration	AmpB, VCZ	None	Partial recovery
Bodey et al., 1993[64]	52	Biopsy, unspecified resection	AmpB	None	Partial recovery
Takeda et al., 2007[65]	53	None	Micafungin, AmpB, ITZ → VCZ	None	Unspecified recovery
Sood et al., 2007[66]	43	Complete resection	VCZ	None	Partial recovery
Partridge et al., 1981[67]	18	Unspecified resection	AmpB	AmpB	Died
Traboulsi et al., 2007[68]	26	Complete resection, biopsy	AmpB → ITZ → VCZ	None	Died—combination with pneumonia
Moling et al., 2002[69]	48	Biopsy	AmpB VCZ → ITZ	None	Complete recovery
	24	None	FLCZ → L AmpB → ITZ	L AmpB	Unspecified recovery
Marinovic et al., 2007[70]	65	Aspiration, unspecified resection	AmpB → L AmpB → AmpB → ITZ	None	Unspecified recovery
Parker et al., 1996[71]	87	Unspecified resection	AmpB	None	Complete recovery
Correa et al.,1975[72]	49	Complete resection	None	None	Died
Dhir et al., 1978[73]	17	Biopsy, partial resection	AmpB	AmpB	Died
Chen et al., 2011[74]	46	Partial resection	VCZ	None	Partial recovery
Wandroo et al., 2006[75]	34	None	AmpB → L AmpB, VCZ	None	Complete recovery
Patiroglu et al., 2012[76]	4	Biopsy	L AmpB, VCZ	None	Partial recovery
Pradhan et al. 2007[77]	43	None	AmpB → L AmpB, ITZ	None	Partial recovery
Roxo et al., 2010[78]	6	None	AmpB → ITZ	None	Partial recovery
Lacerda et al., 2005[79]	52	Unspecified resection	FLCZ → L AmpB	None	Died
Kaffarnik et al., 2008[80]	48	Aspiration	Fluconazole → VCZ, L AmpB	None	Partial recovery
Kulkarni et al., 2007[81]	23	Biopsy, complete resection	Amp B, ITZ	None	Unspecified recovery
Kedziora et al., 2008[82]	43	None	VCZ	None	Died
Crivelli et al., 1970[83]	61	Complete resection	AmpB	None	Complete recovery
Lewis et al., 1999[84]	41	None	AmpB → ITZ	None	Partial recovery
Rodrigo et al., 2007[85]	27	None	FLCZ	None	Died
	22	None	AmpB	None	Died
	26	None	AmpB, VCZ	AmpB	Partial recovery
	34	None	ITZ, AmpB	VCZ	Unspecified recovery

VCZ, voriconazole; L AmpB, liposomal amphotericin B; AmpB, amphotericin B; ABLC, amphotericin B lipid complex; ITZ, itraconazole; 5FC, flucytosine; FLCZ, fluconazole.
*Age is given in years unless specified otherwise.

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Supplementary Table 1. Continued

Reference	Age*	Surgical Intervention	Antifungal	Intrathecal Antifungal	Outcome
Giacchino et al., 2006[86]	14	Aspiration, complete resection	L AmpB, ITZ	None	Complete recovery
	2	Unspecified resection	L AmpB → ITZ	None	Complete recovery
	9	Unspecified resection	L AmpB, 5FC → ITZ, AmpB	None	Complete recovery
	8	Aspiration	L AmpB, caspofungin, VCZ → ITZ	None	Complete recovery
Ng et al., 2000[87]	2	Biopsy	L AmpB, FLCZ → L AmpB, 5FC	None	Complete recovery
Watanabe et al., 2009[88]	9	Unspecified resection	AmpB → ITZ → AmpB, micafungin → VCZ	None	Complete recovery
Colombo et al., 2003[89]	66	Unspecified resection	AmpB → caspofungin → ITZ	None	Complete recovery
Kolbe et al., 2007[90]	51	None	Caspofungin, VCZ	None	Unspecified recovery
Ho et al., 2004[91]	48	None	AmpB, 5FC	None	Died
Li et al., 2014[92]	63	None	VCZ	None	Partial recovery
Fantini et al., 2003[93]	23	None	FLCZ → AmpB	None	Died—combination
Muda et al., 2008[94]	10	None	AmpB → L AmpB, caspofungin	None	Died
Martins et al., 2010[95]	56	None	L AmpB → caspofungin	None	Died
Yoon et al., 2007[96]	59	None	AmpB → VCZ, ITZ	None	Complete recovery
	71	Biopsy	AmpB → VCZ → ITZ	None	Partial recovery
	72	Biopsy	AmpB → VCZ	None	Died—other cause
Sterba et al., 2005[97]	16	Biopsy, resection	AmpB → amphotericin B colloidal dispersion, VCZ	AmpB	Unspecified recovery
Choudhury et al., 2014[98]	50	Biopsy	VCZ, AmpB	None	Unspecified recovery
Notani et al., 2000[99]	56	Complete resection	FLCZ	None	Died
Fernandes et al., 2001[100]	73	Aspiration, complete resection	AmpB	None	Died
Martinez et al., 2009[101]	32	None	AmpB → VCZ → ITZ	None	Partial recovery
Soeffker et al., 2013[102]	51	None	VCZ	None	Complete recovery
Sato et al., 2008[103]	18	None	Micafungin, AmpB, 5FC	None	Died
Sameshima et al., 1998[104]	73	Biopsy	FLCZ	None	Died
Bethell et al., 2004[105]	2	None	L AmpB, 5FC → L AmpB, VCZ	None	Partial recovery
Renard et al., 1998[106]	42	Biopsy	ITZ	None	Complete recovery
Karim et al., 1997[107]	22	Unspecified resection	AmpB, ITZ	None	Died
Tsitsopoulos et al., 2010[108]	59	Complete resection	VCZ	None	Complete recovery
Castro et al., 2009[109]	33	None	AmpB	None	Died
Sadarangani et al., 2015[110]	3	Biopsy	VCZ, L AmpB → VCZ, caspofungin	None	Partial recovery
Ramos-Gabatin et al., 1981[111]	54	Unspecified resection	AmpB, 5FC	None	Complete recovery
Brenet et al., 2016[112]	75	Unspecified resection	VCZ	None	Complete recovery
Balasubramaniam et al., 2007[113]	69	Unspecified resection	ITZ, L AmpB → VCZ, L AmpB	None	Partial recovery
Ahsan et al., 2009[114]	28	None	AmpB, ITZ	None	Died
Aslam et al., 2006[115]	57	Unspecified resection	AmpB → ITZ	None	Complete recovery
	38	Unspecified resection	ITZ	None	Partial recovery

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Supplementary Table 1. Continued

Reference	Age*	Surgical Intervention	Antifungal	Intrathecal Antifungal	Outcome
Letscher et al., 1997[116]	20	Aspiration, unspecified resection	L AmpB → ITZ	AmpB	Complete recovery
Vidal et al., 2005[117]	26	Aspiration	FLCZ → AmpB → ITZ	AmpB	Died—other cause
Hiraga et al., 2009[118]	74	None	AmpB → FLCZ → VCZ	None	Partial recovery
Ellis et al., 2002[119]	25	None	L AmpB, 5FC → ITZ	None	Partial recovery
Tattevin et al., 2004[120]	61	None	AmpB, 5FC	None	Died
	67	Biopsy	AmpB	None	Died
	43	Biopsy	AmpB	None	Died
	67	None	AmpB→ L AmpB → ITZ	None	Complete recovery
	49	Aspiration	AmpB → ITZ	None	Died
	49	None	AmpB → L AmpB → ITZ, VCZ	None	Complete recovery
	53	None	AmpB→ L AmpB → VCZ	None	Complete recovery
van de Beek et al., 2008[121]	56	None	FLCZ → VCZ	None	Died
Alsultan et al., 2006[122]	8	Aspiration	AmpB → L AmpB → VCZ	None	Complete recovery
Toksvang et al., 2014[123]	25	None	AmpB → VCZ, caspofungin	None	Died
Mahlknecht et al., 1997[124]	62	Biopsy	AmpB → L AmpB → ITZ → AmpB	None	Partial recovery
Athanassiadou et al., 2006[125]	2	None	L AmpB, VCZ	None	Complete recovery
Vianna et al., 2007[126]	41	None	Caspofungin, VCZ, AmpB → caspofungin, VCZ, L AmpB	None	Complete recovery
Buxhofer et al., 2001[127]	67	Unspecified resection	L AmpB	AmpB	Complete recovery
Satoh et al., 1995[128]	79	Biopsy	FLCZ	None	Died
Marbello et al., 2003[129]	53	None	AmpB → VCZ	None	Partial recovery
Stiefel et al., 2003[130]	11	Partial resection	AmpB → VCZ	None	Partial recovery
Nabika et al., 2007[131]	21	Partial resection	Amp B, FLCZ → ITZ	AmpB	Complete recovery
Curone et al., 2009[132]	44	Aspiration	AmpB	None	Died
Srikumar et al., 2017[133]	67	Aspiration	VCZ	None	Partial recovery
Papadopoulos et al., 2008[134]	24	None	L AmpB, ITZ	None	Died
Bhatt et al., 2013[135]	72	Aspiration	L AmpB, VCZ	None	Partial recovery
Chowdhury et al., 2014[136]	19	Partial resection	ITZ	None	Complete recovery
Lee et al., 2012[137]	73	Biopsy	AmpB, VCZ	None	Died
Lee et al., 2013[138]	48	Biopsy	AmpB → L AmpB → VCZ	None	Partial recovery
Kim et al., 2013[139]	24	Aspiration	AmpB → VCZ → L AmpB → VCZ	None	Partial recovery
Choi et al., 2012[140]	72	None	Amp B → VCZ	None	Died
Vanfleteren et al., 2018[141]	65	Biopsy	VCZ	None	Partial recovery
Prakash et al., 2012[142]	14	None	AmpB	None	Died
Neyaz et al., 2018[143]	22	Complete resection	AmpB → VCZ	None	Partial recovery
Tang et al., 2016[144]	47	None	AmpB	None	Died
Sathyapalan et al., 2016[145]	35	None	VCZ → L AmpB	None	Partial recovery
Meidani et al., 2016[146]	53	None	VCZ	None	Complete recovery

VCZ, voriconazole; L AmpB, liposomal amphotericin B; AmpB, amphotericin B; ABLC, amphotericin B lipid complex; ITZ, itraconazole; 5FC, flucytosine; FLCZ, fluconazole.
*Age is given in years unless specified otherwise.

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Supplementary Table 1. Continued

Reference	Age*	Surgical Intervention	Antifungal	Intrathecal Antifungal	Outcome
Faisal et al., 2018[147]	76	Biopsy	VCZ, micafungin	None	Complete recovery
Popalzai et al., 2009[148]	79	None	L AmpB → VCZ	None	Died
Lou et al., 2015[149]	43	Unspecified resection	VCZ	None	Partial recovery
Munta et al., 2015[150]	28	None	VCZ, caspofungin	None	Died
Van Sanford et al., 2018[151]	55	None	AmpB → VCZ	None	Died
Estrada et al., 2012[152]	54	Biopsy	Caspofungin → VCZ, micafungin	None	Complete recovery
Matis et al., 2013[153]	32	Biopsy	AmpB	None	Died
Lujber et al., 2003[154]	25	None	L AmpB, 5FC → ITZ	None	Complete recovery
Nowak et al., 2018[155]	64	Unspecified resection	VCZ	None	Partial recovery
Siddiqui et al., 2008[156]	27	Unspecified resection	AmpB	None	Died
Kasper et al., 2011[157]	71	Biopsy, complete resection	L AmpB, VCZ → caspofungin, VCZ	None	Complete recovery
de Martin Truzzi et al., 2017[158]	65	Aspiration	L AmpB → VCZ	None	Died
Gonzales Zamora et al., 2018[159]	71	Complete resection	L AmpB, VCZ	None	Partial recovery
Hadley et al., 2017[160]	19	Biopsy	VCZ	None	Partial recovery
Al-Maskari et al., 2016[161]	12	Unspecified resection	L AmpB → VCZ	None	Complete recovery
Waqas et al., 2016[162]	4	Unspecified resection	VCZ	None	Complete recovery
Barrera-Herrera et al., 2015[163]	18	Biopsy	Posconazole, caspofungin, AmpB	None	Died
Patel et al., 2017[164]	14	None	L AmpB → VCZ	None	Partial recovery
Ahmadzai et al., 2013[165]	90	Complete resection	AmpB → VCZ	None	Complete recovery
Simmonds et al., 2017[166]	68	Biopsy	VCZ → posconazole	None	Partial recovery
Rieber et al., 2016[167]	18	Biopsy, unspecified resection	AmpB	None	Unspecified recovery
Ali et al., 2016[168]	24	Partial resection	VCZ	None	Complete recovery
Tan et al., 2017[169]	5	Aspiration, unspecified resection	VCZ, L AmpB	None	Partial recovery
Kagawa et al., 2008[170]	33	Biopsy	AmpB → FLCZ	AmpB	Unspecified recovery
Bourne et al., 2016[171]	57	Partial resection	VCZ → posaconazole → AmpB	None	Died
Muraoka et al., 2016[172]	56	Partial resection	VCZ	None	Partial recovery
Wang et al., 2017[173]	48	Biopsy	VCZ	None	Unspecified recovery
	64	Unspecified surgery	FLCZ → ITZ	None	Died
	58	Biopsy	VCZ	None	Died
	46	Biopsy, unspecified surgery	VCZ, FLCZ	None	Unspecified recovery
	46	Biopsy, unspecified surgery	VCZ	None	Unspecified recovery
	37	None	FLCZ → VCZ, ITZ	None	Died
	48	None	FLCZ	None	Died
Foley et al., 2016[174]	9	Biopsy	L AmpB	None	Died
Kim et al., 2017[175]	55	Biopsy	VCZ	None	Complete recovery

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Supplementary Table 1. Continued

Reference	Age*	Surgical Intervention	Antifungal	Intrathecal Antifungal	Outcome
Tripathy et al., 2015[176]	5 months	Biopsy	VCZ	None	Complete recovery
Liu et al., 2015[177]	64	Unspecified resection	VCZ	None	Died
Palmisani et al., 2017[178]	6 months	None	Caspofungin, VCZ	None	Complete recovery
Conant et al., 2015[179]	65	Biopsy, aspiration	L AmpB → VCZ → posaconazole	None	Partial recovery
Ouyang et al., 2015[180]	55	Unspecified resection	VCZ	None	Partial recovery
Patel et al., 2015[181]	53	Biopsy	L AmpB → VCZ, micafungin	None	Partial recovery
Peng et al., 2015[182]	53	None	ITZ, caspofungin	None	Partial recovery
Segundo et al., 2014[183]	55	Biopsy	L AmpB → FLCZ	L AmpB	Partial recovery
Ellenbogen et al., 2014[184]	67	Biopsy, complete resection	VCZ → posaconazole	None	Complete recovery
Bao et al., 2014[185]	42	Unspecified resection	FLCZ → VCZ → ITZ	None	Partial recovery
Vijayvargiya et al., 2013[186]	68	Unspecified resection	VCZ	None	Died
Bokhari et al., 2014[187]	13	Complete resection	L AmpB → ITZ → VCZ	None	Died
	16	Biopsy, complete resection	L AmpB → VCZ	None	Complete recovery
	25	Partial resection	L AmpB → VCZ	None	Complete recovery
	26	Complete resection	L AmpB → VCZ	None	Complete recovery
	36	Complete resection	VCZ	None	Complete recovery
Leyngold et al., 2014[188]	61	Biopsy, partial resection	L AmpB → VCZ, micafungin	None	Partial recovery
Liu et al., 2013[189]	40	Unspecified resection	VCZ	None	Complete recovery
Kourkoumpetis et al., 2012[190]	52	None	AmpB	None	Died
	60	Aspiration	AmpB, 5FC	None	Unspecified recovery
	56	None	FLCZ → AmpB	None	Died
	71	None	None	None	Died
	52	Aspiration	ITZ → VCZ → caspofungin, AmpB	None	Unspecified recovery
	69	Aspiration	AmpB	None	Died
	58	None	FLCZ → micafungin → VCZ	None	Died
	48	Unspecified resection	AmpB → VCZ → caspofungin	None	Unspecified recovery
	58	None	AmpB → caspofungin, VCZ	None	Died
	61	Unspecified resection	AmpB, VCZ, micafungin	None	Died
	52	None	None	None	Died
	31	Aspiration	VCZ → AmpB → VCZ → micafungin	None	Unspecified recovery
	68	Unspecified resection	AmpB, VCZ	None	Unspecified recovery
	48	Unspecified resection	AmpB	None	Unspecified recovery
Kruetzelmann et al., 2013[191]	31	None	VCZ → ITZ	None	Complete recovery
Cherian et al., 2012[192]	33	None	VCZ, AmpB	None	Unspecified recovery
Neofytos et al., 2012[193]	17	Biopsy	VCZ, micafungin	None	Died
Koshy et al., 2011[194]	71	Biopsy, unspecified resection	VCZ	None	Complete recovery

VCZ, voriconazole; L AmpB, liposomal amphotericin B; AmpB, amphotericin B; ABLC, amphotericin B lipid complex; ITZ, itraconazole; 5FC, flucytosine; FLCZ, fluconazole.
*Age is given in years unless specified otherwise.

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Supplementary Table 1. Continued

Reference	Age*	Surgical Intervention	Antifungal	Intrathecal Antifungal	Outcome
Köse et al., 2011[195]	23	Biopsy, unspecified resection	VCZ	None	Complete recovery
Mardari et al., 2011[196]	65	Partial resection	ITZ → caspofungin	None	Partial recovery
Yan et al., 2011[197]	56	Unspecified resection	VCZ → caspofungin → VCZ, L AmpB	None	Died
Zhang et al., 2010[198]	54	None	VCZ → caspofungin, AmpB	None	Died

VCZ, voriconazole; L AmpB, liposomal amphotericin B; AmpB, amphotericin B; ABLC, amphotericin B lipid complex; ITZ, itraconazole; 5FC, flucytosine; FLCZ, fluconazole.
*Age is given in years unless specified otherwise.

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