Impact of azole antifungal treatment on outcome in acute invasive fungal rhinosinusitis with orbitocranial involvement: a surgical perspective*

Idit Tessler[1,2,#], Rachel Shemesh[2,3,#], Gilad Sherman[4], Ethan Soudry[2,5], Sharon C-A. Chen[6,7], Oren Ziv[8,9], Sofia Kordeluk[8,9], Dvir Bar-On[2,5], Ilya Novikov[10], Arkadi Yakirevitch[1,2]

[1] Department of Otolaryngology-Head and Neck Surgery, Sheba Medical Center, Tel Hashomer, Israel

[2] Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3] Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Israel

[4] Pediatric Infectious Diseases Unit, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Israel

[5] Department of Otolaryngology-Head and Neck Surgery, Rabin Medical Center, Israel

[6] Centre for Infectious Diseases and Microbiology Laboratory Services, Institute of Clinical Pathology and Medical Research, New South Wales Health Pathology, Westmead Hospital, Westmead, Australia

[7] Sydney Medical School, The University of Sydney, Australia

[8] Department of Otolaryngology-Head and Neck Surgery, Soroka Medical Center, Israel

[9] Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

[10] Biostatistics and Biomathematics unit, Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Israel

Rhinology 61: 6, 561 - 567, 2023
https://doi.org/10.4193/Rhin23.082

***Received for publication:**
February 24, 2023
Accepted: August 6, 2023

# Equal contribution

Abstract

Purpose: To provide real-life data on azole treatment outcomes and the role of surgery in the current management of invasive fungal rhinosinusitis complicated by orbitocranial fungal infection (OCFI).

Methods: Data was collected retrospectively from a chart review from four participating centers and a systematic literature review. The study group included patients with OCFI treated with azole antifungals. The control cases were treated with other antifungal agents. The cranial and orbital involvement degree was staged based on the imaging. The extent of the surgical resection was also classified to allow for inter-group comparison.

Results: There were 125 patients in the azole-treated group and 153 in the control group. Among the patients with OCFI cranial extension, 23% were operated on in the azole-treated group and 18% in the control group. However, meninges and brain resection were performed only in the controls (11% of patients) and never in the azole antifungals group. Orbital involvement required surgery in 26% of azole-treated cases and 39% of controls. Despite a more aggressive cranial involvement, azole-treated patients' mortality was significantly lower than in controls, with an OCFI-specific mortality rate of 21% vs. 52%. A similar, though not statistically significant, trend was found for the extent of the orbital disease and surgery.

Conclusion: Despite less aggressive surgical intervention for cranial involvement, OCFI patients treated with azoles had a higher survival rate. This finding suggests we may improve morbidity with a more conservative surgical approach in conjunction with azole treatment. The same trend is emerging for orbital involvement.

Key words: azoles, orbit, mycoses, brain, sinusitis

Introduction

Orbitocranial fungal infection (OCFI) is an uncommon yet rapidly progressive complication of invasive fungal rhinosinusitis associated with a high mortality rate [1,2]. Increasing causes for immune suppression, such as chemotherapy-induced neutropenia, acquired immunodeficiency syndrome and diabetes mellitus, have

led to a rising incidence of invasive fungal infections [3–5]. Interestingly, a high rate of OCFI was also recently reported among COVID-19 patients, with an alarming mortality of 33% [6]. This association was explained by the impairment of innate defense mechanisms and the utilization of high-dose corticosteroids [7]. Fungus-derived angioinvasion had justified radical surgery as an integral part of OCFI treatment, despite its significant morbidity and long-term effect on survivors' quality of life [8]. The goals of surgical intervention are debridement of necrotic tissue unreachable for antifungal agents, preventing a rapid spread of infection to critical structures, and gaining time until the reconstitution of the immune state [9]. There is no consensus or guidelines regarding the extent of the surgical procedures for OCFI. Some recommend radical surgery, usually complex at the setup of acute inflammation, that may include brain resection and orbit exenteration [8,10]. Others report performing a more conservative debulking of involved tissues [11].

Over the past two decades, azole antifungal (AAF) agents have been introduced as a therapeutic option for systemic fungal infections [3,12–16]. The azole family agents active against molds include posaconazole, isavuconazole, itraconazole, and voriconazole. All these drugs work by inhibiting the sterol 14α-demethylation enzyme essential to the fungus survival, resulting in faulty cell membrane synthesis [14]. The AAF have shown high efficacy and safety profile, emerging as a first-line treatment for invasive fungal disease [3,12,17]. However, whether incorporating AAF agents improves survival rates is currently unclear [18]. In addition, there is no data regarding the contribution of surgery to azole-treated patients' survival and whether aggressive surgery is still justified. Therefore, in this work, we aimed to provide real-life data on the outcomes of AAF treatment and the role of surgery for OCFI.

Materials and methods

Study design

We performed a large-scale retrospective study. In order to obtain a sufficient cohort of this rare entity, we analyzed cases both from participating tertiary medical centers and those identified by a systematic literature review.

The AAF-treated group comprised invasive fungal rhinosinusitis cases with orbitocranial extension treated at one of four participating centers (Sheba Medical Center, Rabin Medical Center, Soroka Medical Center, Israel, and Westmead Hospital, Sydney, Australia) between January 1, 2009, and January 1, 2020. Additional invasive fungal rhinosinusitis cases with OCFI treated with AAF from the literature were included in this group.

A control group collected from the literature comprised invasive fungal rhinosinusitis patients with OCFI who were treated with antifungal therapy other than AAF for the entire length of treatment.

Patients who received no medical treatment were omitted.

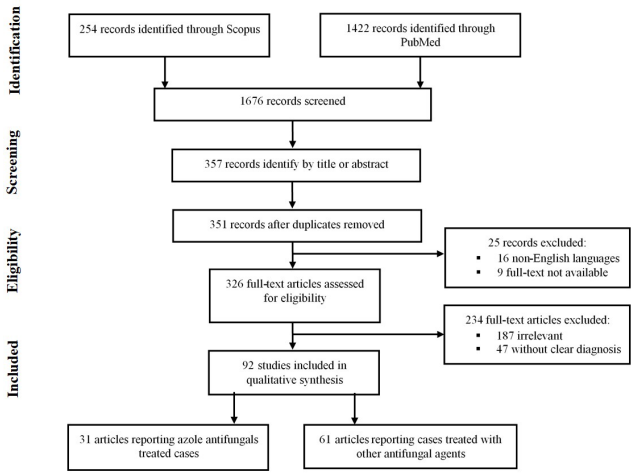


Figure 1. Flowchart for identification, screening, eligibility, and inclusion for the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

The systematic literature review was performed according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines [19]. Using prespecified search terms and phrases, we searched two online databases, PubMed and SCOPUS, between 1990 and 2021. The search algorithm for the AAF-treated cases was: (invasive fungal sinusitis) AND (posaconazole OR isavuconazole OR itraconazole OR voriconazole). The search algorithm for the control group was: (invasive fungal sinusitis) NOT (posaconazole OR isavuconazole OR itraconazole OR voriconazole). Literature cases were eligible for inclusion if they were available as full-text original articles, written in English and published in peer-reviewed journals. Crosschecking of references, citations in review papers, and communication with scientists in this field have been done to provide a comprehensive search. The relevant articles were selected and reviewed by three authors (IT, RS, and AY) in a standardized manner (Figure 1).

All cases were diagnosed according to the criteria for proven invasive fungal sinonasal infection defined by 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) (20). Only those with radiologically verified orbital and cranial involvement were analyzed.

Data collection and extraction

Data extracted from both sources (intuitional cases and literature reports) included demographics, background disease, immune status, fungal pathogen according to culture growth, the extent of orbital and/or cranial involvement, antifungal treatment, surgery extent, length of follow-up, and outcome (OCFI-specific mortality and other-causes mortality). Mortality

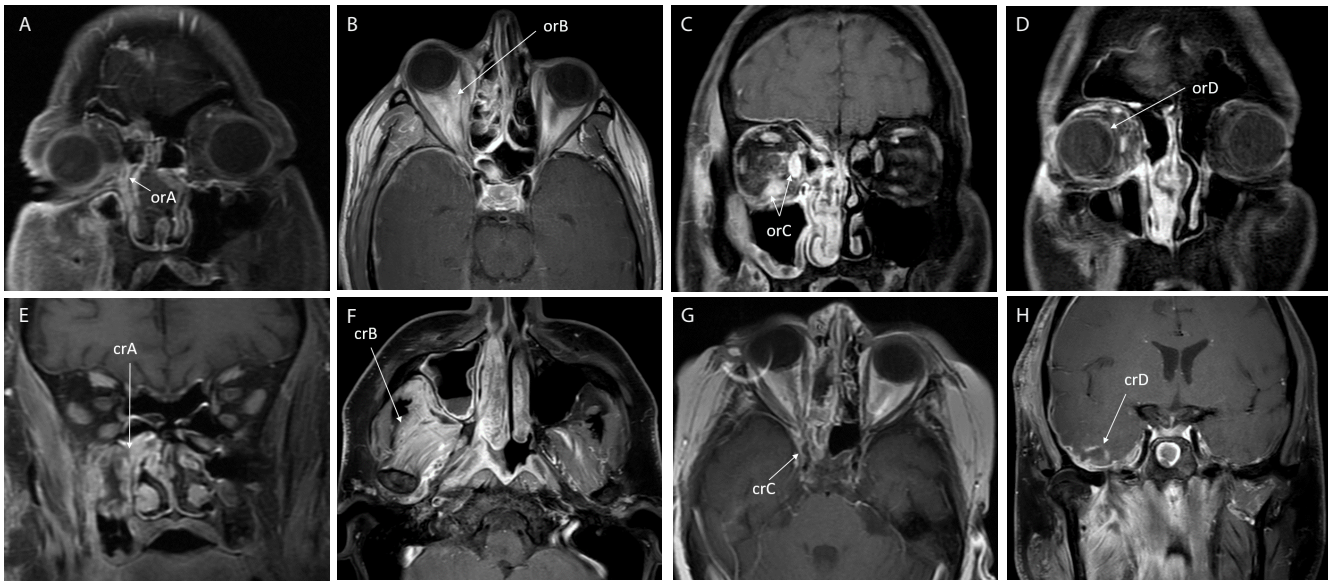


Figure 2. Staging of orbitocranial fungal infection used in the study and T1 contrast-enhanced magnetic resonance images illustrating each stage. A-D: Orbital extent: orA - periorbit, lacrimal apparatus; orB - orbital fat; orC - oculomotor muscles; orD – optic nerve, eyeball. E-H: Cranial extent: crA - pterygopalatine fossa, nasopharynx; crB – temporal/infratemporal fossa; crC – cavernous sinus, dura; crD – brain, spinal cord.

outcomes were measured in up-to three years follow-up period as the OCFI-related effect is not likely to extend beyond this period.

OCFI was graded according to its maximal extent throughout the disease course, as demonstrated by computed tomography and/or magnetic resonance imaging. The orbital extent was graded as A - periorbit, lacrimal apparatus; B - orbital fat; C - oculomotor muscles; D – optic nerve, eyeball. The cranial extent was graded as A - pterygopalatine fossa, nasopharynx; B – temporal/infratemporal fossa; C – cavernous sinus, dura; D – brain, spinal cord. Examples of each grade are presented in Figure 2. The OCFI surgical treatment was also graded according to its maximal extent in each case. This grading is based on the surgery complexity and its potential sequellae and is displayed in Table 2.

Statistical analysis

Variables distributions are presented as mean and SD for continuous variables and as frequencies for categorical ones. The comparison between groups was performed using a t-test with Welch–Satterthwaite correction for unequal variances and Fisher's exact test for cross-tabulation, correspondingly. The monotone relationships between ordered variables were assessed using Kendall tau-B and Kendall rank correlation. We used the propensity score (PS) approach to adjust for the study's observational nature. The PS was defined by logistic regression, including the patient's demographic, immune suppression cause, pathogen, OCFI extent in the orbit and cranium, and the extent of surgery. The PS was used in survival analysis (Cox regression), either including the PS as a covariate (regression adjustment) or through weighted analysis with an inverse probability weight. Only the pathogen was not balanced after PS weighting. Therefore, we performed stratification by the pathogen in the PS analysis when the interaction between the effects of PS and the pathogen was significant. The primary outcome variable was time to death from OCFI in three years. We performed a survival analysis for death from any cause, death from OCFI, and death from other causes. We calculated the cause-specific hazard for OCFI death and death of other causes using Cox regression and the sub-distribution hazard using the Fine-Gray approach. Applying various models is a form of sensitivity analysis, permitting evaluation of the model's influence on the final estimate. All p-values are two-sided. The analysis was done using STATA 16 SE software.

Results

Study cohorts

Overall, our study included 278 OCFI cases. The AAF-treated group comprised 125 patients. Forty-six of them were from the participating centers. The rest of the AAF cases were identified through the systematic literature review. Patients infected with *Aspergillus* species were treated with voriconazole. Most patients with *Mucorales* infection received posaconazole, while few more recent cases received isavuconazole. The control group comprised 153 patients from the literature review. They were all treated with amphotericin B, combined with anidulafungin in three and caspofungin in one case.

A comparison of the study groups' characteristics is presented in Table 1. The AAF and the control group's mean age was 49±21 and 44±19, respectively (mean±SD, p-value=0.13), with male predominance in both groups (60.8% and 58.2%, respectively,

Table 1. Univariate analysis of the study groups' main characteristics.

		Azole antifungal treated group (n=125)	Control group (n=153)	p-value
Demographics	Age	49±21.9	44.4±19.8	0.13
	Males	76 (60.8)	89 (58.2)	0.37
Medical background	Diabetes mellitus	39 (31.2)	64 (41.8)	0.04
	AIDS [a]	4 (3.2)	17 (11.1)	0.01
	Hematologic disease [b]	31 (24.8)	30 (19.6)	0.18
	Chronic renal failure	7 (5.6)	11 (7.2)	0.53
Pathogen	*Mucorales*	35 (28)	102 (66.7)	<0.001
	Aspergillus	90 (72)	51 (33.3)	
Number of surgeries, mean		1.57±1.63	1.65±1.63	0.68

*Categorical variables are presented in n (%); **Continuous variables are represented as mean (±SD); [a]Acquired immunodeficiency syndrome; [b]Hematologic disease leading to immune compromised status; *Including 6 patients with both *Mucorales* and *Aspergillus*.

Table 2. Surgery for rhino-orbital-cerebral mycosis patients.

Orbital surgery			
Surgery extent	**Azole antifungal treated group (n=54)**	**Control group (n=88)**	**p-value**
No orbital surgery in the presence of orbital involvement	40 (74.1%)	54 (61.4%)	
Periorbit removal	1 (1.8%)	1 (1.1%)	
Partial resection of the orbital content	3 (5.7%)	14 (15.9%)	NS
Enucleation	1 (1.8%)	1 (1.1%)	
Orbital exenteration	9 (16.7)	18 (20.5%)	
Cranial surgery			
Surgery extent	**Azole antifungal treated group (n=71)**	**Control group (n=76)**	
No cranial surgery in the presence of cranial involvement	55 (77.4%)	62 (81.6%)	
Extracranial debridement	8 (11.3%)	3 (3.9%)	
Skull base resection	8 (11.3%)	3 (3.9%)	<0.01
Meninges resection	0 (0.0%)	3 (3.9%)	
Brain resection	0 (0.0%)	6 (7.9%)	

p-value=0.37). Diabetes was a significantly more frequent cause of immune deficiency in the control group, and hematological background was more common among the AAF-treated group. Throughout the study period, AAF-treated cases were reported more frequently.

The two main pathogen groups were the *Mucorales*, identified in 28% and 67% of the AAF cases and the controls, respectively, and *Aspergillus* species in 72% and 33%, respectively (p-value<0.001). Six patients with mucormycosis (three in the AAF group and three control cases) also had evidence of *Aspergillus*. Mean follow-up time was similar in both groups (12.9±20.9 months in the AAF group and 12.7±13.7 months in the controls (mean±SD, p-value=0.927). Mucormycosis and Aspergillosis cases were evenly reported throughout the study period.

OCFI extent

The orbital involvement was similar between the groups (p-value=0.09), while the cranial involvement was more aggressive in the AAF group (p-value<0.001, Figure 3).

Surgical intervention

Approximately 1.6 surgeries were performed per case, without significant differences between the study groups (Table 1).

The types of surgical procedures performed in each group are presented in Table 2. Among the patients with OCFI cranial extension, 22.5% were operated on in the AAF-treated group and 18.4% in the control group. However, meninges and brain resection were performed only in the controls (10.5% of patients) and never in the AAF group (p-value=0.045). Orbital involvement required surgery in 26% of AAF-treated cases and 39% of control ones (p-value=0.12).

Outcome

A strong interaction was found between the pathogen (*Mucorales* and *Aspergillus* species) and the treatment type for overall 3-years survival (p-value=0.017). Hence, we analyzed the survival stratified to the pathogen. We found that azole treatment improved survival in the *Aspergillus* cases: hazard ratio (HR)=0.23 (0.08-0.61), p-value=0.004. No significant difference was found between AAF-treated patients and the controls in the mucormy-

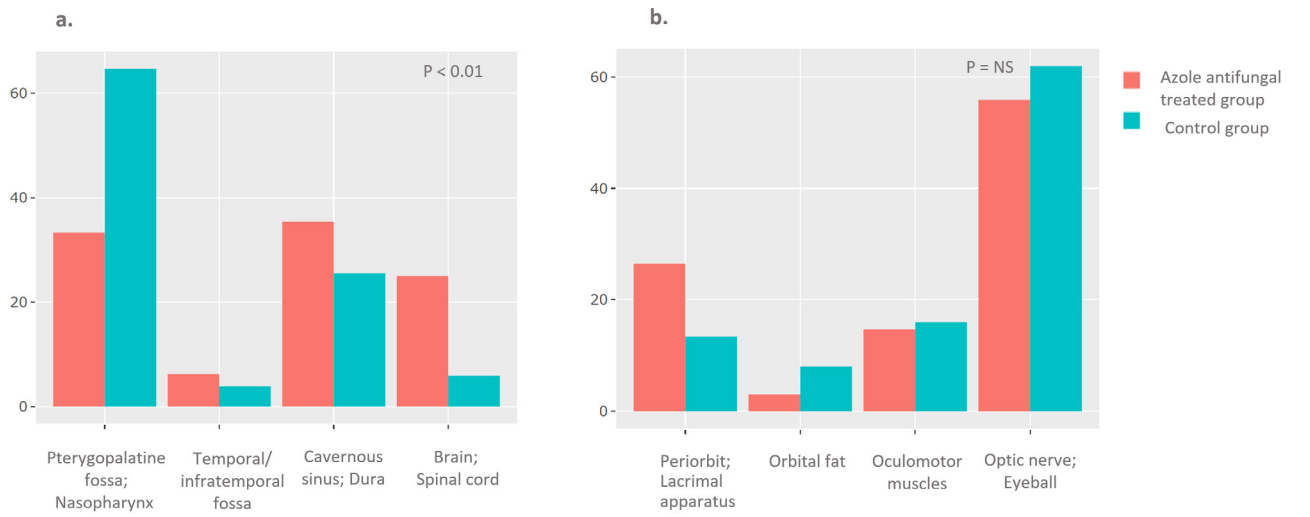


Figure 3. Comparison of the study groups according to the orbitocranial fungal infection extent: a. cranial extent; b. orbital extent.

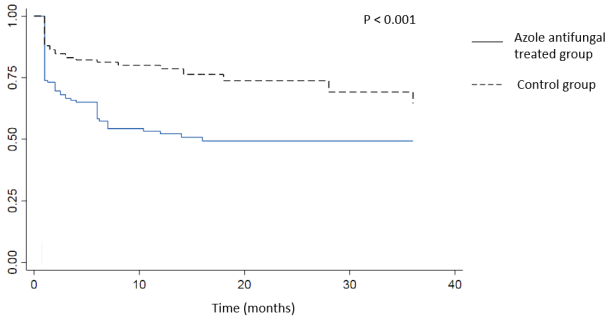


Figure 4. Kaplan-Meier curve on the orbitocranial fungal infection-specific survival during up to 3 years of follow-up.

cosis cases: HR=0.94 (0.46-1.89), p-value=0.86.

When OCFI-specific survival was analyzed with death from other causes as a competing effect, there was no significant interaction between the pathogen and the treatment type (p-value=0.3). Taking this into account, we found that the AAF-treated group had a significantly lower 3-year OCFI-specific mortality compared to controls (21% vs. 52%, respectively) with a subdistribution HR of 0.27 (0.12-0.60, p< 0.001, Figure 4).

Surgical treatment impact

The extent of the surgical intervention for OCFI cranial and orbital involvement did not correlate with the survival rate of the AAF-treated patients (Kendall's tau-b of 0.14 and 0.08, respectively). Due to the small cohort size, this correlation could not be corrected according to the pathogen type.

Discussion

Antifungal therapy, surgical debridement and reversal of immune suppression are the main tools in the treatment armamentarium for potentially lethal invasive fungal rhinosinusitis [18,21]. Over the last two decades, AAF agents were incorporated to treat invasive fungal sinusitis, initially as step-down therapy following amphotericin B and salvage therapy [15,22], demonstrating promising results in clinical studies [14]. Due to their efficacy and high safety profile [23,24], they are now being used early in the course of treatment, with initial reports suggesting isavuconazole to be a valuable option for central nervous system fungal infection [25]. They are well-tolerated with minor side effects, which is an appealing advantage when considering an alternative to amphotericin B formulations. The study aimed to evaluate the role of surgery in managing OCFI treated with AAF agents.

We demonstrated the AAF's powerful protective effect on OCFI-specific mortality, which decreased from 52% to 21%. This effect was robust and remained strongly significant after applying the PS model to control for potential confounding variables. The significantly improved survival rates raise a question regarding the current role of radical surgery. Aggressive intervention, sometimes leading to substantial visual impairment, facial disfiguration, and other mutilation was previously justified to achieve local control and save the patient's life [9,26,27]. Prior studies have demonstrated that surgical intervention was associated with lower mortality rates. However, most of them did not address the extent of surgery [18]; those that referred to the extent of the surgery were not performed on azole-treated cohorts (8,28).

To date, there are no clear guidelines or recommended approaches regarding OCFI surgical treatment. It may be due to the low incidence of this disease [8,29] as well as the high variability of the presentation. Our results demonstrate that a more conservative surgical intervention (Table 2) along with AAF therapy resulted in a higher survival rate, even though the cranial involvement was more extensive (Figure 3). The same trend, though not statistically significant, emerges for the orbital involvement. These data highlight the possibility of shifting trends in the aim of the

surgery for OCFI, from complete local control to debulking with organ preservation. Recent advances in endoscopic approach may facilitate a relatively large resection, yet with reduced morbidity [8,11]. The mean number of surgical procedures was similar in the study groups. Due to the study's retrospective nature, it was impossible to analyze in every case whether the surgery was withheld either because of clinical and/or radiological improvement or because of local or general disease progression making the surgery irrelevant. We presume that better survival in the azole-treated group combined with worse cranial and similar orbital disease extension in this group shows that the former option is the predominant one in the AAF-treated cases.
As established in previous reports, the two most common pathogens in our cohort were the *Mucorales* (predominant in the control group) and *Aspergillus* species (more frequent in the azole-treated cases) (Table 1) [18,30]. The reasonable explanation for this uneven distribution is that amphotericin B remains the drug of choice for mucormycosis according to most guidelines, including EORTC/MSG ones [31]. Nevertheless, AAF use increased chronologically both in aspergillosis and mucormycosis (Suppl. 1 and 2).
We have demonstrated better survival in AAF-treated aspergillosis. In cases of mucormycosis, disease-specific survival in AAF-treated and control groups was similar, even though all control group patients received amphotericin B. This finding is important in light of the better safety profile of azole therapy compared to amphotericin B.
Our study has the inherent limitation of retrospectively analyzed data. Over the years, the use of azoles for OCFI has increased, and early diagnosis crucial for an optimal outcome has been improved. It creates a potential bias. Nevertheless, even in the presence of such development in OCFI treatment, the clinical implications suggested by our findings are still valid in the current approach to OCFI. Other causes of death, including the baseline immune suppressive disease, did not differ between groups, implying that there is no significant difference due to the patients' medical background. Our study design did not include a comprehensive assessment of individual complications but rather addressed the significance of the disease extent. The data sources, including the literature, varied in their reporting of complications, leading to inconsistencies and potential bias for complication analysis. An additional limitation of our study is the potential bias introduced by the study timeframe. The AAF cases are likely to be the newer cases bringing a potential bias due to other advances, such as the intensive care units' capabilities. It should also be mentioned that we did not analyze the cases treated with liposomal and non-liposomal amphotericin B separately. Though these agents are deemed to have the same antifungal activity, their safety profile differs [32]. As mortality related to amphotericin toxicity was classified as the death of other causes, we believe this difference did not bias the disease-specific mortality primary end-point analysis. Another limitation is the combination of the original case series and a systematic literature review. In addition, by using published data, the survival rates may be affected by publication bias, i.e., authors may tend to publish more successful cases. However, such a bias would affect both study groups similarly, suggesting the improvement is valid. We believe the statistical power of providing a large-scale cohort for this rare condition surpasses the potential biases.

Conclusion

Despite less radical surgical intervention in OCFI with cranial involvement and more aggressive disease, patients treated with azoles had significantly better survival. The same trend emerged for orbital involvement. These findings suggest that a more conservative surgical approach in conjunction with azole treatment may improve morbidity without compromising survival. Further studies are required to decide whether this treatment paradigm can also be modified for orbital surgeries.

Authorship contribution

Material preparation, data collection and analysis were performed by IT, RS, GS, ES, SC, OZ, SK, DBO, IN and AY. The first draft of the manuscript was written by IT, RS and AY. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

None of the authors has any conflict of financial or non-financial interest.

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of each participating hospital approved this study. Informed consent of the participants was waived due to the study's retrospective nature (chart review and literature reports withdrawal) and the complete anonymity of the patients' data transferred to the statistical analysis.

Data sharing and reproducibility

The datasets generated and/or analyzed during the current study are available on www.synapse.org syn51009289.

Funding

The authors did not receive support from any organization for the submitted work.

References

1. Wandell GM, Miller C, Rathor A, et al. A multi-institutional review of outcomes in biopsy-proven acute invasive fungal sinusitis. Int Forum Allergy Rhinol 2018;8(12):1459–68.
2. Consultant, Laboratory Diagnostic Services, Department of Microbiology, ST Stephens Hospital, Delhi, India. Diagnosis and clinical outcomes for Rhino-Cerebral/ Orbital Mucormycosis: An experience sharing. J Clin Images Med Case Rep 2022;3(4).
3. Pettit NN, Carver PL. Isavuconazole: A new option for the management of invasive fungal infections. Ann Pharmacother 2015;49(7):825–42.
4. Davies BW, Smith JM, Hink EM, Durairaj VD. Increased Incidence of Rhino-Orbital-Cerebral Mucormycosis After Colorado Flooding. Ophthal Plast Reconstr Surg 2017;33(3S Suppl 1):S148–S151.
5. Sen M, Honavar SG, Bansal R, et al. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India - Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. Indian J Ophthalmol 2021;69(7):1670–92.
6. Pal R, Singh B, Bhadada SK, et al. COVID-19-associated mucormycosis: An updated systematic review of literature. Mycoses 2021;64(12):1452–9.
7. Dilek A, Ozaras R, Ozkaya S, Sunbul M, Sen EI, Leblebicioglu H. COVID-19-associated mucormycosis: Case report and systematic review. Travel Med Infect Dis 2021;44:102148.
8. Vironneau P, Kania R, Morizot G, Elie C, Garcia-Hermoso D, Herman P, et al. Local control of rhino-orbito-cerebral mucormycosis dramatically impacts survival. Clin Microbiol Infect 2014;20(5):O336–9.
9. Yakirevitch A, Barg AA, Bedrin L, Primov-Fever A, Wolf M, Migirov L. Acute invasive fungal rhinosinusitis in children with hematologic malignancies: outcome of surgical treatment. Pediatr Hematol Oncol 2015;32(8):568–75.
10. Gupta S, Goyal R, Kaore NM. Rhino-Orbital-Cerebral Mucormycosis: Battle with the Deadly Enemy. Indian J Otolaryngol Head Neck Surg 2020;72(1):104–11.
11. Nishimura K, Takahashi Y, Yamagishi Y, et al. Advanced surgical technique for invasive fungal sinusitis: endoscopic orbit-sinus combined approach. Minim Invasive Ther Allied Technol 2017;26(5):307–13.
12. Falci DR, Pasqualotto AC. Profile of isavuconazole and its potential in the treatment of severe invasive fungal infections. Infect Drug Resist 2013;6:163–74.
13. Wissen CPWGMV, Burger DM, Verweij PE, Aarnoutse RE, Brüggemann RJM. Simultaneous determination of the azoles voriconazole, posaconazole, isavuconazole, itraconazole and its metabolite hydroxy-itraconazole in human plasma by reversed phase ultra-performance liquid chromatography with ultraviolet detection. J Chromatogr B, Analyt Technol Biomed Life Sci 2012;887-888:79–84.
14. Greenberg RN, Mullane K, van Burik JAH, et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother 2006;50(1):126–33.
15. van Burik J-AH, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis 2006;42(7):e61–5.
16. Vehreschild JJ, Birtel A, Vehreschild MJGT, et al. Mucormycosis treated with posaconazole: review of 96 case reports. Crit Rev Microbiol 2013;39(3):310–24.
17. Ledoux MP, Denis J, Nivoix Y, Herbrecht R. Isavuconazole: A new broad-spectrum azole. Part 2: pharmacokinetics and clinical activity. J Mycol Med 2018;28(1):15–22.
18. Vaughan C, Bartolo A, Vallabh N, Leong SC. A meta-analysis of survival factors in rhino-orbital-cerebral mucormycosis-has anything changed in the past 20 years? Clin Otolaryngol 2018;43(6):1454–64.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6(7):e1000097.
20. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46(12):1813–21.
21. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev 2000;13(2):236–301.
22. Manesh A, John AO, Mathew B, et al. Posaconazole: an emerging therapeutic option for invasive rhino-orbito-cerebral mucormycosis. Mycoses 2016;59(12):765–72.
23. Jović Z, Janković SM, Ružić Zečević D, et al. Clinical pharmacokinetics of second-generation triazoles for the treatment of invasive aspergillosis and candidiasis. Eur J Drug Metab Pharmacokinet 2019;44(2):139–57.
24. Ullmann AJ, Cornely OA, Burchardt A, et al. Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. Antimicrob Agents Chemother 2006;50(2):658–66.
25. Schwartz S, Cornely OA, Hamed K, et al. Isavuconazole for the treatment of patients with invasive fungal diseases involving the central nervous system. Med Mycol 2020;58(4):417–24.
26. Hachem RY, Boktour MR, Hanna HA, et al. Sinus surgery combined with antifungal therapy is effective in the treatment of invasive Aspergillus sinusitis in neutropenic patients with cancer. Infection 2008;36(6):539–42.
27. Zappasodi P, Rossi M, Castagnola C, et al. Resolution of invasive fungal sinusitis in immunocompromised patients: neutrophil count is crucial beside a combined medical and surgical approach. Ann Hematol 2010;89(7):737–9.
28. Gillespie MB, O'Malley BW, Francis HW. An approach to fulminant invasive fungal rhinosinusitis in the immunocompromised host. Arch Otolaryngol Head Neck Surg 1998;124(5):520–6.
29. Meas T, Mouly S, Kania R, et al. Zygomycosis: an uncommon cause for peripheral facial palsy in diabetes. Diabetes Metab 2007;33(3):227–9.
30. Trief D, Gray ST, Jakobiec FA, et al. Invasive fungal disease of the sinus and orbit: a comparison between mucormycosis and Aspergillus. Br J Ophthalmol 2016;100(2):184–8.
31. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis 2019;19(12):e405–e421.
32. Sperry PJ, Cua DJ, Wetzel SA, Adler-Moore JP. Antimicrobial activity of AmBisome and non-liposomal amphotericin B following uptake of Candida glabrata by murine epidermal Langerhans cells. Med Mycol 1998;36(3):135-41.

Arkadi Yakirevitch, MD
Department of Otolaryngology
Head and Neck Surgery
Sheba Medical Center
Tel Hashomer
Ramat-Gan, 52621
Israel

Tel: +972525860004
Fax: +97235302238
E-mail: arkadiyak@gmail.com

ORCID 0000-0002-2540-3549

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Cases distribution along the study period.

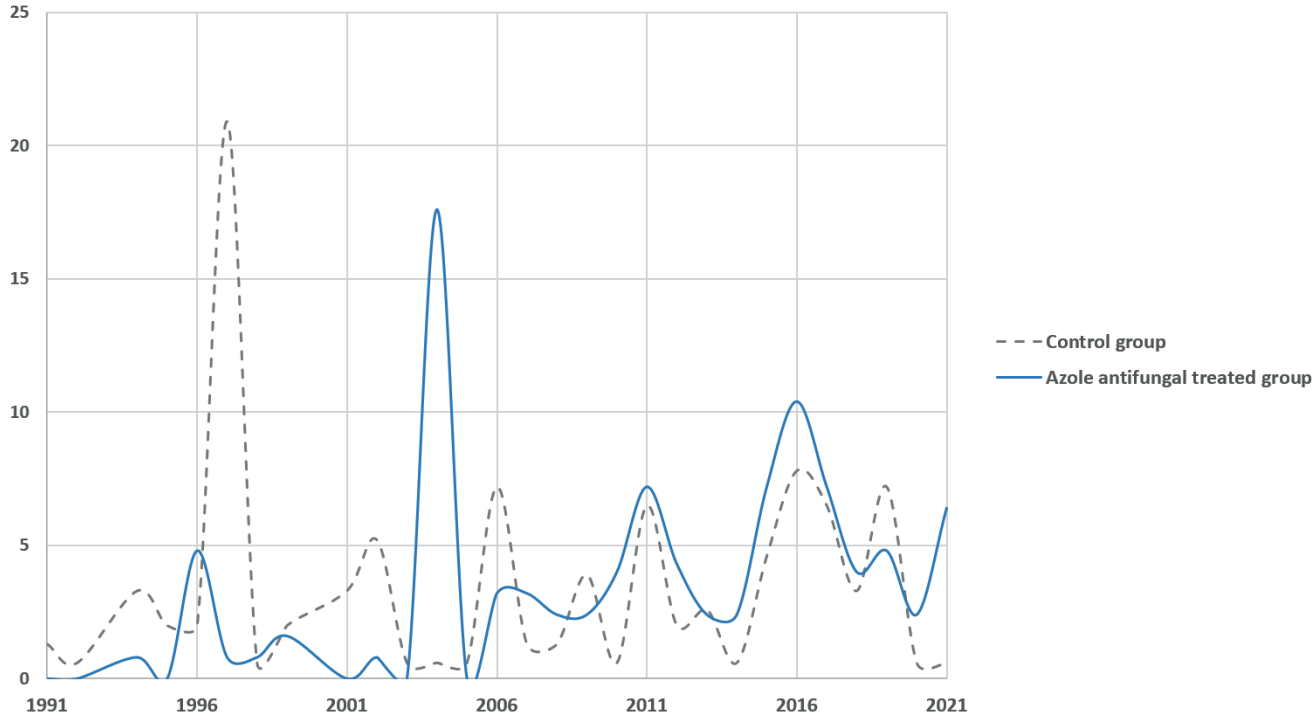
Year	Control cases	AAF treated case
1991	2 (1.3)	0
1992	1 (0.6)	0
1994	5 (3.3)	1 (0.8)
1995	3 (2)	0
1996	3 (2)	6 (4.8)
1997	32 (20.9)	1 (0.8)
1998	1 (0.6)	1 (0.8)
1999	3 (2.0)	2 (1.6)
2001	5 (3.3)	0
2002	8 (5.2)	1 (0.8)
2003	1 (0.6)	0
2004	1 (0.6)	22 (17.6)
2005	1 (0.6)	0
2006	11 (7.2)	4 (3.2)
2007	2 (1.3)	4 (3.2)
2008	2 (1.3)	3 (2.4)
2009	6 (3.9)	3 (2.4)
2010	1 (0.6)	5 (4.0)
2011	10 (6.5)	9 (7.2)
2012	3 (2.0)	4 (4.3)
2013	4 (2.6)	3 (2.4)
2014	1 (0.6)	3 (2.4)
2015	7 (4.6)	9 (7.2)
2016	12 (7.8)	13 (10.4)
2017	10 (6.5)	9 (7.2)
2018	5 (3.3)	5 (4.0)
2019	11 (7.2)	6 (4.8)
2020	1 (0.6)	3 (2.4)
2021	1 (0.6)	8 (6.4)

Data is presented in n (%). Spearman correlation, P<0.01.

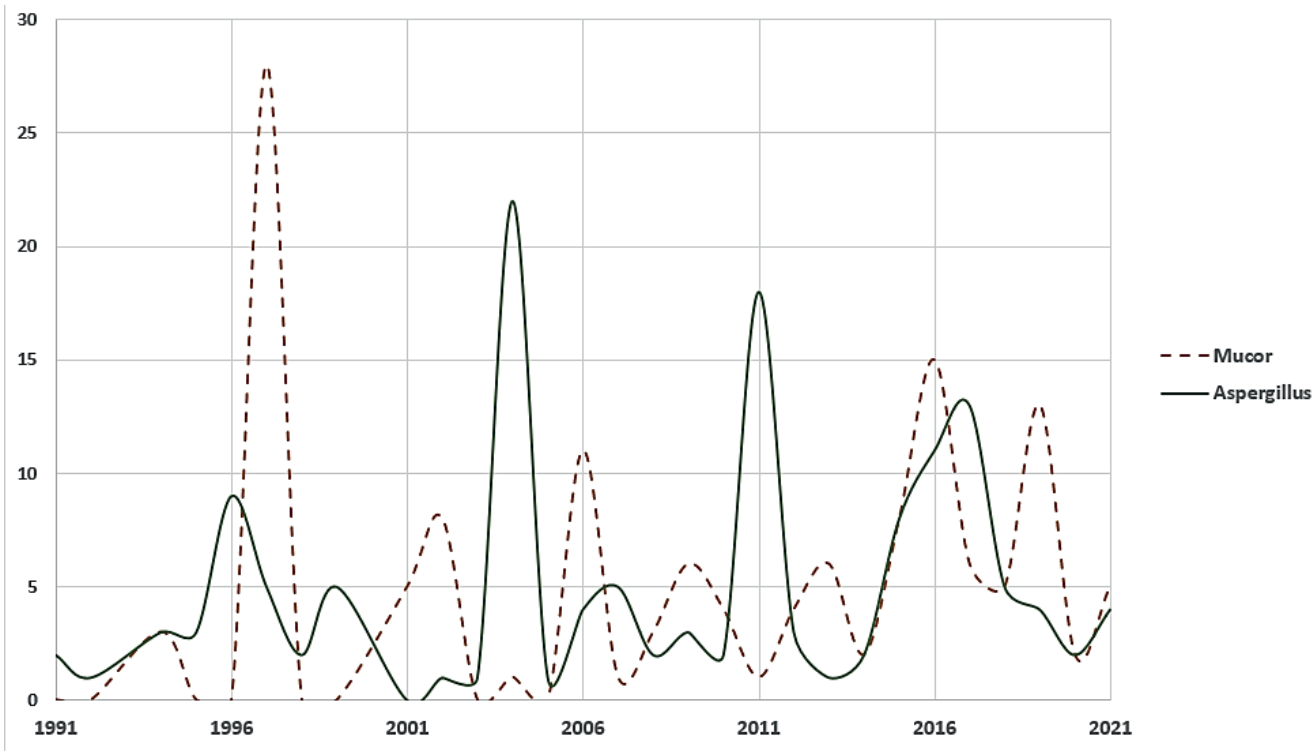
Supplementary Table 2. Cases distribution according to pathogen.

Year	*Mucor*	*Aspergillus*
1991	0	2
1992	0	1
1994	3	3
1995	0	3
1996	0	9
1997	28	5
1998	0	2
1999	0	5
2001	5	0
2002	8	1
2003	0	1
2004	1	22
2005	0	1
2006	11	4
2007	1	5
2008	3	2
2009	6	3
2010	4	2
2011	1	18
2012	4	3
2013	6	1
2014	2	2
2015	8	8
2016	15	11
2017	6	13
2018	5	5
2019	13	4
2020	2	2
2021	5	4

Spearman correlation coefficient is 0.3592713 with a p-value of 0.1447.
Cuzick test: p-value = 0.61.



Supplementary Figure 1. Graphical presentation of the study cohort distribution over time: azole-treated group and controls.



Supplementary Figure 2. Graphical presentation of the study cohort distribution according to pathogen over time.