



Treatment outcomes in acute invasive fungal rhinosinusitis

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Purpose of review

Acute invasive fungal rhinosinusitis (AIFR) is an aggressive and often fatal infection with wide variability of both presentation and survival rate across several published case reports and small case series. This review discusses treatment outcomes for this challenging disease.

Recent findings

For several decades, the use of medical therapy (consisting primarily of intravenous antifungals) combined with surgical resection and/or debridement has been widely recommended for the treatment of AIFR. Unfortunately, because of the rarity of AIFR, few large-scale studies have evaluated 'best options' for disease management. Most recent studies show few changes in either survival outcomes or management over time.

Summary

Although overall survival rates remain below about 60%, outcomes are significantly more favorable for those patients undergoing surgical/endoscopic resection and who have reversible predisposing factors that can be rapidly managed (e.g., diabetes). The indications for orbital exenteration remain unclear, but recent studies suggest that this procedure may not change outcome in most patients.

Keywords

Aspergillus, invasive fungal sinusitis, *Mucor*, mucormycosis, survival, treatment outcomes

INTRODUCTION

Acute invasive fungal rhinosinusitis (AIFR) is a disease that occurs infrequently, but often has fatal outcomes. The invasive nature of the fungus causing AIFR is characterized by rapid disease extension into blood vessels, resulting in vasculitis with thrombosis, hemorrhage, tissue infarction, and central nervous system involvement [1]. The most common causative pathogens are the Zygomycetes (*Rhizopus*, *Mucor*, *Rhizomucor*) and the *Aspergillus* species. These organisms are commonly found in air and function as saprophytes, which inhabit decomposing organic matter. These opportunistic organisms are commonly inhaled into the sinuses and lungs without sequelae, but under certain circumstances (e.g., immunosuppression, acidosis), they can rapidly proliferate and invade the sinonasal cavity. Patients with hematologic malignancies, chronic immunosuppression, and poorly controlled diabetes are more susceptible to infection by these organisms. As treatment advancements continue to grow for these patient populations, so do the number of individuals most susceptible to AIFR.

The clinical presentation of AIFR varies across different published case series and reports. This poses a challenge to establishing an early and accurate diagnosis, which is generally considered fundamental to achieving a more favorable prognosis. A recent systematic review of published cases of AIFR identified the most common signs and symptoms in 481 cases from a total of 38 articles [2^{••}]. These included facial swelling (present in 65% of reported cases), fever (63%), nasal congestion (52%), and ophthalmoplegia (51%). These and other symptoms including epistaxis, decreased vision, and meningitis can progress in a matter of hours, with mortality rates ranging from approximately 20 to 80% in spite of adequate treatment. Therefore, it is imperative to

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KEY POINTS

- AIFS has high mortality rates and should be suspected in immunocompromised patients complaining of facial swelling, fever, nasal congestion, and visual changes in order to establish an early diagnosis and initiate therapy immediately.
- The indications for orbital exenteration remain unclear and clinical signs of orbital involvement alone should not necessitate removal of the eye. Recent studies suggest that orbital exenteration does not affect survival.
- Surgery for AIFS is an independent prognostic factor for improved survival and the use of surgical debridement in combination with intravenous antifungal therapy should be considered standard of care.

maintain a high index of suspicion for AIFR in the immunocompromised patient presenting with new-onset, rapidly progressive sinusitis or facial discomfort.

The initial workup of AIFR should include nasal endoscopy, biopsy, and pathologic evaluation. Nasal endoscopy often demonstrates signs of ischemia, such as white or pale discoloration of mucosal surfaces, whereas the necrosis that results from fungal angioinvasion typically presents as eschars, black crusts, or sloughing of the nasal septum with or without perforation (Fig. 1) [3]. Biopsies from these sites should be taken to establish histopathologic confirmation and to select the most appropriate antifungal therapy, which differs between mucormycosis and aspergillosis. The *Zygomycetes* demonstrate broad, ribbon-like, irregular, and nonseptate hyphae, whereas *Aspergillus* sp. are septate and have narrow hyphae at 45° angles. The use of frozen section biopsy can often support the diagnosis of

AIFR intraoperatively [4], and although it generally cannot be used for speciation of fungal pathogens, it does often allow for earlier instatement of broad antifungal therapy [5].

Imaging studies including both computed tomography (CT) and MRI can be used during the primary evaluation of AIFR. CT findings in the early stages are nonspecific and include sinus opacification, soft tissue thickening, and infiltration of perimaxillary fat (Fig. 2a) [6]. CT is the ideal imaging modality for evaluation of bony erosion; however, this finding typically occurs at late stages of the disease. MRI more accurately characterizes soft tissue abnormalities, with perhaps its greatest utility being the evaluation of disease extent, that is, the presence of vascular occlusions, intracranial or cavernous sinus involvement, and so on (Fig. 2b) [6–8]. Both imaging modalities can be used to assist with surgical planning [9].

The mainstay of treatment of AIFR consists of reversal or control of underlying disease processes, early surgical debridement, and antifungal therapy. Identification of the best treatment modality for AIFR has unfortunately presented a formidable challenge, given the high variability of treatment outcomes reported in different case series.

SURGICAL OUTCOMES

Surgical intervention has been reported as the most important factor in the treatment of AIFR by several authors [10¹¹,11–13]. Debridement of infected tissue reduces the fungal burden and allows for better penetration of antifungals into involved areas. In patients with hematologic malignancies, it may also improve recovery of immunologic status by reducing the burden on recovering neutrophils [10¹¹]. Historically, surgery was performed primarily via an open approach; however, this has changed

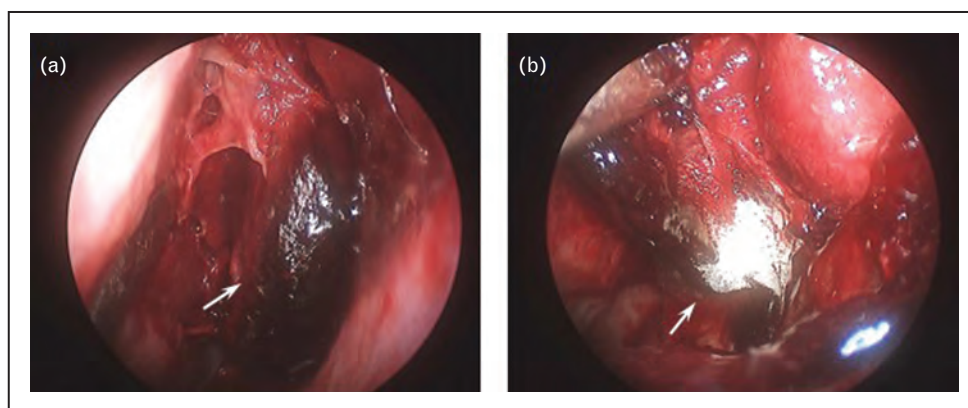


FIGURE 1. Nasal endoscopy revealing a black, necrotic middle turbinate (a) and white fungal hyphae on the posterior wall of the maxillary sinus and inferior turbinate (b).

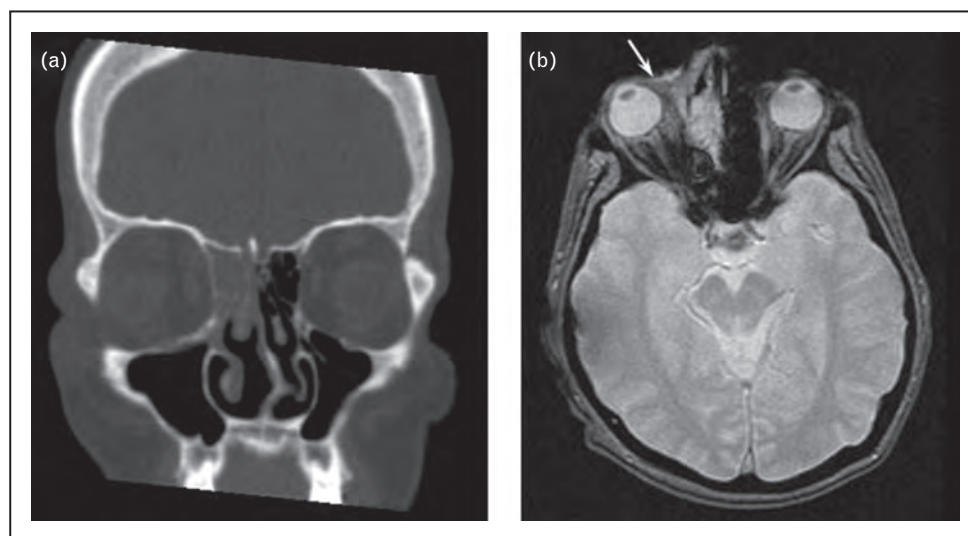


FIGURE 2. Imaging studies used in the diagnosis and management of acute invasive fungal sinusitis. Images are from a single patient. (a) Computed tomography depicts ethmoid opacification and other nonspecific findings, whereas (b) MRI shows orbital extension, preseptal cellulitis, and proptosis.

considerably over the past 20 years with the introduction of modern endoscopic techniques.

Preendoscopic era

Previous works have reported that early and extensive surgical debridement can improve survival rates. Initial reports described an increase in survival rate of up to 15–21% [14,15]. Open approaches included the Caldwell-Luc operation, middle meatal antrostomy, ethmoidectomy, sphenoidotomy, frontoethmoidectomy, palatotomy, and orbital exenteration. However, even with these interventions, the overall mortality rate remained high, ranging from 64 to 84% despite early treatment and combination with medical pharmacotherapy [16–18].

These poor survival rates may be related to other factors, including underlying condition, extension of disease, and time course for treatment initiation. For example, Anaissie and Shikhani [19] reported that cases with internal carotid artery involvement had a survival rate of only 16%. Thus, in some cases, poor survival rates may be a consequence of delayed diagnosis and subsequent advanced disease stage rather than failure of the surgical procedure itself. Denning and Stevens [20] conducted a review of 2121 cases of invasive aspergillosis, in which they describe 102 cases involving the sinuses. The authors reported that whereas surgery was curative in cases without immunocompromise, it conversely increased mortality in patients with neutropenia [20]. Some patients died as a consequence of hemorrhage following the procedure, again reflecting the influence of other factors (thrombocytopenia

associated with underlying medical condition) rather than the ineffectiveness of the operation to eradicate AIFR.

Of note, other reports described cases in which open surgery resulted in good survival outcomes [13,21,22]. These reports commonly described a combination of surgery with medical therapy (amphotericin B) and again emphasized the importance of early treatment. In our experience, nonendoscopic procedures are now rarely necessary to manage AIFR.

Postendoscopic era

The introduction of endoscopic approaches for the treatment of AIFR resulted in better visualization and possibly better preoperative staging [23]. In fact, endoscopic procedures favor earlier treatment because they serve both as a therapeutic and a diagnostic intervention. The first published accounts of AIFR treated with endoscopic surgery reported substantially improved survival rates ranging from 66 to 100% [23–25]. Wiatrak *et al.* [25] reported the first pediatric cases of AIFR treated with endoscopic sinus surgery. In their series, four out of six cases required additional open surgery as a result of extensive disease. Approximately 20 years later, open procedures are still recommended when endoscopic approaches are not curative or when AIFR is at an advanced stage or very extensive [10¹¹]. However, there are also emerging works suggesting that even cases with extensive disease can be managed with endoscopic surgery alone [26–28]. For example, a series published by Avet *et al.* [24] described three cases of sinonasal mucormycosis treated with

endoscopic surgery and antimicrobial therapy. All three patients presented with cranial nerve involvement, ptosis, and ophthalmoplegia. All of them survived and even avoided orbital exenteration. This work suggested that endoscopic approaches may allow for more effective debridement of devitalized tissue, making it more likely that one could avoid orbital exenteration. A subsequent report by Hosseini and Borghei [29] encouraged visualization of the pterygopalatine fossa, a task made much simpler with endoscopy. It was suggested that the pterygopalatine fossa may act as a primary reservoir for fungal infection and subsequent spread into the orbit and intracranial spaces. Debridement of this area in their 10 cases resulted in a survival rate of 60%, with four patients dying of other medical causes.

The use of endoscopic surgery in the treatment of AIFR has now become the standard of care. Recent studies have demonstrated better outcomes with endoscopic resection compared with open surgery [22,12,30]. Kasapoglu *et al.* [30] reported AIFR-specific survival rates of 90% with an endoscopic approach versus only 57% with open surgery. Chen *et al.* [12] described 46 patients with hematologic malignancies who developed acute invasive fungal sinusitis (AIFS) and found that the only independent prognostic factor for survival was endoscopic sinus surgery. Confirming these findings, a recent systematic review of AIFR cases reported that patients treated with endoscopic surgery had improved survival (63%) relative to those receiving open surgery (54%) [22] and again identified endoscopic sinus surgery as an independent positive prognostic factor.

One of the most challenging choices in AIFR management has long been the decision to sacrifice the eye. Regarding orbital complications and the decision to proceed with exenteration, we have generally observed an evolving approach. In the past, exenteration was considered life-saving in the presence of ocular symptoms [18], whereas now it is generally only recommended in the specific presence of loss of vision or complete ophthalmoplegia [31,32]. Even then it could be argued that more conservative approaches may be tried. Whereas Bhansali *et al.* [33] reported decreased survival in the presence of vision loss and ophthalmoplegia, Avet *et al.* [24] reported that preservation of the orbit can be achieved without compromising survival, despite the presence of ophthalmoplegia and ptosis with cranial nerve involvement. A more recent study by Hargrove *et al.* [34] tried to identify evidence-based indications for orbital exenteration in patients with orbital mucormycosis. In their review of 113 articles, no such indications were

identified and orbital exenteration did not result in any statistical improvement in survival. The systematic review of AIFR by Turner *et al.* [22] also concluded that orbital findings were not predictors of survival. In that report, one out of five patients from a total of 398 cases underwent orbital exenteration with no statistical impact on survival. As a result, we believe that orbital exenteration is best reserved for a completely nonfunctioning eye that could theoretically serve as a reservoir for disease and a path to access intracranial structures. Patients with orbital symptoms of fungal infection, but with preserved vision should be advised that removal of the eye may not change their prognosis. They can also be advised to 'wait-and-see', with very close ophthalmologic monitoring of disease progression [22]. In our opinion, because of the lack of clear evidence supporting this radical approach, the decision to proceed with exenteration often depends largely on the wishes of the patient and relatives.

MEDICAL OUTCOMES

Antifungal therapy with amphotericin B should be initiated as soon as AIFR is suspected. While voriconazole has been reported as the drug of choice against *Aspergillus* sp., mucormycosis is resistant to this drug. Amphotericin B is considered to be the mainstay of pharmacologic treatment of AIFR and has been so since its initial introduction in the 1950s [32,35]. Prior to that, treatment was primarily directed at controlling underlying diseases, surgical debridement, anticoagulation, and use of solutions with sodium or potassium iodide [36–38]. These treatment modalities were frequently unsuccessful.

Despite the wide use of amphotericin B in the treatment of AIFR, few studies have assessed its use on treatment outcomes. Kara *et al.* [39] performed multivariate analyses of 20 patients with hematologic malignancies and AIFR and found that treatment with liposomal amphotericin B resulted in a significant improvement in outcomes. The systematic review by Turner *et al.* found that patients receiving liposomal amphotericin B had a greater than 60% survival rate, compared with less than 50% for patients treated with deoxycholate amphotericin B. The disadvantage of liposomal amphotericin B continues to be its expense and it is, thus, still reserved for patients with renal impairment or who cannot otherwise tolerate deoxycholate formulations. Furthermore, most studies continue to show that antifungal therapy should be combined with surgical resection and debridement of involved tissues whenever possible. Talmi *et al.* [40] recommended that treatment of AIFR based on purely medical therapy should not be a frequent practice

and should only be left for cases in which surgery cannot be performed. The work of Khor *et al.* [13] supports this recommendation. They reported 16 cases of sinonasal mucormycosis with an overall survival rate of 94% in patients treated with combined surgical resection and amphotericin B versus only 20% in patients treated with amphotericin B alone.

Reversal of underlying disease

Diabetes mellitus is a cause of immunosuppression that can be controlled or reversed more easily than other predisposing morbidities such as hematologic malignancies or AIDS. Whereas some studies have reported diabetes mellitus to be a poor prognostic factor [21,41,42], most have described favorable survival rates in diabetic patients – even up to 70–89% when treated in conjunction with surgical resection and amphotericin B [14,43,44]. The systematic review by Turner *et al.* [2^{••}] confirmed that diabetic patients have higher survival rates. The assumed rationale for this finding is that hyperglycemia is generally reversible and that with tighter glucose control regimens, the general environment becomes much less hospitable for fungal growth.

Patients with hematologic malignancies and/or bone marrow transplant have better outcomes when their neutrophil count and bone marrow recover [3,10^{••},45]. In fact, patients who recover from AIFR can suffer recurrence if their neutropenia recurs [41]. An alternative for these patients that has been used sparingly is the use of granulocyte-colony stimulating factor [46,47]. Although this may not result in better overall survival rates, this therapy has been reported to significantly improve local control of AIFR [48]. Other adjunctive therapies have been suggested, including hyperbaric oxygen therapy, immunotherapy, and iron chelation [49,50]. However, these therapies have not yet shown significant improvement in survival and are rarely indicated.

OVERALL OUTCOMES

Mortality rates across reports remain very high with a recent systematic review calculating an overall survival rate of 49.7%, despite medical and surgical treatment in most cases [2^{••}]. These outcomes are not significantly different from those reported over the past 4 decades (Fig. 3) [51]. The failure to identify factors impacting patient survival is certainly responsible, in part, for the continuing lack of improvement in survival rates over time. Several series have reported putative prognostic factors in AIFR; however, most series were small and lacked

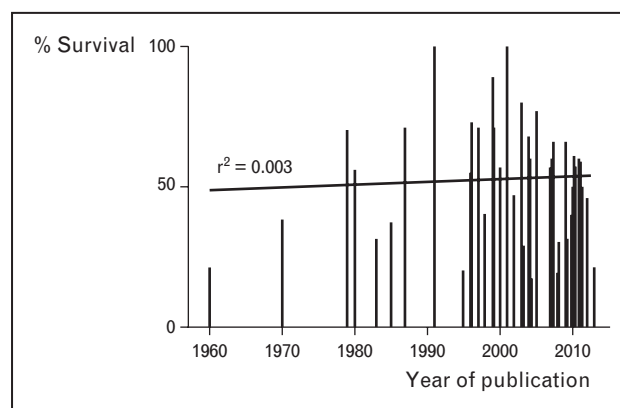


FIGURE 3. Survival in acute invasive fungal sinusitis patients. Survival rates reported in the literature have failed to show any significant improvements, despite purported advances in treatment. Data from 1970s and earlier obtained from citations of [51]. Reports of less than five cases from more recent years (1990+) are not included.

appropriate power to make generalized conclusions (Table 1) [11–13,21,33,39,41,42,44,52[•],53].

A recent review of 398 cases of AIFR identified several factors associated with improved survival, including diabetes mellitus and the use of liposomal amphotericin B [2^{••}]. Likewise, use of surgery in the treatment algorithm for AIFR also improved survival, in agreement with prior reports [11–13]. Predictors of poor prognosis primarily included factors associated with disease extension or spread, including altered mental status, intracranial extension, and renal/liver disease. When all factors were taken into account, the only independent positive predictors of survival were diabetes mellitus and surgery. This same multivariate analysis identified only intracranial extension and advanced age as negative prognostic factors [2^{••}]. The role of age in treatment outcomes is unclear, but may be due to the presence of greater comorbidities or limitations in the ability to proceed with aggressive interventions.

CONCLUSION

AIFR continues to result in high mortality rates. Presenting symptoms are often nonspecific; however, signs like facial swelling, orbital involvement, and cranial nerve deficits should raise concern for this condition, particularly in high-risk patients. The most common predisposing factors continue to be uncontrolled diabetes mellitus and hematologic malignancy, with the former showing better outcomes. In addition, older age and intracranial involvement are associated with lower survival rates. Although there is increasing awareness of this

Table 1. Reported prognostic factors in patients with acute invasive fungal rhinosinusitis

Authors	Year	Patients (n)	Overall survival (%)	Positive prognostic factor	Negative prognostic factor
Monroe <i>et al.</i> [52 ^a]	2013	29	18	N/A	Intracranial involvement (U) Cranial neuropathy (U)
Chen <i>et al.</i> [12]	2011	46	59	Endoscopic sinus surgery (U, M)	Acute myelogenous leukemia (U) Refractory hematologic malignancy (U)
Saedi <i>et al.</i> [44]	2011	38	60	Diabetes mellitus (U)	Hematologic malignancy (U) Orbital exenteration (U) Elevated blood glucose (U) Maxillary sinus involvement (U)
Valera <i>et al.</i> [42]	2011	32	50	N/A	Extension beyond nasal cavities (U) Diabetes mellitus (U) Aplastic anemia (U)
Sun <i>et al.</i> ^a [11]	2010	90	61	Liposomal amphotericin B (U, M) Surgery (U, M)	Intracranial involvement (U) Older age (M)
Kara <i>et al.</i> ^b [39]	2009	20	40	Amphotericin B (U) Neutrophil recovery (U) Liposomal amphotericin B (M) Liposomal amphotericin B dose (M) Length of treatment (M)	N/A
Bhansali <i>et al.</i> [33]	2004	35	68	N/A	Delay in amphotericin B initiation (U) Facial/lid gangrene (U) Hemiplegia (U) Intracranial involvement (U) Altered mental status (U) Vision loss (U) Ophthalmoplegia (U) Palatal necrosis (U)
Parikh <i>et al.</i> [41]	2004	43	88	N/A	Intracranial involvement Persistent neutropenia
Khor <i>et al.</i> [13]	2003	21	80	Surgery (U) ^c	Delay in diagnosis (U)
Dhiwakar <i>et al.</i> [53]	2003	9	29	N/A	Intracranial involvement (U)
Butugan <i>et al.</i> [21]	1996	11	73	N/A	Diabetic ketoacidosis (U) Hemiplegia (U)

M, multivariate; U, univariate.

^aIncluded cohort ($n = 13$) and literature review ($n = 77$).^bIncluded one patient with lung as site of infection.^cSurgery + amphotericin B versus amphotericin B alone.Adapted from [2[■]].

condition in populations at greatest risk, the poor survival outcomes may reflect late initiation of treatment. Surgical resection with either open or endoscopic approaches improves survival rates and, thus, should be offered to all patients, even those with advanced disease and other medical comorbidities. The decision to proceed with orbital exenteration should be very deliberate, as most evidence suggests that this procedure may not change survival outcomes in most patients. Unfortunately, despite

advances in both surgical and medical treatments for AIFS, overall survival has changed very little over time.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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