

Management of Acute Invasive Fungal Sinusitis

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Abstract

Acute invasive fungal sinusitis (AIFS) is an uncommon and usually life-threatening clinical condition. Mortality in AIFS is very high. The colonization of the fungi at the sinonasal tract does not indicate the infection. The status of the immune condition of the patient plays an integral part in different manifestations of AIFS. AIFS is an aggressive type of fungal infection and often leads to a fatal situation, particularly in patients who are immunocompromised. Diagnostic nasal endoscopy, as well as a computed tomography scan, is warranted in these patients. Magnetic resonance imaging improves diagnostic accuracy and assesses the spread of the disease into orbit and the brain. Histopathological and microbiological examinations confirm the diagnosis. To save lives, early diagnosis and treatment are essential. Therefore, clinicians need to have a high level of suspicion for this illness. Management of AIFS requires a multidisciplinary approach with significant predictors of survival being surgical debridement and antifungal treatment. Patients require urgent hospitalizations with intravenous antifungal therapy and surgical debridement. As soon as AIFS is identified, antifungal medication should begin. Higher survival rates are achieved with complete endoscopic resection of the disease than with incomplete resection. Liposomal amphotericin B has a more favorable outcome and fewer side effects than amphotericin B. The mainstays of AIFS management continue to be early surgical debridement and antifungal treatment. This review article discusses the epidemiology, etiopathogenesis, clinical features, investigations, and current treatment options of AIFS.

Keywords: Acute invasive fungal sinusitis, endoscopic debridement, immunocompromised patients, liposomal amphotericin B

INTRODUCTION

Acute invasive fungal sinusitis (AIFS) is an uncommon clinical entity and is often associated with severe morbidity and mortality.^[1] It is commonly found in immunocompromised persons.^[2] The common predisposing factors for AIFS include neutrophilia, poorly controlled diabetes mellitus or diabetic ketoacidosis, bone transplant, chronic immunosuppressive therapy, and acquired immunodeficiency syndrome.^[3] When sinusitis symptoms have been present for 1 month or less and there are fungal hyphae present in the sinonasal mucosa, submucosa, bone, or blood vessels, this condition is known as AIFS.^[3] This morbid clinical entity requires early diagnosis and treatment for improved survival of the patients.^[1] It rapidly progresses and affects the vital structures of the skull base region. Clinicians suspect AIFS in cases of patients with impaired immunity presenting with fever and sinonasal infection. The mortality rate in AIFS is ranging from 20% to 80%.^[4] The higher mortality requires strongly standardized diagnostic and therapeutic algorithms in AIFS which improve the survival of the patients. AIFS is considered one of the most aggressive infections of the

head-and-neck region which require aggressive surgery such as endoscopic debridement, intravenous antifungal medications, and correction of certain clinical conditions of compromised immunity.^[5] Improved patient survival requires early detection of AIFS in immunocompromised individuals, followed by endoscopic debridement, antifungal therapy, and immunodeficiency reversal.^[4] The purpose of this review article is to discuss the epidemiology, etiopathogenesis, clinical presentations, investigations, treatment, and prevention of the AIFS.

METHODS OF LITERATURE SEARCH

Multiple scientific systematic methods were used to find current research publications on AIFS and its epidemiology,

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etiopathology, clinical manifestations, diagnosis, and treatment. We started by searching the Scopus, PubMed, Medline, and Google Scholar databases online. A search strategy using Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines was developed. This search strategy recognized the abstracts of published articles, whereas other research articles were discovered manually from the citations. Randomized controlled studies, observational studies, comparative studies, case series, and case reports were evaluated for eligibility. There were a total number of articles 78 (22 case reports; 20 case series; 36 original articles) [Figure 1]. This article focuses only on the details of the AIFS including its epidemiology, etiopathology, clinical manifestations, diagnosis, treatment, and prevention. This analysis provides a better understanding of AIFS and its clinical profile along with its management. It will also serve as a catalyst for further study of the etiopathogenesis and management of AIFS along with the development of a newer surgical technique for the management of this lesion.

EPIDEMIOLOGY

AIFS is a relatively uncommon disease that primarily affects immunocompromised individuals. AIFS is a rapidly progressive and fatal type of fungal sinusitis that is uncommon in the general population and immunocompetent patients. However, this is common among immunocompromised patients. Neutropenia is the most common predisposing factor for AIFS.^[6] Patients of AIFS have often a medical history of hematologic malignancies, hematopoietic stem cell transplantation, solid organ transplantation, advanced human immunodeficiency virus infection, or any other types of immunosuppression.^[7] Patients with uncontrolled diabetes mellitus or those with diabetic ketoacidosis are at a higher chance of AIFS. Historically, the mortality rate ranged from 30% to 80%; however, more recent data showed <20% mortality rate, which is attributed to early diagnosis and aggressive surgical and medical treatment.^[8]

ETIOPATHOLOGY

Fungal spores are deposited on the mucosal lining of the sinonasal tract and are a natural component of the sinonasal microbiome. Fungi are prevalent in nature and are inhaled into the nasal cavity with every breath.^[9] In an immunocompetent person, spores are destroyed either by the tissue macrophages or through immunogenic cascades which recruit neutrophils for the removal of the fungal spores.^[10] Although phagocytic cells are the body's main line of defense against fungus, helper and cytotoxic T-cells are also crucial.^[10] The fungus spores can develop into hyphae and enter the mucosa and possibly neurovascular tissues in the case of an immunocompromised person.^[11] Fungi that penetrate the intravascular space disseminate and cause tissue ischemia, necrosis, or bleeding both locally and more widely. *Rhizopus* spp. and *Mucor* are the two most prevalent fungi that cause AIFS. From the zygomycetes class/Mucorales order, and *Aspergillus* spp. The uncommon fungi in AIFS include *Alternaria* spp., *Candida* spp., and *Fusarium* spp.^[12] Immunocompromised patients with a history of uncontrolled diabetes, hematological cancers, recent chemotherapy, hematopoietic stem cell transplantation, and solid organ transplantation are frequently reported to have AIFS [Table 1].^[4] Patients with cancer, who have severe neutropenia, which is defined as an absolute neutrophil count of <500 cells/mm³, are at increased risk for developing AIFS.^[13] However, a multicentric investigation found that at least 50% of the patients with AIFS had an absolute neutrophil count of >1000/mm³, indicating that this disease may have additional patient-related risk factors contributing to its pathogenesis.^[14] A study observed severe thrombocytopenia (<60 × 10⁹/L) in 40% of the study population; however, the platelet count has not been considered an established risk factor ASIF.^[15] Platelets have been thought to have antifungal properties. Platelets may suppress the fungal growth and attach to the cell walls of *Aspergillus fumigatus* hyphae, aiding neutrophils in the host's defense against invasive fungal infections. Myelosuppression makes thrombocytopenic patients with a platelet count of <81,000 cells/mm³ susceptible to fungal infections.^[16] Therefore, thrombocytopenia may be a key

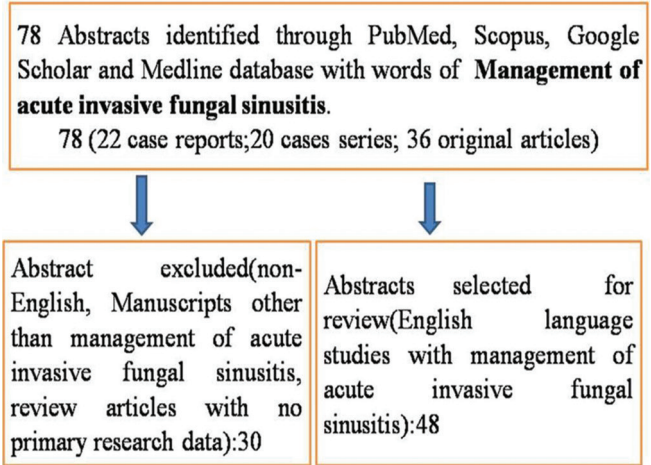


Figure 1: Flowchart showing methods of literature search

Table 1: Risk factors for acute invasive fungal sinusitis	
Risk factors	
Impaired neutrophil function	
Hematological malignancy	
Aplastic anemia	
Poorly controlled diabetes mellitus	
Hematochromosis+deferoxamine treatment	
Protein calorie malnutrition	
AIDS	
Iatrogenic immunosuppression	
Solid organ transplant	
Hematopoietic stem cell transplant	
Chemotherapy	
Corticosteroid therapy	
AIDS: Acquired immune deficiency syndrome	

factor in the pathogenesis of AIFS. Absolute neutrophil count, blood glucose, and ketones are some laboratory values that are frequently linked to the risk of developing AIFS. Abnormalities of these laboratory data may be managed through medical management. In immune-compromised patients, germination takes place after the inhalation of fungal spores into the nasal cavity and paranasal sinuses, and hyphae invade the blood.^[8]

CLINICAL MANIFESTATION

In AIFS, the symptoms are unfortunately nonspecific and may cause delayed diagnosis with worse outcomes.^[4] AIFS can exhibit nonspecific, overlapping symptoms that are consistent with a number of diseases, but clinical manifestations are frequently quite quick.^[17] AIFS typically manifests clinically as nasal congestion, rhinorrhea, fever, facial pain, and swelling.^[4] Advanced forms of the AIFS may cause visual changes, proptosis, weakness of the extraocular muscles, and cranial neuropathies.^[18] A significant clinical feature of AIFS is facial pain, which is frequently attributed to the vascular invasion of the anterior periantral soft tissues.^[19] Seizures or altered mental status are important clinical manifestations in AIFS with intracranial invasion.^[20] Hemoptysis, wheezing, shortness of breath, or chest pain may be signs of a sinopulmonary involvement. Immunocompromised patients may stay afebrile.^[21] Proper head, neck, and pulmonary evaluations are required in AIFS. Clinical indicators of orbital involvement include periorbital edema, ophthalmoplegia, loss of vision, proptosis, and reduced intraocular movements.^[22] Preseptal cellulitis, orbital cellulitis, subperiosteal abscess, orbital abscess, and vision loss are the problems of the orbit. Anterior rhinoscopy reveals ulcers, pale nasal mucosa that may indicate ischemia, and the presence of eschar (which is pathognomonic for AIFS).^[23] Nasal mucosa may be seen as edematous and hypervascular secondary to acute inflammation.^[24] As an alternative, ischemia may cause the nasal mucosa to be pale and have little bleeding when biopsied.^[25] Examination of the oral cavity in AIFS may show palatal ulceration, which can progress to bony necrosis and follow by oronasal fistula.^[26] Comprehensive neurological tests, including assessments of the cranial nerves and mental status, are necessary for AIFS and must be performed at the patient's bedside. Epidural or subdural abscesses, brain abscesses, meningitis, encephalitis, and cavernous sinus thrombosis are some of the intracranial problems.^[27]

DIAGNOSIS

Diagnostic nasal endoscopy shows mucosal discoloration, crusting, and ulcerations in the nasal cavity.^[28] The affected mucosa is often seen at the turbinates, nasal septum, and paranasal sinuses. The biopsy from this affected mucosa provides a definitive diagnosis.^[29] Biopsy from the location of the middle turbinate is often considered a positive sample for AIFS.^[29] A prevalent and maybe unique intranasal finding

in AIFS is middle turbinate necrosis.^[30] Unilateral or bilateral facial symptoms along with opacification of the paranasal sinuses in computed tomography (CT) scan increase the likelihood of AIFS.^[31] The early indications of AIFS and intracranial extension can both be detected using magnetic resonance imaging (MRI) and CT scan imaging.^[32] Both CT and MRI are found to have similar specificities. MRI is more sensitive than CT scans for the diagnosis of AIFS. CT scan often shows unilateral sinus opacification and soft-tissue thickening of the mucosa of the nasal floor and lateral wall. Bony destruction can be detected early in a CT scan. Bone destruction, however, is found relatively late in the disease process, and late diagnosis may be partially explained as a cause of high mortality. The results of a CT scan should be compared to the negative results of the diagnostic nasal endoscopy because they can reveal bone erosion in the paranasal sinuses, a sign of advanced disease, as well as unilateral opacification and mucosal thickness that may be present in the early stages of AIFS.^[32] The extranasal invasion can be evaluated with great accuracy using MRI scans, which are also very useful for examining the possible spread of disease to the orbit and cerebral area.^[33] In CT scans, involvement of the ethmoid or sphenoid sinuses and bony destruction are negative prognostic features and increase the chance of extension to surrounding structures. MRI findings in AIFS include obliteration or infiltration of periantral fat, inflammatory changes in the orbital fat and extraocular muscles, and leptomeningeal enhancement. The following MRI characteristics are present: nonenhancing hypointense turbinates (black turbinate sign), sinus opacification, air-fluid levels, erasure of the nasopharyngeal planes, variable intensity within the paranasal sinuses on T1- and T2-weighted images (more likely hypointense on T2), loss of contrast enhancement of sinonasal mucosa and extraocular muscles, and inflammatory changes in muscles, fat, and enhancement of leptomeninges.^[34] Sometimes MRI may be delayed due to unavailability in the hospital. The MRI wait times should never delay getting a tissue biopsy. Hence, MRI should be used after the diagnosis of AIFS is confirmed by tissue biopsy if intracranial invasions are suspected. An intranasal biopsy is an important consideration for the diagnosis. The majority of the AIFS involves the middle turbinate, nasal septum, or nasal floor mucosa, so attention should be given to these areas for a possible biopsy. The most common paranasal sinuses to be damaged by AIFS are the maxillary and ethmoidal sinuses, although in conscious patients, these sinuses are rarely accessible for biopsy. The middle turbinate has been discovered to be the most often affected area by fungi in AIFS (40%–90% of cases), with pallor or necrosis being the most frequent symptoms. A middle turbinate biopsy can diagnose AIFS with a sensitivity of 75%–86% and a specificity of 100%.^[35] The surgical debridement has been guided by the intraoperative frozen section. The presence of fungi can be determined using potassium hydroxide 20% preparation on tissues or nasal discharge, as well as through histological analysis, mycologic testing, and molecular analysis.

TREATMENT

The prognosis for people with AIFS depends on early disease diagnosis, intensive medical treatment, and, if necessary, surgery.^[15] Treatment includes managing diabetic ketoacidosis, reversing the underlying immunocompromised state, if possible, antifungal treatments, and if necessary, prompt surgical surgery.^[36] As soon as AIFS is identified, antifungal medication should begin.^[37] The treatment of AIFS includes surgical intervention and antifungal therapy. To stop the spread of necrosis and reduce the fungal load, all afflicted tissues are aggressively debrided during the surgical intervention.^[38] Urgent surgical intervention usually reduces mortality.^[38] Surgery is frequently time-consuming, necessitating numerous visits to the odds ratio for debridement.

An essential surgical procedure in the management of AIFS is endoscopic sinus surgery, which normally entails full excision of the mucosa and bone in the troubled regions up to the dura while preventing the cerebrospinal fluid leak.^[39] Despite the minimal survival benefits of these surgical treatments, neurosurgical debridement and orbital exenteration may be performed in cases with intracranial invasions and/or ocular invasion by AIFS due to the dismal prognosis of these advanced stages of the disease.^[40] Delaying the surgery reduces the survival of patients with AIFS.^[41] Hence, endoscopic sinus surgery with debridement of the disease is the primary intervention for the AIFS. The decision of whether or not to undertake a disfiguring orbital exenteration is complicated by orbital involvement. Studies to date have not shown higher survival with orbital exenteration. One study showed no survival benefit in 80 patients who underwent orbital exenteration.^[4] Another study showed that 15 AIFS patients with orbital involvement had nearly the same survival as patients with disease limited to the sinuses, and only one of those patients had an orbital exenteration.^[42] Hargrove *et al.* did a meta-analysis of 224 patients with orbital mucormycosis and reported no survival benefit from orbital exenteration except in patients with a fever of more than 101.5°F.^[43] Any necrotic bone should be removed if it can be performed safely. Invaded bone by AISF appears as discolored or just thinner and weaker in comparison to healthy bone. Extended endoscopic approaches are often required in AIFS. For maxillary sinus disease, it could need endoscopic medial maxillectomy, endoscopic Denker's approach, or Caldwell-Luc antrostomy. In the case of pterygopalatine or infratemporal fossa diseases, a transmaxillary approach may be needed. For frontal sinus disease, an endoscopic Draf III may be required.^[44] (T3P) Management algorithm of the AIFS is explained in Figure 2.

Antifungal therapy

Antifungal treatment should be started as early as possible once the diagnosis of AIFS is confirmed. The survival declined substantially if amphotericin is delayed by 6 days after the symptom of onset.^[45] Amphotericin B, voriconazole, and posaconazole are the most often prescribed antifungal drugs in AIFS. The medicine of choice for initial treatment is IV

amphotericin B. Posaconazole, a triazole antifungal, is the first drug in this family to demonstrate amphotericin B-like activity *in vitro* against the majority of zygomycosis.^[10] If AIFS is suspected, empirical IV antifungal therapy should be started. The result of the histopathological study will further guide the medical treatment. Although amphotericin B is considered the gold standard treatment for AIFS, it is often unfavorable due to its adverse reactions.

Liposomal amphotericin B

Liposomal amphotericin B is a lipid-associated formulation of the broad-spectrum polyene antifungal agent amphotericin B. It is active against *Candida* spp., *Aspergillus* spp., and filamentous molds like Zygomycetes.^[46] The standard antifungal therapy for AIFS is liposomal amphotericin B until mucormycosis is ruled out, at which point voriconazole or isavuconazole can be used to treat *Aspergillus*.^[46] Implementing antifungal medication with a 6-day or longer delay increases the risk of mortality by twofold.^[47]

Adjuvant therapy

Granulocyte colony-stimulating factor has been suggested for mucormycosis patients who also have hematological cancer and persistent neutropenia, but no conclusive evidence of a survival benefit has been identified.^[48] By generating oxygen free radicals, hyperbaric oxygen (HBO) has an antifungal impact.^[49] One study found that HBO significantly increased survival rates, particularly for diabetic individuals.^[49] More research is needed on iron chelation, although one study found that patients receiving desferrioxamine and liposomal amphotericin had a lower survival rate than those receiving liposomal amphotericin alone.^[50]

PROGNOSIS

The best results are achieved by patients who are diagnosed with AIFS early and receive treatment when the fungus load is minimal.^[6] Orbital and intracranial extension of the AIFS has often been found to be poor prognostic factors.^[51] The recovery of the patient's neutrophil count is the key determinant that determines the result, even though surgical debridement and antifungal medication are essential to control the condition.^[6] A multidisciplinary approach involving hematology, otolaryngology, and neuroradiology is better able to identify AIFS at an early stage, resulting in a mortality reduction from 78.6% to 7.1%. Adjuvant therapies include HBO therapy, interferon-gamma, and granulocyte-macrophage colony-stimulating factor.^[6]

PREVENTION

Immunocompromised patients should always be warned to stay away from moist areas, soil, gardening, yard work, and other activities that increase the danger of inhaling significant amounts of mold.^[6] Patients with uncontrolled diabetes mellitus, neutropenic patients, and hematopoietic or solid organ transplantation patients need close monitoring and

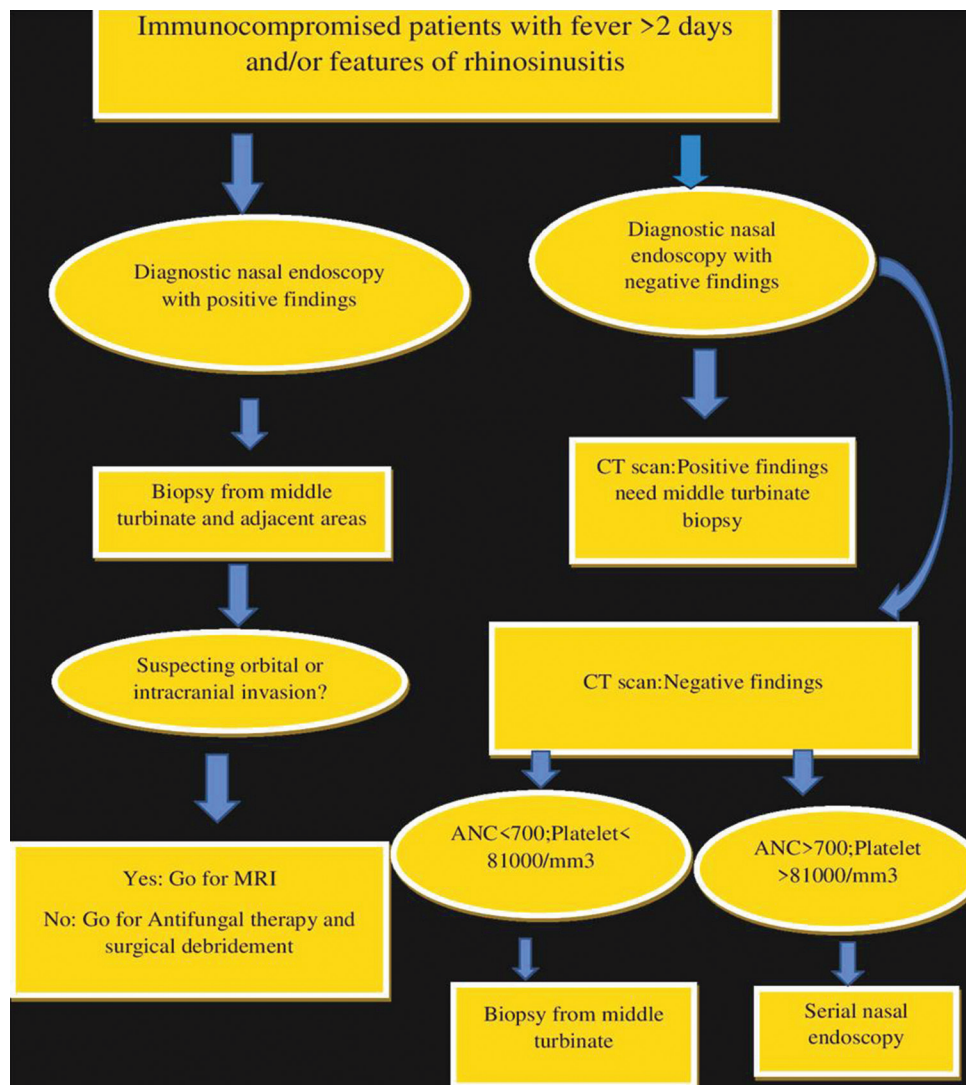


Figure 2: Management algorithm of a suspected case of AIFS. AIFS: Acute invasive fungal sinusitis

follow-up.^[52] To obtain the best glycemic control, medical treatment for uncontrolled diabetes mellitus may be necessary. The early clinical manifestations of AIFS that can aid in early management should be explained to patients. Antifungal prophylaxis is an option for individuals with neutropenia, those undergoing stem cell transplantation, and those with hematological malignancies.^[53] Daily posaconazole treatment has been found to reduce the risk of AIFS, as well as the severity of graft versus host disease in allogeneic stem cell recipients, as well as the mortality in patients with acute myelogenous leukemia or myelodysplastic syndrome.^[54] One study showed that patients at high risk of AIFS received empirical antifungal prophylaxis against zygomycetes who did not receive this treatment.^[55]

CONCLUSION

AIFS is a challenging clinical entity for health-care providers to diagnose and treat. AIFS has a rapid onset with significant disease progression in a very short period. It is often found

in patients with immunocompromised conditions such as hematological malignancy, poorly controlled diabetes, recent chemotherapy, hematopoietic stem cell transplantation, or solid organ transplantations. Typical clinical manifestations include fever, nasal congestion, facial swelling, facial pain, and rhinorrhea. AIFS is a fatal disease, with around a 50% mortality rate. Diagnostic nasal endoscopy, imaging, microbiological, and histopathological study give a definite diagnosis of AIFS. Early diagnosis and endoscopic debridement along with antifungal therapy and immunodeficiency reversal are an important part of the management and essential for improving the survival of the patient. Clinicians should be alert for symptoms of AIFS in immunocompromised patients to manage AIFS appropriately.

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Conflicts of interest

There are no conflicts of interest.

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