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Acute Invasive Fungal Sinusitis

Gamal Abdelhamid Abdelmaqsoud, Ismail Seddik Alnashar, Ahmed Abobakr Saber Mahmoud Abdallah, Tamer Abdelkader Oraby

ENT Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Ahmed Abobakr Saber Mahmoud Abdallah

Email: a.abobakr25@gmail.com

Abstract

Acute invasive fungal sinusitis (AIFS) is a rapidly progressive and life-threatening infection of the paranasal sinuses that predominantly affects immunocompromised individuals. The disease is characterized by aggressive fungal invasion of mucosal tissues and blood vessels, leading to tissue necrosis and potential extension to the orbit and intracranial structures. Predisposing factors include uncontrolled diabetes mellitus, hematologic malignancies, immunosuppressive therapy, corticosteroid use, and recent viral infections such as COVID-19. The most common causative organisms belong to the orders Mucorales and Aspergillus. Early diagnosis is challenging because initial symptoms may resemble bacterial sinusitis, yet delayed recognition significantly increases morbidity and mortality. Diagnostic evaluation relies on a combination of clinical suspicion, imaging modalities such as CT and MRI, histopathological examination, and microbiologic culture. Effective management requires a multidisciplinary approach involving prompt surgical debridement, systemic antifungal therapy—most commonly liposomal amphotericin B—and correction of underlying predisposing factors. Despite advances in diagnostic techniques and antifungal therapy, AIFS remains associated with high mortality rates, particularly in patients with severe immunosuppression or delayed treatment. Understanding the etiology, pathophysiology, clinical manifestations, diagnostic strategies, and management options is essential for improving early detection and patient outcomes. This review summarizes the current knowledge regarding acute invasive fungal sinusitis, highlighting risk factors, pathogenic mechanisms, diagnostic challenges, and contemporary therapeutic approaches.

Keywords: Acute invasive fungal sinusitis; Mucormycosis; Aspergillus; Immunocompromised patients; Antifungal therapy; Surgical debridement.

Introduction:

AIFS is a rapidly progressive, life-threatening infection driven by a combination of host factors, pathogen virulence, and environmental or iatrogenic exposures. Key predisposing factors include diabetes mellitus, immunosuppression, hematologic malignancies, corticosteroid use, COVID-19, and hospital-related exposures. The aggressive nature of the fungi is enhanced by mechanisms such as angioinvasion, tissue necrosis, and evasion of immune defenses. Clinically, AIFS causes serious complications so understanding it is essential for early recognition, risk stratification, and timely intervention. Preventive strategies, careful monitoring of high-risk patients can significantly improve outcomes, prognosis and reduce mortality of AIFS (**Spellberg et al., 2005).**

1. Etiology

Acute invasive fungal sinusitis (AIFS) is a rapidly progressive infection of the paranasal sinuses caused by opportunistic fungi that invade mucosal tissues and blood vessels. Unlike chronic fungal sinusitis, which evolves slowly, AIFS progresses within days, often leading to extensive tissue necrosis and intracranial or orbital complications if untreated. The condition is considered a medical emergency with high mortality, and understanding its etiology is essential for early recognition and targeted intervention **(petrovic et al., 2024).**

Understanding the etiology of acute invasive fungal sinusitis is crucial because it shapes both clinical and preventive approaches. Recognition of predisposing factors such as diabetes, hematologic malignancies, and immunosuppression helps physicians identify individuals at greatest risk and allows earlier intervention ***(Turner et al., 2017).***

In addition, familiarity with the fungal organisms most frequently responsible enables the timely initiation of appropriate antifungal therapy, often before laboratory confirmation is possible ***(Montone, 2016).***

On a broader scale, understanding causative mechanisms also aids in reducing incidence through targeted preventive strategies in susceptible patient populations ***(Radojicic, 2020).***

Predisposing factors

1. **Diabetes Mellitus**
   Diabetes mellitus, particularly when poorly controlled, is one of the most important predisposing factors for acute invasive fungal sinusitis. Hyperglycemia, combined with acidosis, creates an environment that enhances fungal growth and impairs the function of neutrophils, the primary defense cells against fungal invasion. Patients with diabetic ketoacidosis are especially vulnerable, as elevated glucose and acidic pH reduce the fungicidal activity of serum proteins and immune cells. These metabolic abnormalities explain why individuals with uncontrolled diabetes represent a large proportion of reported AIFS cases **(Roden et al., 2005).**
2. **COVID-19**
   Coronavirus disease 2019 (COVID-19) has emerged as a major contributor to acute invasive fungal sinusitis, particularly in individuals with severe infection requiring hospitalization. The viral illness itself causes immune dysregulation, endothelial damage, and altered iron metabolism, which together enhance susceptibility to fungal invasion. In addition, COVID-19 patients frequently experience hypoxia and metabolic disturbances that further compromise host defenses. During the pandemic, an alarming rise in COVID-19–associated mucormycosis was observed, especially in countries with high baseline diabetes prevalence, underscoring the strong relationship between viral illness and invasive fungal infections **(Singh et al., 2021).**
   The relationship between these two infections is unclear as mucormycosis were diagnosed several days to weeks after being admitted for COVID-19,and it assumes that the mucormycosis was a secondary infection arising in critically ill patients on steroids. Other cases were reported to have rhino cerebral mucormycosis and COVID-19 simultaneosly. Immunodeficiences like diapetes not only create immune imbalance that allow fungal infection to thrive, but also predispose patients to COVID-19**.(Özbek et al.,2023)**
3. **Immunosuppressive Therapy and Transplantation**
   Solid organ and hematopoietic stem cell transplant recipients are highly susceptible to AIFS due to prolonged use of immunosuppressive drugs, including corticosteroids and calcineurin inhibitors. These medications impair both innate and adaptive immune responses, reducing the host's ability to clear inhaled fungal spores. In addition, episodes of graft-versus-host disease and associated treatment regimens further heighten vulnerability. As a result, invasive fungal sinusitis remains a recognized complication in transplant populations, often with poor outcomes **(Kontoyiannis et al., 2006).**

4. **Corticosteroid Therapy as a Risk Factor**
   Corticosteroid administration is a recognized contributor to the development of acute invasive fungal sinusitis. Although effective for controlling inflammation, these drugs suppress host defenses by impairing neutrophil activity and T-cell–mediated immunity. They also raise blood glucose levels, creating an environment favorable for fungal proliferation. Prolonged or high-dose steroid therapy therefore predisposes patients to opportunistic infections. This association was particularly evident during the COVID-19 pandemic, when widespread corticosteroid use for respiratory complications was linked to increased cases of mucormycosis and related invasive fungal diseases **(Kontoyiannis et al., 2006).**
5. **Hematologic Malignancies and Chemotherapy**
   Patients with hematologic malignancies, such as leukemia and lymphoma, are at significantly increased risk for AIFS, largely due to disease-related immunosuppression and chemotherapy-induced neutropenia. Neutrophils are the primary defense against filamentous fungi, and their depletion allows fungal spores to germinate and invade sinus tissues unchecked. In addition, cytotoxic therapy damages mucosal barriers, creating additional entry points for fungal organisms. These factors combined explain why invasive fungal infections are a major complication in oncology patients **(Pagano et al., 2004).**
6. **Organ Transplantation**
   Solid organ and hematopoietic stem cell transplant recipients are also at increased risk for acute invasive fungal sinusitis due to long-term immunosuppressive therapy. Calcineurin inhibitors, corticosteroids, and other agents used to prevent graft rejection weaken host immune responses, predisposing these individuals to opportunistic fungal infections. The risk is highest in the early post-transplant period, when immunosuppression is most intense, but persists as long as immune-modulating medications are continued. Infections in transplant patients often present atypically, further complicating early recognition **(Husain et al., 2003).**

Causative organism

1. **Mucorales Species**

   The most frequent pathogens responsible for acute invasive fungal sinusitis are members of the order *Mucorales*, particularly *Rhizopus oryzae*, *Rhizomucor*, and *Mucor* species. These organisms thrive in environments with elevated glucose and acidic conditions, making them particularly aggressive in patients with diabetic ketoacidosis. Their ability to invade blood vessels and cause extensive tissue necrosis distinguishes them from many other fungi. Because of their angioinvasive nature, infections due to Mucorales progress rapidly and require urgent surgical and medical intervention **(Roden et al., 2005).**

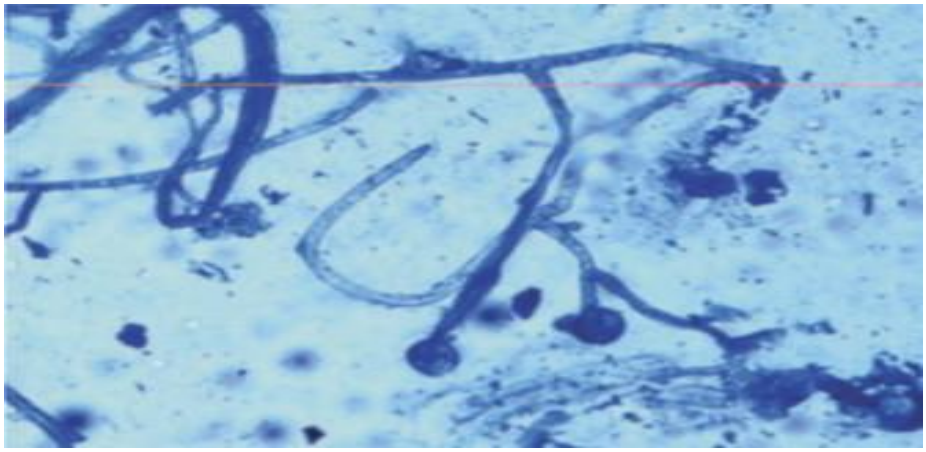

Figure 1: Rhizomucor Bacillus under microscope (Audrey Wanger et al., 2017)

2. **Aspergillus Species**
   Aspergillus species are another significant cause of AIFS, particularly in immunocompromised patients. *Aspergillus fumigatus* and *Aspergillus flavus* are the most frequent pathogens and are especially common in individuals with hematologic malignancies or prolonged corticosteroid exposure. Although the disease may initially present as localized sinus infection, vascular invasion and potential intracranial extension make it highly dangerous. Increasing antifungal resistance in *Aspergillus* adds further complexity to management **(Latgé, 1999)**
3. **Other Rare Fungi**
   Less common fungi, such as *Fusarium*, *Scedosporium*, and occasionally *Candida*, have also been implicated in cases of acute invasive fungal sinusitis. These pathogens are usually seen in severely immunocompromised individuals, including those with HIV/AIDS or post-transplant immunosuppression. Their clinical relevance lies in their frequent resistance to conventional antifungal therapies, which contributes to high mortality if diagnosis and treatment are delayed **(Nucci et al., 2002).**

Environmental Reservoirs

The fungi responsible for acute invasive fungal sinusitis are commonly found in natural and hospital environments, making exposure nearly unavoidable. *Mucorales* species, for example, are abundant in soil, decaying organic matter, and even in air conditioning and hospital construction sites. *Aspergillus* species are frequently isolated from air, dust, and stored grains. While healthy individuals typically resist infection, patients with impaired immunity or metabolic dysregulation are particularly vulnerable when exposed to these environmental reservoirs. Outbreaks have also been linked to contaminated medical supplies and hospital environments, emphasizing the importance of infection control practices in healthcare settings **(Ribes et al., 2000).**

Pathogen Virulence Mechanisms

The ability of fungi to cause acute invasive fungal sinusitis depends not only on host susceptibility but also on the virulence mechanisms of the pathogens themselves. *Mucorales* species demonstrate rapid growth, strong tissue tropism, and marked angioinvasion, leading to vessel thrombosis and tissue necrosis. Their spores can also bind to endothelial receptors, enhancing vascular invasion. *Aspergillus* species produce small conidia that readily penetrate deep into the respiratory tract, where they release proteolytic enzymes and mycotoxins that damage epithelial barriers. Additionally, both groups of fungi can evade host immune defenses by resisting oxidative killing from phagocytes. These combined mechanisms explain the aggressive tissue destruction and high mortality associated with AIFS **(Ibrahim et al., 2012).**

2.Pathophysiology

The pathophysiology of acute invasive fungal sinusitis is characterized by a combination of host vulnerability and fungal aggression. Once fungal spores are inhaled into the nasal cavity or sinuses, impaired host immunity allows unchecked germination and hyphal invasion. A key mechanism is angioinvasion, where fungal hyphae penetrate blood vessels, leading to vascular thrombosis, tissue ischemia, and necrosis. This vascular involvement not only promotes rapid tissue destruction but also facilitates hematogenous dissemination to the orbit and brain. The combination of local ischemia and impaired immune cell recruitment creates an environment where the fungi can expand aggressively, resulting in the fulminant clinical course typical of AIFS **(Spellberg et al., 2005).**

How Fungi Invade Mucosa and Blood Vessels

In acute invasive fungal sinusitis, infection begins when fungal spores adhere to and penetrate the nasal or sinus mucosa. Normally, epithelial barriers and innate immune cells provide protection, but in immunocompromised or metabolically dysregulated hosts, these defenses are impaired. *Mucorales* species exploit host cell receptors, such as glucose-regulated protein 78 (GRP78), to attach and invade epithelial and endothelial cells. Once hyphae breach the

mucosa, they extend into blood vessels, where they induce endothelial damage and trigger platelet adhesion and thrombosis. This vascular invasion restricts blood supply, leading to ischemia and necrosis of surrounding tissue. Angioinvasion also creates a route for fungal dissemination into the orbit and central nervous system, accounting for the high morbidity and mortality associated with the disease **(Ibrahim et al., 2010)**

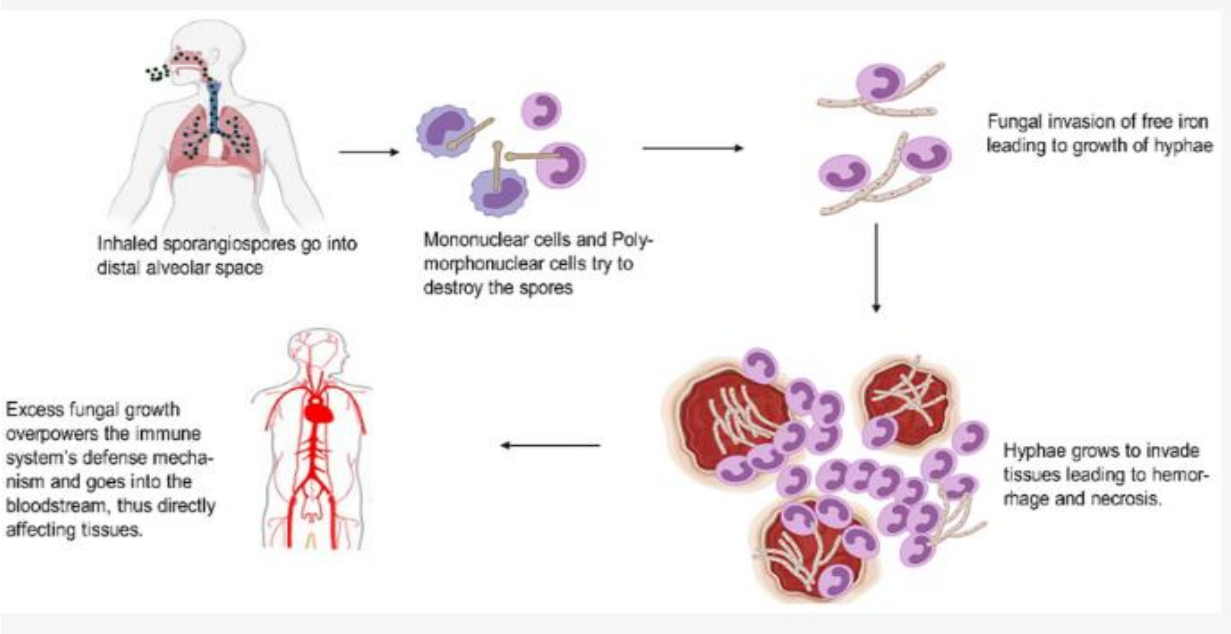

Figure 2: Pathophysiology of Mucormycosis (Asdaq et al., 2021)

Role of Impaired Neutrophil Function

Neutrophils are the primary defense cells against filamentous fungi, playing a critical role in controlling hyphal growth through phagocytosis and oxidative killing. In patients with neutropenia or neutrophil dysfunction, such as those receiving chemotherapy, corticosteroids, or suffering from uncontrolled diabetes, this defense mechanism is significantly weakened. Reduced oxidative burst activity and impaired chemotaxis allow fungi like *Mucorales* and *Aspergillus* to proliferate unchecked, invade blood vessels, and disseminate rapidly. The strong correlation between neutropenia and invasive fungal infections highlights the pivotal role of neutrophils in preventing AIFS **(Chamilos et al., 2008).**

Angioinvasion and Tissue Necrosis

A defining feature of acute invasive fungal sinusitis is the ability of fungal hyphae to invade blood vessels, a process known as angioinvasion. Once inside the vasculature, the hyphae cause direct endothelial injury, leading to platelet aggregation, vascular occlusion, and thrombosis. This results in reduced blood supply, ischemia, and extensive tissue necrosis, which not only facilitates fungal growth but also impairs the delivery of immune cells and antifungal drugs to the infected site (**Waldman et al., 2021).**

The ischemic environment therefore creates a vicious cycle of uncontrolled invasion and tissue destruction, explaining the rapid progression and poor prognosis of AIFS if not treated promptly **(Cornely et al., 2019).**

Iatrogenic and Environmental Factors

Iatrogenic and environmental factors also contribute significantly to the development of acute invasive fungal sinusitis. Prolonged hospitalization and use of invasive devices such as endotracheal tubes or central venous catheters can increase the risk of fungal invasion by disrupting natural barriers and exposing patients to nosocomial fungal spores **(Weber et al., 2007).**

Environmental conditions, such as construction or demolition activities in healthcare settings, can elevate airborne fungal spore concentrations, thereby heightening exposure risks for immuno-compromised individuals **(Kanamori et al., 2017).**

Furthermore, inadequate ventilation and high humidity in hospital wards may facilitate fungal proliferation. Collectively, these iatrogenic and environmental elements act as important co-factors, particularly in patients with underlying immunosuppression **(Nucci & Anaissie, 2007).**

1. Hospital Environment (Contaminated Air Filters, Humidifiers)
   The hospital environment itself may act as a reservoir for fungal pathogens contributing to acute invasive fungal sinusitis. Contaminated air filtration systems, poorly maintained ventilation ducts, and humidifiers have all been implicated in outbreaks of fungal infections within healthcare facilities. These systems can harbor spores of *Aspergillus* and other opportunistic fungi, which are then dispersed into patient care areas, especially affecting individuals with compromised immunity **(Anaissie et al., 2003).**
2. Broad-Spectrum Antibiotic Overuse
   Excessive use of broad-spectrum antibiotics has been recognized as a major iatrogenic factor predisposing patients to acute invasive fungal sinusitis. By suppressing the normal bacterial flora of the upper respiratory tract and paranasal sinuses, prolonged antibiotic therapy disrupts the microbial balance, creating an ecological niche favorable for fungal overgrowth. This alteration reduces colonization resistance and enhances fungal adherence to mucosal surfaces, increasing the likelihood of invasive infection in immunocompromised individuals. The risk is particularly pronounced in patients receiving empirical or prophylactic antibiotics for extended periods during hospitalization **(Baddley et al., 2001)**
3. Medical Interventions (Nasal Packing, Intubation)
   Certain medical interventions, such as nasal packing and endotracheal intubation, can inadvertently increase the risk of acute invasive fungal sinusitis. These procedures disrupt the integrity of the nasal or sinus mucosa, providing a direct portal of entry for fungal spores. Additionally, they may create localized areas of ischemia or reduced mucociliary clearance, conditions that favor fungal adherence and hyphal invasion. In hospitalized or immuno-compromised patients, even brief exposure to contaminated instruments or materials can precipitate severe fungal infections. Awareness of these risks is crucial for clinicians, who should employ strict aseptic techniques and monitor high-risk patients closely **(Baddley et al., 2001).**

3.Clinical presentation

Acute invasive fungal sinusitis typically presents as a rapidly progressive infection affecting the paranasal sinuses and surrounding structures. The disease course is often fulminant, evolving over days to weeks, and can result in serious complications if not recognized promptly. Patients usually present with nonspecific sinonasal symptoms initially, such as nasal congestion, rhinorrhea, facial pain, or headache. However, due to the angioinvasive nature of the causative fungi, these mild early symptoms can quickly escalate to severe local and systemic manifestations **(Spellberg et al., 2005).**

Nasal and Sinus Manifestations

Local sinonasal involvement is usually the earliest and most consistent clinical feature. Patients may report unilateral nasal obstruction, purulent discharge, and crusting, often with black or necrotic tissue visible in the nasal cavity. Epistaxis is also common due to vascular invasion. Facial swelling, tenderness over the affected sinus, and periorbital edema frequently accompany these symptoms. The rapid progression of necrosis can be visualized as black eschars on the palate or turbinates, a hallmark feature indicative of angioinvasive fungal activity **(Roden et al., 2005)**

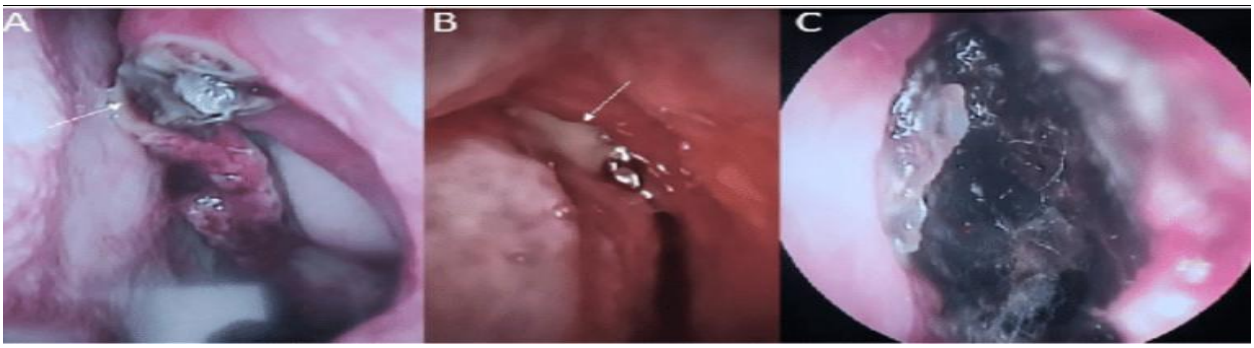

Figure 3: Black crustations and necrotic tissue on turbinates (kumari et al., 2019).

Orbital Involvement

Invasion into the orbit is a serious complication of AIFS, often occurring within days of symptom onset. Clinical signs include proptosis, periorbital swelling, chemosis, ophthalmoplegia, and sudden vision loss. These manifestations result from fungal angioinvasion causing thrombosis of orbital vessels, ischemia, and nerve compression. Rapid recognition of orbital involvement is crucial, as delayed intervention can lead to irreversible vision loss and increased mortality **(Chakrabarti et al., 2009).**

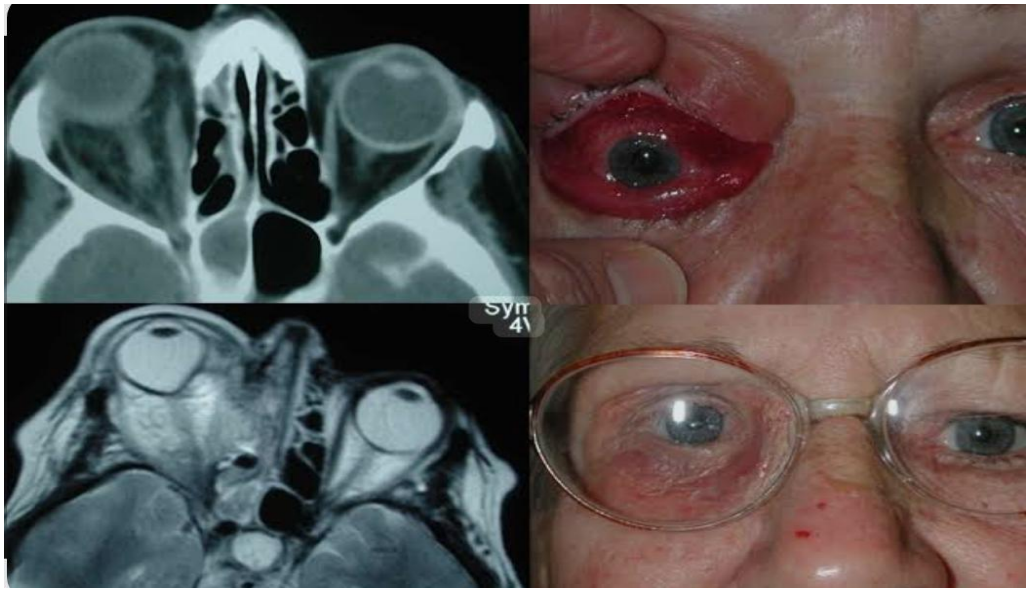

Figure 4: orbital involvement in AIFS (lee et al., 2019).

Palatal and Oral Findings

The palate is often involved in AIFS, especially in patients with uncontrolled diabetes or immunosuppression. Palatal necrosis manifests as black eschar formation or ulceration, usually on the hard palate. Patients may experience sudden

tooth mobility or maxillary pain. These oral findings often precede more extensive orbital or intracranial involvement, serving as an early clinical clue for physicians **(Chamilos et al., 2008)**

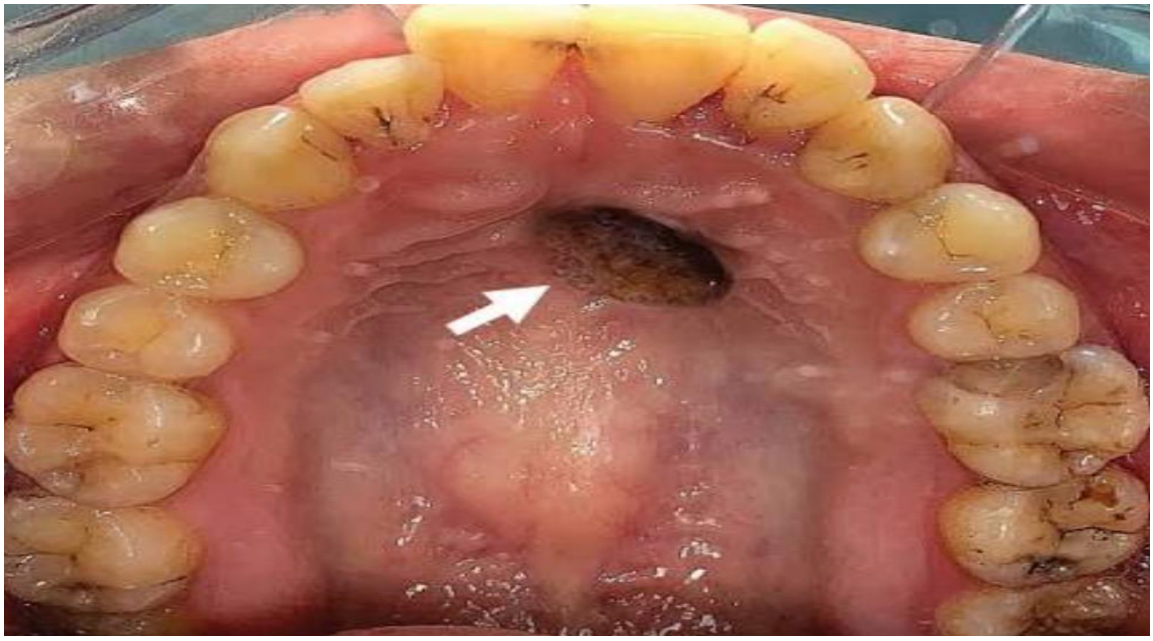

Figure 5: Palatal eschars in AIFS *(Venugopal & Marya, 2021).*

Intracranial Complications

Intracranial extension represents a life-threatening progression of AIFS. Patients may develop headache, altered mental status, cranial nerve deficits, or focal neurological signs, reflecting involvement of the cavernous sinus, brain parenchyma, or meninges. Angioinvasion facilitates rapid fungal spread from the paranasal sinuses to the intracranial compartment. Early detection with imaging and clinical suspicion is critical, as intracranial involvement significantly worsens prognosis **(Kontoyiannis et al., 2006).**

Systemic and Fever Symptoms

Although local findings predominate, systemic symptoms such as fever, malaise, and fatigue are common, particularly in immunocompromised patients. Fever may be the initial presenting feature in neutropenic patients, even before localized necrosis is evident. The combination of systemic signs and rapidly progressing local tissue destruction often distinguishes AIFS from chronic or noninvasive fungal sinusitis **(Spellberg et al., 2005)**

The clinical manifestations of AIFS are closely linked to underlying predisposing factors. Diabetic patients often present with palatal and orbital necrosis, whereas neutropenic or transplant patients may have subtle early mucosal changes but rapid systemic spread. COVID-19–associated cases frequently show aggressive orbital involvement. Recognizing these patterns in high-risk populations allows clinicians to maintain a high index of suspicion and initiate early diagnostic and therapeutic measures **(Singh et al., 2021).**

Late manifestations of AIFS typically indicate extensive local invasion and systemic involvement. As the infection progresses, patients may develop severe facial edema, extensive necrosis of the palate or nasal septum, and black eschar formation that can extend beyond the initial sinus region. Orbital involvement becomes more pronounced, with worsening proptosis, ophthalmoplegia, and complete vision loss in severe cases. Intracranial extension may present as altered mental status, seizures, or focal neurological deficits, reflecting cavernous sinus thrombosis, brain abscess, or meningitis. The presence of these late signs often correlates with delayed diagnosis and carries a significantly worse

prognosis, emphasizing the need for early recognition of initial symptoms in high-risk patients **(Chakrabarti et al., 2009)**

Complications of Acute Invasive Fungal Sinusitis

Acute invasive fungal sinusitis can result in severe and potentially life-threatening complications if not diagnosed and treated promptly. The most common complications include orbital involvement leading to vision loss, cranial nerve deficits, and proptosis due to angioinvasion and tissue necrosis. Intracranial extension may cause meningitis, cavernous sinus thrombosis, brain abscess, or stroke, significantly increasing morbidity and mortality. Systemic dissemination can also occur, particularly in immunocompromised patients, affecting organs such as the lungs and kidneys. Early recognition and aggressive management are crucial to prevent these complications, and prognosis worsens dramatically once these advanced sequelae develop **(Kontoyiannis et al., 2006).**

4.Diagnosis of Acute Invasive Fungal Sinusitis

Diagnosis of AIFS is challenging due to its rapid progression and nonspecific early symptoms. Early recognition relies on a high index of suspicion in at-risk populations, including patients with diabetes, hematologic malignancies, or immunosuppression. Because initial clinical signs may mimic bacterial sinusitis, delayed diagnosis is common, contributing to high morbidity and mortality. Rapid assessment using a combination of clinical evaluation, imaging studies, and microbiological confirmation is critical for timely intervention **(Spellberg et al., 2005)**

1. **Clinical Suspicion**
   Clinical suspicion is the first step in diagnosing AIFS. High-risk patients presenting with facial pain, nasal obstruction, black nasal eschars, or rapid progression of symptoms should be evaluated urgently. Orbital symptoms such as proptosis, ophthalmoplegia, or sudden vision changes increase suspicion of orbital or intracranial extension. Early recognition relies on clinicians correlating these findings with underlying risk factors like immunosuppression, steroid use, or COVID-19–related vulnerability **(Chakrabarti et al., 2009)**
2. **Laboratory Finding**
   Laboratory tests provide supportive evidence but are rarely diagnostic on their own. Complete blood counts may reveal neutropenia or leukocytosis, reflecting host immune status. Also ELISA can be used to detect antibodies against Rhizomucor bacillus and other species **(Gupta et al 2022).**
3. **Histopathology**
   Definitive diagnosis often requires tissue biopsy for histopathologic examination, which demonstrates broad, ribbon-like, non-septate hyphae in Mucorales infections or septate hyphae in Aspergillus infections. Special staining techniques, such as Periodic acid–Schiff (PAS) or Gomori methenamine silver (GMS), are commonly used to highlight fungal elements. Histopathology not only confirms infection but also distinguishes AIFS from chronic or noninvasive fungal sinusitis **(Roden et al., 2005)**

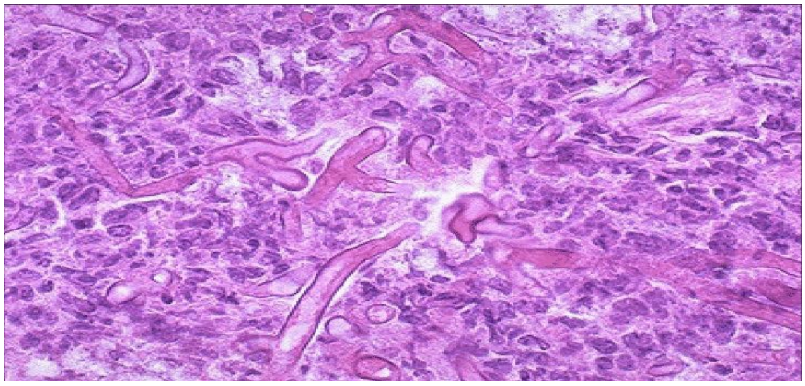

Figure 6: Histopathology smear showing hyphae of Mucor (kalidas et al., 2014)

4. Imaging

Computed tomography (CT) is the primary imaging modality for evaluating sinonasal involvement in AIFS. CT scans can detect bony erosion, sinus opacification, and orbital extension, which are indicative of aggressive fungal invasion. Non-enhanced CT is particularly useful for visualizing bone destruction, while contrast-enhanced CT can identify vascular involvement and early soft tissue changes. Imaging guides the extent of surgical debridement and helps in planning therapy **(Patel et al., 2020)**

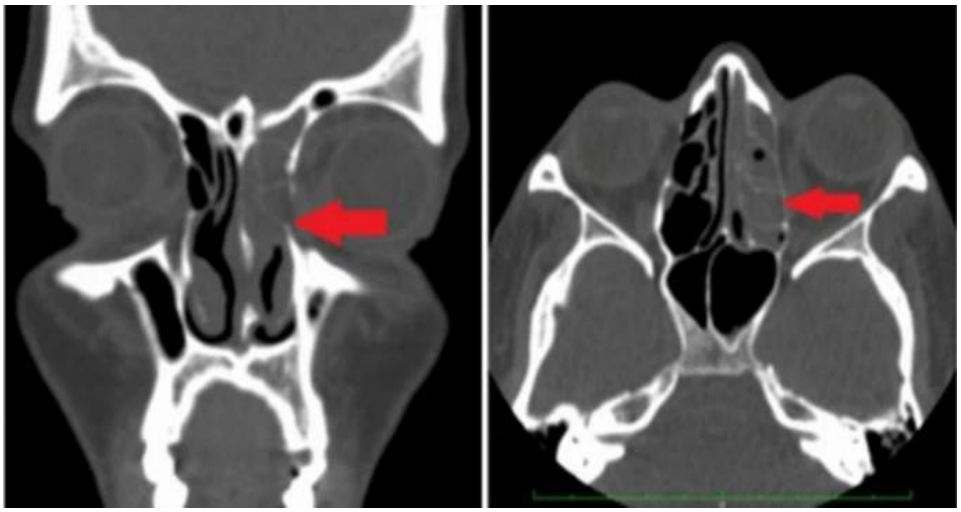

Figure 7: CT scan showing total opacification of left frontal, ethmoid and maxillary sinus in mucormycosis (Saldanha M et al., 2021).

Magnetic resonance imaging (MRI) complements CT by providing superior soft tissue contrast and detecting early orbital or intracranial involvement. MRI is particularly sensitive for assessing perineural spread, cavernous sinus thrombosis, and brain abscesses. T1-weighted images can identify tissue necrosis, while T2-weighted sequences highlight edema and inflammatory changes. Contrast-enhanced MRI further delineates viable versus necrotic tissue, aiding in surgical planning **(Kumar et al., 2019).**

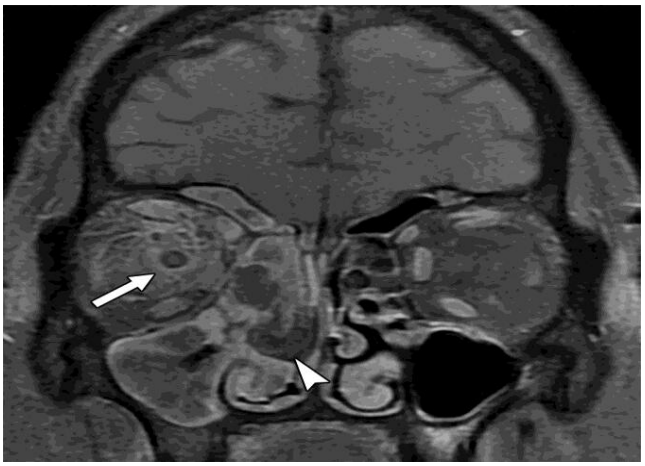

Figure 8: Coronal contrast-enhanced fat-saturated T1-weighted MR image shows hypo enhancing mucosal thickening involving right maxillary sinus with nonenhancing right middle turbinate (*arrowhead*), consistent with black turbinate sign (Joshi et al.,2021).

5. Microbiologic Culture

Microbiologic culture remains a critical adjunct to histopathology for species identification. Tissue samples are cultured on Sabouraud dextrose agar or other fungal media to isolate Mucorales or Aspergillus species. Culture allows antifungal susceptibility testing, which is particularly important in resistant Aspergillus infections. However, culture sensitivity is limited because Mucorales are fragile and may fail to grow, making histopathology essential for rapid diagnosis **(Kontoyiannis et al., 2006).**

Tissue samples obtained via biopsy or debridement are inoculated on fungal media such as Sabouraud dextrose agar, potato dextrose agar, or brain-heart infusion agar. Mucorales species typically grow rapidly within 24–48 hours, producing cottony, grayish-white colonies, whereas Aspergillus species often take 3–5 days to develop characteristic septate hyphae and conidial structures. **(Roden et al., 2005)**

Figure 9: Cottony-fluffy growth of *Rhizopus arrhizus* on SDA agar (Gupta et al 2022).

Diagnostic Challenges

Diagnosing acute invasive fungal sinusitis is notoriously challenging due to its rapid progression and nonspecific early symptoms. Early-stage AIFS may mimic bacterial sinusitis, allergic rhinitis, or viral upper respiratory infections, leading to misdiagnosis. Immunocompromised patients often present with subtle mucosal changes without classic necrosis, delaying suspicion. Additionally, tissue cultures may yield false negatives because Mucorales are fragile and may not survive transport, and overgrowth of contaminant organisms can obscure true pathogens. Imaging may also be inconclusive in the early phase, as bone destruction or soft tissue involvement might not yet be apparent. These challenges necessitate a high index of clinical suspicion and early biopsy for histopathologic confirmation to avoid treatment delays **(Spellberg et al., 2005)**

Early vs. Late Diagnostic Findings

Early diagnostic findings in AIFS often include subtle mucosal discoloration, mild nasal obstruction, or localized facial pain. Black eschars, palatal ulcers, or necrosis of turbinates typically appear later, marking advanced tissue invasion. Radiologically, early CT or MRI may reveal minimal sinus opacification or soft tissue swelling, whereas late imaging shows bony erosion, orbital involvement, or intracranial extension. Laboratory findings, such as neutropenia, may be present at both stages but are more pronounced in late disease due to systemic involvement.

Recognizing these early clinical and radiologic clues is critical, as delayed diagnosis is associated with rapid progression and higher mortality **(Chakrabarti et al., 2009)**

Integration of Clinical, Radiologic, and Laboratory Data

Optimal diagnosis of AIFS relies on integrating clinical assessment with radiologic and laboratory findings. High-risk patients with suspicious clinical signs should undergo prompt imaging, including CT to evaluate bony involvement and MRI to assess soft tissue and orbital or intracranial spread. Tissue biopsy remains the gold standard, with histopathology confirming fungal invasion and culture identifying the species. Laboratory data, such as complete blood counts, inflammatory markers, and immune function tests, provide additional context regarding the patient's vulnerability and disease severity. The combined approach enhances diagnostic accuracy, guides surgical planning, and informs timely initiation of antifungal therapy, which is crucial to reducing morbidity and mortality **(Prakash et al., 2019).**

5.Management

Management of AIFS is challenging due to its rapid progression and high morbidity. Successful treatment requires a combination of **early diagnosis, reversal of underlying predisposing factors, prompt surgical intervention, and systemic antifungal therapy**. Mortality remains high, particularly when therapy is delayed or in immuno-compromised patients. Therefore, a multidisciplinary approach involving otolaryngologists, infectious disease specialists, ophthalmologists, and critical care teams is essential to optimize outcomes **(Spellberg et al., 2005).**

A critical initial step in management involves correcting or mitigating underlying risk factors. Hyperglycemia should be aggressively controlled in diabetic patients, and immunosuppressive therapies, such as corticosteroids or chemotherapy, should be minimized if clinically feasible. Neutropenic patients may benefit from granulocyte colony-stimulating factors to enhance host immunity. Addressing these factors not only improves the patient's ability to fight infection but also increases the efficacy of antifungal agents **(Roden et al., 2005).**

Surgical Management (Endoscopic)

Surgical debridement is a cornerstone of AIFS treatment. Early and aggressive removal of necrotic tissue reduces fungal burden and prevents further angioinvasion and orbital or intracranial extension. Endoscopic sinus surgery is often preferred for limited disease, while extensive involvement may require open approaches such as maxillectomy or orbital exenteration. Surgery should be guided by imaging and intraoperative findings, aiming to remove all necrotic tissue while preserving vital structures whenever possible **(Chakrabarti et al., 2009).**

Endoscopic surgery offers several advantages. It is less invasive, preserves normal anatomy, and reduces postoperative recovery time. It also facilitates **repeated interventions**, which may be necessary in rapidly progressing cases or when residual disease is detected on follow-up imaging. Surgeons can employ angled endoscopes and specialized instruments to reach difficult-to-access areas such as the sphenoid sinus, posterior ethmoid, or pterygopalatine fossa, which are often involved in AIFS (**Kumar et al., 2019).**

However, endoscopic management requires expertise and careful judgment. Extensive involvement of the orbit, skull base, or intracranial structures may necessitate combined endoscopic and open approaches. Preoperative imaging with CT or MRI is essential to plan the extent of debridement and avoid injury to critical neurovascular structures. Intraoperative frozen section biopsy can also guide the surgeon in identifying margins of viable versus necrotic tissue **(Patel et al., 2020).**

Endoscopic surgery is not only therapeutic but also diagnostic, as tissue obtained during the procedure can be sent for histopathology and culture, confirming the diagnosis and guiding antifungal therapy. Frequent postoperative surveillance with endoscopy ensures complete removal of necrotic tissue and early detection of recurrence, which is critical for improving outcomes in high-risk patients **(Cornely et al., 2007)**

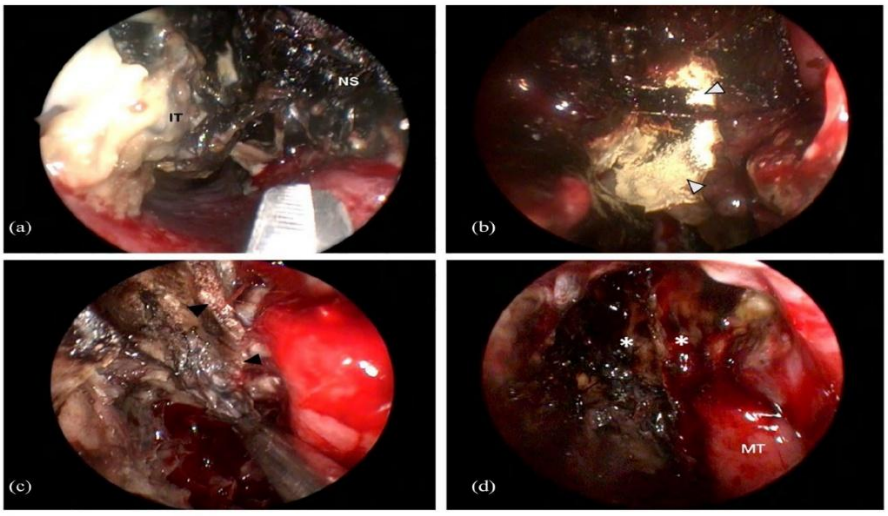

Figure 10: Mucormycosis in in type 2 diabetes patient (Chussi et al., 2022)

Antifungal Therapy

Systemic antifungal therapy should be initiated immediately once AIFS is suspected. Liposomal amphotericin B is the first-line agent due to its efficacy against Mucorales species and favorable tissue penetration. Typical dosing ranges from 5 to 10 mg/kg/day, adjusted for renal function. Early initiation of amphotericin B has been shown to significantly reduce mortality. In patients intolerant to amphotericin B, alternatives such as posaconazole or isavuconazole may be considered, particularly as step-down therapy after initial stabilization **(Cornely et al., 2007)**

In selected cases, combination antifungal therapy may be employed to enhance efficacy. For example, amphotericin B combined with echinocandins has been investigated, though clinical evidence remains limited. Following initial control, step-down therapy with oral agents such as posaconazole or isavuconazole allows prolonged treatment while minimizing hospitalization. Duration of therapy is typically individualized based on immune status, radiologic improvement, and surgical outcomes, often lasting several weeks to months **(Petrikkos et al., 2012).**

Close monitoring is required to assess therapeutic response and detect recurrence. Clinical examination, serial imaging, and repeat endoscopy allow evaluation of residual disease. Laboratory markers, such as renal function and inflammatory parameters, guide the safety of ongoing antifungal therapy. Early detection of treatment failure permits timely escalation, including re-debridement or adjustment of antifungal regimens. Long-term follow-up is particularly important for patients with persistent immunosuppression or structural sinonasal defects **(Cornely et al., 2007).**

Postoperative evaluation of visual acuity

Visual acuity assessment is a crucial aspect of post-operative care in patients with acute invasive fungal sinusitis, particularly in cases involving orbital extension. Orbital involvement can lead to optic nerve compression, ischemia, or direct fungal invasion, making early detection and monitoring of visual changes essential. Post-operatively, patients undergo baseline and serial ophthalmologic evaluations, including visual acuity testing, pupillary reactions, intraocular pressure measurements, and fundoscopic examination. These assessments help detect early deterioration or improvement in vision following surgical debridement and antifungal therapy. **(Patel et al., 2020)**

Post-operative care also includes **optimization of underlying conditions**, such as strict glycemic control in diabetics and careful management of immunosuppressive medications, to reduce the risk of recurrence. Long-term follow-up may extend for several months to ensure complete resolution and to allow planning for reconstructive procedures in cases with extensive tissue loss **(Cornely et al., 2007).**

6.Prognosis

The prognosis of acute invasive fungal sinusitis depends heavily on timing of diagnosis, underlying comorbidities, and adequacy of treatment. Early recognition and prompt initiation of antifungal therapy, combined with aggressive surgical debridement, are strongly associated with improved survival. Conversely, delayed diagnosis, particularly in immunocompromised patients, significantly increases mortality, which can range from 30% to over 70% depending on the extent of disease and host factors. Overall, prognosis is closely tied to the ability to rapidly control fungal invasion and manage underlying predisposing conditions **(Spellberg et al., 2005)**

Factors affecting prognosis

1. **Host Immune Status**
   One of the most critical determinants of prognosis in acute invasive fungal sinusitis is the patient's immune status. Immunocompromised individuals—such as those with hematologic malignancies, post-transplant immunosuppression, or prolonged corticosteroid therapy—have a significantly higher risk of mortality. Neutropenia and impaired neutrophil function reduce the body's ability to contain fungal invasion, making early detection and aggressive therapy essential. Conversely, immunocompetent patients with localized disease typically have better outcomes **(Spellberg et al., 2005).**
2. **Extent of Disease**
   The anatomical spread of infection heavily influences prognosis. Disease confined to the nasal cavity or paranasal sinuses is associated with higher survival rates compared to cases with orbital or intracranial extension. Orbital involvement increases the risk of permanent vision loss, whereas intracranial invasion is a strong predictor of mortality due to complications like cavernous sinus thrombosis, meningitis, or cerebral abscess **(Chakrabarti et al., 2009)**
3. **Timeliness of Diagnosis and Intervention**
   Early recognition and rapid initiation of therapy are pivotal in improving prognosis. Delays in diagnosis allow the fungus to invade blood vessels, leading to angioinvasion, tissue necrosis, and rapid progression. Prompt surgical debridement combined with systemic antifungal therapy significantly reduces mortality, whereas delayed intervention correlates with poor outcomes **(Cornely et al., 2007)**
4. **Underlying Comorbidities**
   Chronic diseases such as diabetes mellitus, particularly with ketoacidosis, significantly worsen prognosis. Hyperglycemia and acidic serum promote fungal growth and impair phagocyte function. Other comorbid conditions like renal insufficiency, liver disease, or malnutrition further compromise the patient's ability to respond to infection and tolerate antifungal therapy, increasing mortality risk **(Roden et al., 2005)**
5. **Effectiveness of Surgical Debridement**
   The urgency and extensiveness of the debridement are critical prognostic factors; delays often allow the infection to progress into vital structures like the orbits and brain, drastically reducing survival rates. While disfiguring, this aggressive approach is lifesaving. Ultimately, the highest success rates are achieved through a multimodal strategy where thorough and early surgical debridement is combined with prompt systemic antifungal therapy and, when possible, reversal of underlying immunosuppression **(Roden et al., 2005).**
6. **Choice and Timing of Antifungal Therapy**

   The type, dosage, and timing of systemic antifungal therapy also influence outcomes. Liposomal amphotericin B initiated early is associated with better survival, while delays or suboptimal dosing can allow rapid fungal dissemination. Step-down therapy with posaconazole or isavuconazole provides prolonged coverage, particularly in patients with ongoing immunosuppression **(Kontoyiannis et al., 2006)**

7. **COVID-19 and Steroid-Related Risk**
   COVID-associated mucormycosis often presents with more aggressive disease, including rapid orbital and intracranial invasion, necessitating prompt multidisciplinary intervention to improve survival **(Patel et al., 2020).**

Survival rate

Survival rates in acute invasive fungal sinusitis vary widely and are influenced by host factors, disease extent, timeliness of intervention, and adequacy of therapy. Overall mortality is reported between 30% and 70%, with immunocompromised patients and those with delayed diagnosis experiencing the highest mortality **(Spellberg et al., 2005).**

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