



## Acute Invasive Fungal Rhinosinusitis

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Numerous fungi are present almost everywhere in the environment, which numbers approximately 80,000 species. But, mycosis is not very common condition; only approximately 400 species are medically important and 50 of them produce more than 90% infection in man & other animals<sup>1</sup>.

Fungal Rhinosinusitis may be invasive or noninvasive. Acute invasive fungal rhinosinusitis (AIFR) is an emergency condition which may be either sinonasal or pulmonary in type. The organisms responsible for AIFR may be aspergillus, mucorales, candida, Curvularia or fusarium. Aspergillus (*A. Fumigatus*) and *Mucor* are the commonest ones<sup>2</sup>. *Mucor* is more common in diabetic patients and in others *Aspergillus* is more common<sup>3-6</sup>.

### **Pathogenesis:**

In an immunocompetent individual after inhalation from the environment spores phagocytosed & killed by neutrophils & macrophages and thus unable to produce the disease. In immune-compromised state number or function (chemotactic & phagocytic activities) of neutrophils and macrophages are compromised enough to kill the organisms. Then they grow, colonize and invade the nasal mucosa and deeper tissue, vessels and perineural tissue<sup>7</sup>. It spreads locally by invasion into the surrounding tissues rapidly

– nasal septum, lateral wall of nose, paranasal sinuses, palate, alveolar process, orbit, skull base and intracranial structures<sup>8,9</sup>.

Vascular invasion causes vasculitis and thrombosis which leads to pallor and then blackish discoloration of nasal mucosa. Perineural invasion causes anaesthesia of nasal mucosa. Ischemic necrosis of bones causes brittleness of involved bones resulting in septal destruction, palatal perforation, loosening or loss of teeth and oronasal or oroantral fistulae. Orbital spread may involve orbital fat, vessels, muscles and nerves resulting in pain, ptosis, ophthalmoplegia and blindness<sup>10</sup>. Intracranial spread can occur by direct spread by bone erosion, perineural spread or by vascular spread, particularly to cavernous sinus. Cavernous sinus thrombosis can result in involvement of 3<sup>rd</sup> to 6<sup>th</sup> cranial nerves, orbital congestion and swelling, and thrombosis of cavernous carotid and branches of circle of Willis resulting in cerebral and brain stem infarction.

Risk factors included diabetes mellitus, metabolic acidosis, cytotoxic chemotherapy, long standing systemic steroid therapy, hematological malignancy, aplastic anemia, organ transplantation, HIV/AIDS, iron overload and treatment with deferoxamine, malnutrition and severe covid-19 infection<sup>4,11,12</sup>.

**Diagnosis:**

Diagnosis is based on clinical features, nasoendoscopy, laboratory tests, direct microscopy, biopsy, culture, RT-PCR and imaging: CT, MRI in different combinations in different individuals and different situations.

Clinical features, their severity and course depends on the pattern of invasion, structures involved and degree of compromised immunity. Patients may present with fever, nasal congestion, facial pain, headache, crusting, blood stained nasal discharge, palatal/alveolar process involvement and in more advanced case with features of orbital presentations & intracranial extension<sup>4,7,13,14</sup>.

**Clinical suspicion may be based on:**

- Febrile neutropaenia with facial pain (+ Nasal congestion + Orbital sign)
- Fever of unknown origin fails to respond to 48 hrs of IV broad spec. antibiotics
- Recent H/O severe Covid-19 with H/O DM, Steroid, ICU & other comorbidities

**Nasoendoscopy Reveals:**

- Anaesthesia anolor of nasal mucosa in early stage
- Black discolouration with crusting, ulceration and granulation later
- Septal perforation, palatal perforation, Denude dead bone in more advanced cases

Cases with orbital involvement may present with one or more of presentations like proptosis, orbital pain, ophthalmoplegia, ptosis, diplopia and loss vision<sup>4,7</sup>.

Cases with CNS involvement may present with headache, neurological deficit, seizures, coma altered mental status, features of cavernous sinus thrombosis and in very advanced stage cerebral and brain stem infarction.

In some cases, nasoendoscopy may be essentially normal

High degree of suspicion is of paramount importance in an immunocompromised patient for prompt diagnosis and management

**Laboratory Diagnosis:**

Microscopic examinations of nasal swab/debris can be done for identification of fungus and its species. But, biopsy and histological examination are essential for definitive diagnosis i.e. to see its tissue invasion in addition to identification of fungus and its species. Biopsy is taken from multiple sites, specially from MT & Septum. Histopathological examination is done by hematoxylin and eosin stain.

Frozen section may be helpful to avoid delay in diagnosis and treatment. It provides rapid evidence of invasiveness with high degree of sensitivity & specificity in comparison to gold standard permanent section. There is no significant difference in sensitivity & specificity between aspergillus and mucor in the case of frozen section test<sup>15</sup>.

Species identification is essential to select the specific antifungal drug. Hyphae are typical and specific for each species.

Aspergillus shows Regular branching, Even thickness, Narrow hyphae (4 µm), Septate hyphae. Fungal hyphae with dichotomous branching diagnostic of aspergillus species are depicted Mucor shows Broad ribbon-like, non-septate hyphae (10-15 µm in width) with uneven thickness.

Tissue invasion/angioinvasion is hallmark for AIFR

**Fungal Culture:** Aims of culture are confirmation of species and to see the sensitivity to antifungal drugs. It has high false positive rate and false negative rates. It commonly fails to have fungal growth<sup>16</sup>.

**CT scan** is an effective screening tool in diagnosing AIFR. should be done in all cases to know involvement at presentation and in follow up cases. It may show:

- Hypoattenuating unilateral sinus and nasal mucosal thickening / complete nasal cavity obliteration (early)
- Focal bony erosion (later)
- Lacks sinus expansion
- Thickening/ obliteration of periantral fat planes (later)
- Orbital / intracranial extension of opacification in advanced cases

In advanced stages there may be more disease outside than inside the sinus<sup>17</sup>.

AIFR correlates most strongly with disease involvement in pterygopalatine fossa, periantral fat, nasolacrimal duct and lacrimal fossa<sup>2</sup>.

**MRI** gives a better assessment of soft tissue involvement particularly in early cases like:

- Obliteration of periantral fat plane
- Early mucosal and skin involvement
- Early orbital fat and extraocular muscle involvement and
- Cerebral involvement like leptomeningeal involvement, abscess, granuloma or infarcts (due to thrombosis of ICA or its branches)

In comparison to MRI is found to have relatively higher sensitivity and PPV for AIFR<sup>18,19</sup>.

Postcontrast MRI shows foci of non-enhancement in the nasal cavity which would be present in normal mucosa. This is called black turbinate sign<sup>20</sup>.

**Management:**

Medical and surgical management should be started immediately and simultaneously.

Early and aggressive surgical debridement, systemic antifungal therapy and management of underlying disease is the cornerstone of the management of AIFR<sup>5,10</sup>.

Improvement of host immune status and general condition includes:

- \* Strict control of blood sugar level
- \* Correction of ketoacidosis
- \* Reversal of neutropenia, if possible (improves survival)
- There may be a role of Granulocyte Colony Stimulating Factor<sup>3,21</sup>.
- \* Improvement of general condition (anaemia, protein deficiency, dehydration, electrolyte imbalance & other comorbidities)

#### **Systemic antifungal drugs:**

Amphotericin B is broad spectrum systemic antifungal drug Acts against both Mucorales & Aspergillus. Conventional one is Amphotericin B deoxycholate. Although it is cheaper, it has a limitation for its nephrotoxicity. Liposomal amphotericin B is safer and more effective<sup>22</sup>, although it is much costlier than Amphotericin B deoxycholate.

Triazoles (Itraconazole, Voriconazole, Posaconazole) are less effective against mucorales than amphotericin B.

Voriconazole is recommended 1<sup>st</sup> line treatment against aspergillus by IDSA. It's safer, has fewer side effects and is well tolerated<sup>23</sup>.

Posaconazole is newer, safe and Broad spectrum antifungal drug more effective against mucorales than voriconazole.

Hyperbaric oxygen therapy (HBOT): Although there are trials there is no clear evidence of efficacy of HBOT in the treatment of AIFR till date<sup>24,25</sup>.

#### **Surgical Management (Endoscopic/Open)**

The aims of surgery are to confirm the diagnosis and to remove the nonviable tissue.

Surgical treatment halts or slows the progression of disease and thereby allows time for bone marrow recovery. Surgical debridement reduces fungal load and provides tissue for further histopathological and microbiological examination including tissue culture<sup>26</sup>.

#### Prognosis:

- Without early treatment reported mortality in AIFR is 50-80% (from rapid progression of disease to orbit &/or brain)<sup>3,26,27,28</sup>. In favourable condition with prompt attempt to treatment it may be as low as 17%<sup>2</sup>.
- Endoscopic resection is associated with significantly improved survival (It may partly be due to the fact that those undergoing open surgery are in more advanced stages of disease)<sup>29</sup>.
- There is no correlation of species of fungus with outcome. Prognosis is related to underlying disease and extent of the disease (AIFR)<sup>4</sup>. Intracranial extension carries poor prognosis<sup>5</sup>.

High degree of suspicion is required in order to correctly and promptly diagnose & manage the condition and for better prognosis<sup>7</sup>.

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