My Perspective on Invasive Fungal Sinusitis

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Disclosures

none
Invasive Fungal Sinusitis

Rare angioinvasive infection of the sinuses with rapid extrasinus extension
   Other sites can include: Pulmonary, cutaneous, GI, Disseminated

Siderophoric saporophytic fungi
   Mucorales
   Aspergillus

Typically Immune compromised hosts
High Mortality

Mucormycosis: Epidemiology

0.1-0.2/100,000 incidence

Worldwide distribution
   All inhabited continents
   70x higher in India

Seasonal Variation
   Present on autopsy in up to 8% of Leukemia pts

Abdelwahab Hassan and Voight, Medical Mycology 2019, 57, S245-S256
Mucorales

- Phylum representing first terrestrial fungal organisms
- Heterogenous filamentous fungi
  - Soil, compost, feces, decaying organic matter, agricultural debris
- 24 identified species cause human disease
  - Mucor, Rhizomucor, Rhizopus, Cunninghamella, actinomucor, etc
- Broad based Nonseptate hyphae
- Typical inoculation
  - Spores aerosolized and inhaled or ingested
  - Contact via open wound (natural disasters, contaminated hospital equipment)

Abdelwahab Hassan and Voight, Medical Mycology 2019, 57, S245–S256

Aspergillus

- Filamentous fungi
  - Septate hyphae
- Conidia spores aerosolize readily
  - Decaying organic matter
- Ubiquitous
- Pathologic conditions
  - Mycetoma
  - Allergic fungal Sinusitis
  - Chronic invasive fungal sinusitis
- Gliotoxin
  - Inhibits Neutrophil function

https://en.wikipedia.org/wiki/Aspergillus_fumigatus
Kamei, Med Mycol. 43 Suppl 1: S95–9
Tissue Invasion

- Break in Mucocutaneous Barrier
- Mucorales adheres to exposed Laminin and Type 4 collagen
- Specific receptor-mediated endocytosis through endothelium
- Fungal invasion and growth accelerated by:
  - Elevated glucose
  - Acidic environment
  - PMN suppression
  - Increased Fe availability


Unifying Immune Deficiency

absolute or functional deficits of granulocyte function

**Absolute**
ANC < 0.5 cells/uL
Chemotherapy  
  hematologic malignancy  
  stem cell transplantation
Aplastic anemia
Hemophagocyticlymphohistiocytosis (HLH)

**Functional**
Diabetic Ketoacidosis
Metabolic Acidosis
Solid Organ Transplantation  
  Cellcept
Rheumatologic treatment  
  Prednisone  
  Methotrexate

Hyperglycemia and low pH reversibly impairs granulocyte chemotaxis and intracellular killing
Diagnosis of IFS starts with:

Evaluation of sinusitis in an immunocompromised patient

Early Diagnosis is Critical

Delay >5 days in therapy initiation is an independently poor predictor of outcome on multivariate analysis

Mortality 49% -> 83%
Classic signs = Late signs

- Cranial Neuropathy
- Chemosis
- Proptosis
- Ophthalmoplegia
- Vision Loss
- Cutaneous necrosis
- Altered Mental Status

Early Symptoms of IFS

New Onset
1. Nasal congestion
2. Rhinorrhea
3. Facial pain and pressure
4. Decreased olfaction
Sinonasal symptoms in immune compromised patients requires high index of suspicion

DDx:
- Turbinate hypertrophy/Rhinitis
- URI
  - Respiratory viral swab
- Chronic Sinusitis
- Acute bacterial sinusitis
  - Endoscopy, CT sinus
- Complicated Bacterial Sinusitis
  - Endoscopy, CT Sinus with contrast
- Invasive Fungal Sinusitis
  - Endoscopy, MRI with Gad

Diagnosis

Nasal Endoscopy
CT Sinus
MRI with Gad
Biopsy
A Brief Word on Pathology

• Angioinvasion of fungus on pathologic analysis is the gold standard for IFS.
  • Too slow to be useful prior to debridement

• Bedside biopsy of suspicious lesions
  • Frozen section
    • Can demonstrate hyphae
    • Cannot demonstrate angioinvasion
    • May support decision to operate

Imaging in IFS

**CT Sinus with Contrast**

• Most Sensitive Findings
  • Retromaxillary Fat Stranding
  • Premalar Fat Stranding
  SN 57-87%
  PPV 89-93%

• Limitations
  • Poor NPV- 45-67%
  • Does not identify early disease contained within sinonasal cavity

**MRI with Gadolinium**

• Most Sensitive Findings
  • T1 fat-saturated post-gadolinium
  • Loss of Contrast Enhancement (LoCE)
  SN 87-100%
  SP 83%
  PPV 93%
  NPV 71-100 %

• Limitations
  • Time
  • Motion artifact
Caution: unilateral complete opacification in high risk patients

Treatment

Antifungal Medication
Surgical Debridement
Immune Reconstitution
Antifungal Medications

Empiric
- Liposomal Amphotericin B (5-10 mg/kg/day)
  AND
- Caspofungin (0.5 mg/kg BID)

Mucorales
- Continuation of Ampo/Caso until stable - ideally with culture and sensitivity data
- Maintenance Therapy: Posaconazole, Isavuconazole ~70% susceptible

Aspergillus
- Voriconazole (85% susceptibility) +/- Caspofungin
- Amphotericin for clinical failure with Posaconazole salvage

Immune Reconstitution

- Recovery of immune function
  - strict blood glucose control
    - Medicine/endocrinology consultation
  - Withdrawal of immune suppression meds
    - Transplant/Rheumatology
  - Oncology patients
    - Typical ANC recovery 14-21 days post ablation
    - Can often support with surgery/antifungals
    - Limited data
      - G-CSF/GM-CSF
      - White cell transfusion
Surgical Debridement

Goal
Removal of all necrotic tissue
Surgical margins are not necessary*

Surgical Plan
Necrotic tissue = Loss of Contrast Enhancement on MRI
Enhancing Tissue on MRI stays (for now)
Plan for each involved space with LoCE
Neurovascular bundles are primary routes of spread
MRA may be helpful to evaluate occluded branches of Internal Maxillary Artery

[Images of MRI scans with labels for different regions: Orbit, Maxillary sinus, Turbinates/Ethmoids, Infratemporal Fossa/PPF, Pre-maxillary soft tissue, Maxilla Bone/Palate]
Surgical Plan

• Sinonasal cavity
• Infratemporal fossa

• Skin
• Orbit
• Palate

• Cavernous sinus
• Intracranial disease
  • Dural involvement
  • Meckel’s Cave
  • Anterior Cranial Fossa
  • Cavernous Carotid Fistula

Endoscopic

Open

Inoperable

Orbital Management

• Done in collaboration with Ophthalmology
• Orbit
  • Enhancement
    • Retrobulbar injection Amphotericin
  • Necrosis
    • Exenteration

Post Operative Algorithm

MRI POD 3
- Sooner with worsening symptoms

Staged debridement after first MRI
- Demarcation of devitalized tissue

Repeat imaging at POD 10

Transition to Oral Azoles per ID recs
- Mucor: Pozaconazole, Isavuconazole
- Aspergillus: Voriconazole

Imaging @6wks

Follow-up imaging patient specific
- Clinical status
- Complete resection
- Suppression of unresectable disease

Prognosis
Prognosis

- Mortality 20-80%
  - (approaches 100% in persistent neutropenia)
- Best: reversible neutrophil dysfunction (i.e. DM2)
- Worst: intracranial involvement*
  - Classically reported @ <10%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (of total n)</th>
<th>Survival at 3 months n (%)</th>
<th>Survival at 12 months n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range) – yr</td>
<td></td>
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</tr>
<tr>
<td>Pediatric &lt;18 years</td>
<td>2 (2 – 7 yrs)</td>
<td>2 (100%)</td>
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<tr>
<td>Adult &gt;18</td>
<td>54 (20 – 88 yrs)</td>
<td>31 (57.4%)</td>
<td>20 (37%)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>31 (55.4%)</td>
<td>20 (64.5%)</td>
<td>13 (41.9%)</td>
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<tr>
<td>Female</td>
<td>25 (44.6%)</td>
<td>13 (52%)</td>
<td>8 (32%)</td>
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<tr>
<td>Underlying Immunodeficiency</td>
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<td></td>
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</tr>
<tr>
<td>Hematologic malignancy</td>
<td>18 (31.6%)</td>
<td>7 (38.9%)</td>
<td>3 (16.7%)</td>
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<tr>
<td>Diabetic ketoacidosis</td>
<td>14 (24.6%)</td>
<td>9 (64.3%)</td>
<td>6 (42.9%)</td>
</tr>
<tr>
<td>Immunosuppressive medications</td>
<td>12 (21.1%)</td>
<td>9 (75%)</td>
<td>7 (58.3%)</td>
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<tr>
<td>Poorly-controlled diabetes</td>
<td>8 (14.0%)</td>
<td>6 (75%)</td>
<td>4 (50%)</td>
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<tr>
<td>HIV</td>
<td>2 (3.5%)</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (3.5%)</td>
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<td>Fungal Organism</td>
<td></td>
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<tr>
<td>Mucormycosis</td>
<td>33 (58.9%)</td>
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<tr>
<td>Aspergillus</td>
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<td>Other</td>
<td>9 (16.1%)</td>
<td>2 (22.2%)</td>
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<tr>
<td>Anti-fungal Regimen</td>
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<tr>
<td>Amphotericin</td>
<td>19 (33.9%)</td>
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<td>4 (21.1%)</td>
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<tr>
<td>Transformed to azole</td>
<td>37 (66.1%)</td>
<td>28 (75.7%)</td>
<td>17 (46.0%)</td>
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<tr>
<td>Extent of Disease</td>
<td></td>
<td></td>
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<tr>
<td>Isolated sinonasal disease</td>
<td>20 (35.7%)</td>
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<td>9 (45%)</td>
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### Survival: Immune Status

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A: Underlying Immunosuppression 1

B: Underlying Immunosuppression 2

### Survival: Bugs and Drugs

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C: Fungal Organism

D: Anti-fungal Therapy
**Take Home Points:**

- **Sinusitis in immune compromised patient**
  - Include Invasive Fungal disease on DDx
  - Especially if signs of complicated sinus/orbital disease
- **Start (Empiric) Liposomal Amphotericin B**
  - Slows progression: could be life saving
- **Nasal endoscopy and CT do not exclude IFS**
  - MRI with Gad
  - Loss of Contrast Enhancement (T1 fat-sat post-gad)
- **Surgical goal: debride necrotic tissue**
- **Prognosis variable**
  - Oral Azoles provide some long-term benefit
Thank You

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