CLINICAL PRESENTATION AND MANAGEMENT OF MUCORMYCOSIS

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POTENTIAL CONFLICTS OF INTEREST

• Advisory boards:
  • Avir Pharma Inc.
  • Merck Canada Inc.

• Research grants:
  • bioMérieux Canada Inc.
  • Merck Canada Inc.
OBJECTIVES

1. Discuss the **clinical presentation** of mucormycosis;
2. Outline **standard treatment strategies** for the management of mucormycosis.
CLINICAL PRESENTATION
• **Necrotizing infection**
  - Angioanvasion
  - No respect for anatomical barriers

• **Clinical forms:**
  - Primary:
    - Rhino-orbito-cerebral (ROC)
    - Pulmonary
    - Cutaneous
    - Gastointestinal
  - Disseminated

RELATIVE FREQUENCIES

N=929

- Rhinocerebral: 41%
- Pulmonary: 14%
- Cutaneous: 14%
- Gastrointestinal: 7%
- Others: 5%
- Disseminated: 19%

RHINO-ORBITO-CEREBRAL (ROC)

- Paranasal sinuses
  - Contiguous spread to: nose, sinuses, orbits, cavernous sinus, skull base, brain
- 2/3 of cases among patients with DIABETES

RHINO-ORBITO-CEREBRAL (ROC)

- Manifestations:
  - Hallmark = black eschar (50%)
  - Fever 50%
  - Eye/facial pain
  - Others: facial numbness, blurry vision, chemosis, proptosis, cranial nerve palsies

• Imaging:
  • CT:
    • Edematous mucosa, fluid in sinuses (= bacterial sinusitis)
    • Bone destruction (suggestive of IFI, but late)
    • **No sinusitis = excellent negative predictive value**
  • MR:
    • Orbital / intracranial extension, vascular complications (late, Px/Sx)

**At-risk patient with confirmed sinusitis:**
**Gold standard = endoscopy + biopsies**

Lung:
- Contiguous spread to: mediastinum, pericardium, chest wall

Most common form in cancer (neutropenia) and HSCT recipients

• Manifestations:
  • Fever unresponsive to antibacterial therapy
  • Cough (unproductive)
  • Pleuritic chest pain, hemoptysis

• CT:
  • Consolidations, nodules, cavitation, air-crescent sign
  • Vessel occlusion

• **Indistinguishable from other IFI**

PULMONARY

Mucormycosis vs. Aspergillosis

• Clinical cues:
  • Voriconazole breakthrough
  • Concomitant sinusitis

• Radiological cues:
  • >10 nodules
  • Pleural effusion
  • Reversed halo sign

Reversed halo sign: solid ring with central ground-glass opacities
### Imperfect specificity

#### Table 5. Spectrum of Diseases with the Reversed Halo Sign (RHS)

<table>
<thead>
<tr>
<th>Category</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infections</td>
<td>Mucormycosis&lt;sup&gt;a&lt;/sup&gt;, Invasive aspergillosis, Paracoccidioidomycosis</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>Slow-resolving pneumococcal pneumonia, <em>Chlamydia psittaci</em>, <em>Legionella pneumophila</em></td>
</tr>
<tr>
<td>Mycobacterial infections</td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>Wegener granulomatosis, Sarcoïdosis, Churg–Strauss syndrome, Dermatomyositis</td>
</tr>
<tr>
<td>Neoplastic diseases</td>
<td>Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>Various pulmonary diseases</td>
<td>Cryptogenic organizing pneumonia&lt;sup&gt;b&lt;/sup&gt;, Acute fibrinous and organizing pneumonia, Lipid pneumonia</td>
</tr>
</tbody>
</table>

62-YO MAN WITH AML
62 YO MAN WITH AML
TRANSTHORACIC NEEDLE BIOPSY

Photo: Simon Dufresne
CUTANEOUS

- Direct inoculation of spores in the skin
  - Association with **penetrating trauma** and **burns**
  - Contiguous spread to: subcutaneous tissue, muscles, tendons, bones

- Clinical manifestations:
  - **Necrotic eschar**
  - Others: plaques, macules

Apophysomyces cutaneous mucormycosis after a tornado (Joplin, Missouri, 2011)

13 cases along the tornado path

Macroscopical Fungal material

Neblett Fanfair et al.
65-YO MAN WITH FACE TRANSPLANT

- Posterior left thigh
- Erythematous nodule
- 2-week evolution
- Painless

Photo: Sylvain Durocher, Multimedia services, HMR
Culture = *Lichtheimia* sp.

Photo: Dr Delphine Désy, Pathology, HMR
DISSEMINATED

• Hematogenous spread from any site
  • Pulmonary > other forms
• Immunocompromised patients at higher risk
• Mortality >95%

COURSE OF DISEASE

- Time from onset of symptoms to diagnosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyvernitakis (2016)</td>
<td>4 (0-30)</td>
</tr>
<tr>
<td>Lanternier (2015)</td>
<td>46 (4-344)</td>
</tr>
<tr>
<td>Lanternier (2012)</td>
<td>14 (0-210)</td>
</tr>
</tbody>
</table>

Fulminant-Acute-Subacute-Chronic

MANAGEMENT
LOW LEVEL OF EVIDENCE

- *In vitro* (antifungal susceptibility)
- Animal models
- Retrospective studies

**Clinical trials (n=3)**
- 1 uncontrolled
- 1 single arm with case-control analysis
- 1 controlled (2 arms)
- **No RCT**
MANAGEMENT BUNDLE

Antifungal agents

Surgery

Adjuvantive therapies
## ANTIFUNGAL AGENTS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Specific mucormycosis indication in Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate (AmB-d)</td>
<td>Yes</td>
</tr>
<tr>
<td>Amphotericin B lipid complex (ABLC)</td>
<td>No</td>
</tr>
<tr>
<td>Liposomal Amphotericin B (L-AmB)</td>
<td>No</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>No</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>Yes</td>
</tr>
</tbody>
</table>
I. DEFEAT:deferasirox

- Dr Sheppard!

2. AMBIZYGO: HIGH-DOSE L-AMB

- Single-arm study on high-dose (10 mg/kg/day) L-AmB
  - 40 patients
  - HM > DM
  - Lung > ROC > cutaneous
  - Surgery in 71%
  - Mean duration at high-dose: 13.5 days (0-28)
- Survival at W12 = 62%

- Creatinine doubling: 16/40 (40%)
  - Management
    - 5 treatment interruption
    - 1 treatment discontinuation
  - Outcome
    - 2 did not recover

3. VITAL: ISAVUCONAZOLE

- Single-arm study on isavuconazole with case-control analysis
  - Controls from FungiScope Registry
    - Amphotericin B
    - Contemporary
    - Matched: HM, severe disease, surgery
  - 37 patients
    - 21 primary, 16 salvage
    - HM > DM
    - ROC > lung > cutaneous
    - Surgery in 43%


Survival at W12 = 57%
COMBINATION THERAPY

• Is more better?
AMB + CASPOFUNGIN (HARBOR-UCLA)

- Rhino-orbito-cerebral mucormycosis
- 1992-2006
- N=41
- Combination: 7
- Mono: 34

• Mucormycosis all forms
• 1994-2014
• N=106
  • Combination: 59
    • Amb+caspo: 27
    • AmB+posa: 16
    • AmB+posa+caspo: 16
  • Mono: 47

SURGERY

• No clinical trial
• ID 101: infected necrotic tissue must be removed
• Association between surgery and cure/survival in retrospective studies
  • Difficult to “dissect” the role of surgery: complex interplay of confounding factors
• General approach:
  • Cutaneous: radical debridement with clear margins
  • ROC: complete debridement avoiding unnecessary resection
  • Lung: data lacking, consider ”elective” surgery
  • Disseminated: no data supporting multi-site de-bulking

FACE TX WITH CUTANEOUS MUCORMYCOSIS
6 WEEKS AFTER 1ST SURGICAL RESECTION

Photo: Dr Daniel Borsuk, Plastic surgery, HMR
<table>
<thead>
<tr>
<th>First-line</th>
<th>Surgical debridement with antifungal therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungals</td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td>Alternative</td>
</tr>
<tr>
<td></td>
<td>Avoid AmB deoxycholate</td>
</tr>
<tr>
<td>Salvage</td>
<td>Monotherapy</td>
</tr>
<tr>
<td></td>
<td>Combination therapy</td>
</tr>
</tbody>
</table>

If success, may switch to oral therapy with Isavuconazole or Posaconazole.

- Unpublished 2019 Global guidelines (in revision at *Clin Microbiol Infect*)
TIMING OF ANTIFUNGALS

• The earlier, the better

70 HM patients
At MD Anderson

SHOULD WE GUIDE ANTIFUNGAL THERAPY BASED ON SUSCEPTIBILITY TESTING?

Recommended to increase knowledge


<table>
<thead>
<tr>
<th>MIC cutoff (µg/ml)</th>
<th>Response rate (no. [%]) (n = 10\textsuperscript{a})</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC \leq cutoff</td>
<td>MIC &gt; cutoff</td>
</tr>
<tr>
<td>0.25</td>
<td>2/2 (100)</td>
<td>3/8 (38)</td>
</tr>
<tr>
<td>0.5</td>
<td>5/6 (83)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td>1</td>
<td>5/7 (71)</td>
<td>0/3 (0)</td>
</tr>
<tr>
<td>2</td>
<td>5/7 (71)</td>
<td>0/3 (0)</td>
</tr>
<tr>
<td>4</td>
<td>5/8 (63)</td>
<td>0/2 (0)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Rhizopus spp. (n = 6), Mucor spp. (n = 1), Cunninghamamella spp. (n = 1), Scedosporium apiospermum (n = 1), Purpureocillium lilacinum (n = 1).
<table>
<thead>
<tr>
<th>Species</th>
<th>% Above 0.5 μg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lichtheimia corymbifera</em></td>
<td>17%</td>
</tr>
<tr>
<td>(n=136)</td>
<td></td>
</tr>
<tr>
<td><em>Mucor circinelloides</em></td>
<td>15%</td>
</tr>
<tr>
<td>(n=123)</td>
<td></td>
</tr>
<tr>
<td><em>Rhizopus arrhizus</em></td>
<td>60%</td>
</tr>
<tr>
<td>(n=257)</td>
<td></td>
</tr>
<tr>
<td><em>Rhizopus microsporus</em></td>
<td>38%</td>
</tr>
<tr>
<td>(n=146)</td>
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</tbody>
</table>

CONCLUSIONS

• Clinical presentation of mucormycosis is diverse and non specific, hence a high degree of suspicion is needed.
• Surgical debridement and antifungal are the cornerstone of therapy.
• Liposomal amphotericin B is still considered the agent of choice for mucormycosis.
• Unanswered questions remain regarding optimal management:
  • Role of isavuconazole as first-line agent
  • Role of initial combination therapy
  • Role of high-dose L-AmB
  • Role of surgery in pulmonary mucormycosis
  • Use of in vitro susceptibility data to tailor antifungal therapy
THANKS!
QUESTIONS?
“REAL-LIFE” USE OF COMBINATION THERAPY

• First-line combination therapy across retrospective studies and registries:
  • Harbor-UCLA ≈2005: 100%
  • MD Anderson 2005-2014: 83%
  • USA/Canada 2004-2008 (PATH Alliance): 40%
  • Urmia (Iran) 2002-2016: 30%
  • Australia 2004-2012: 19%
  • France 2005-2007: 17%

COMBINATIONS STUDIES

- Reed et al.
  - 7 patients with combo
  - 100% ROCM
  - 46% *Rhizopus* spp.
  - 56% Hispanic
  - 83% DM, 34% cancer
  - 100% AmB+caspo
  - 10% L-AmB
  - 100% surgery

- Kyvernitisakis et al.
  - 59 patients with combo
  - 87% 2+ sites
  - 47% *Rhizopus* spp.
  - 66% White
  - 100% cancer, 47% DM
  - 46% AmB+caspo
  - 94% L-AmB
  - 38% surgery
EFFECT OF SITE AND UNDERLYING DISEASE ON MORTALITY