Aspergillosis in the ICU

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Aspergillosis in the ICU
Faculty Disclosure

Advisory Boards
- MERCK USA, Bayer Europe, MSD Europe, Clinigen UK, Cardeas USA, Virogates Denmark, Cempra USA, Tetraphase USA, Gilead UK

Lectures fees
- Pfizer (Asian Pacific, USA, Korea, Taiwan, Australia)
- Astellas (UK, Japan)
- MediaHealth New Delhi –India
- Baxter France
- Bayer Germany

Research Grants
- EU-FP7 Project
- EU-Horizon FP8 Project

Societies
- ESICM, ERS, ESCMID, International Society of Chemotherapy
- Asian-Pacific Society of Infectious Diseases
# Aspergillosis in the ICU

## Incidence

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meersseman</td>
<td>2003</td>
<td>5.8</td>
</tr>
<tr>
<td>Garnacho-Montero</td>
<td>2005</td>
<td>1.1</td>
</tr>
<tr>
<td>Vandewoude</td>
<td>2006</td>
<td>0.33</td>
</tr>
<tr>
<td>Roosen</td>
<td>2000</td>
<td>15</td>
</tr>
<tr>
<td>Valles</td>
<td>2002</td>
<td>19</td>
</tr>
<tr>
<td>Dimopoulos</td>
<td>2004</td>
<td>3.7</td>
</tr>
<tr>
<td>Kumar</td>
<td>2006</td>
<td>0.7</td>
</tr>
</tbody>
</table>

# Aspergillosis in the ICU

## Patients in risk

<table>
<thead>
<tr>
<th>High-risk category</th>
<th>Low-risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Neutropenia (500/mm³)</td>
<td>- Severe burns</td>
</tr>
<tr>
<td>- Hematological malignancy</td>
<td>- Solid organ transplant</td>
</tr>
<tr>
<td>- Allogeneic HSCT</td>
<td>- Steroid treatment, 7 d</td>
</tr>
<tr>
<td><strong>Intermediate-risk category</strong></td>
<td>- Prolonged stay in the ICU (21 d)</td>
</tr>
<tr>
<td>- Prolonged treatment with corticosteroids</td>
<td>- Malnutrition</td>
</tr>
<tr>
<td>- Autologous HSCT</td>
<td>- Post cardiac surgery</td>
</tr>
<tr>
<td>- <strong>COPD, especially on ICS</strong></td>
<td>- Near drowning</td>
</tr>
<tr>
<td>- Liver cirrhosis</td>
<td></td>
</tr>
<tr>
<td>- Solid organ cancer</td>
<td></td>
</tr>
<tr>
<td>- HIV infection</td>
<td></td>
</tr>
<tr>
<td>- Lung transplantation</td>
<td></td>
</tr>
<tr>
<td>- Systemic immunosuppressive therapy</td>
<td></td>
</tr>
</tbody>
</table>

Liver disease promote bacterial and fungal infections development because of:
- depression of both humoral and cell-mediated immunity
- defects in neutrophil migration and phagocytosis
- absence of the oxidative burst activity of neutrophils

The weak immune system response is influenced by:
- corticosteroid therapy
- transfusions of allogeneic blood products
- hemodialysis
- sepsis associated immunoparalysis
- malnutrition
- poorly controlled glycemia

Fiuza C et al, J Infect Dis 2000; 182: 526 – 533,
Aspergillosis in the ICU
Uncommon manifestations - Mediastinitis

Aspergillus mediastinitis
- mainly affects patients after cardiosurgery operations with predisposing factors
- unusual in immunocompetent patients
- Identification of Aspergillus spp. source is difficult
- There are no guidelines for pre-emptive therapy

Dimopoulos et al. Journal of Medical Case Reports 2010, 4:312
Aspergillosis in the ICU
Uncommon manifestations - Mediastinitis
Aspergillosis in the ICU
Uncommon manifestations - Mediastinitis
Aspergillosis in the ICU
Uncommon manifestations - Mediastinitis
Aspergillosis in the ICU
Uncommon manifestations - Tracheobronchitis

Invasive fungal tracheobronchitis in mechanically ventilated critically ill patients: underlying conditions, diagnosis, and outcomes

Chun-Yu Lin, Wei-Lun Liu, Che-Chia Chang, Hou-Tai Chang, Han-Chung Hu, Kuo-chin Kao, Ning-Hung Chen, Ying-Jen Chen, Cheng-Ta Yang, Chung-Chi Huang, and George Dimopoulos

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>64.7 ± 13.7</td>
</tr>
<tr>
<td>Gender, male</td>
<td>24 (77.4)</td>
</tr>
<tr>
<td>Current/ex-smoker</td>
<td>15 (48.4)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>30 (96.8)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>18 (58.1)</td>
</tr>
<tr>
<td>COPD/asthma</td>
<td>12 (38.7)</td>
</tr>
<tr>
<td>Old TB</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Solid organ cancer</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Hematologic disease</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Systemic steroids before diagnosis</td>
<td>17 (54.8)</td>
</tr>
<tr>
<td>Duration of steroids before ICU admission, day, median (IQR)</td>
<td>49 (14–90)</td>
</tr>
<tr>
<td>Daily dosage of steroids, mg, median (IQR)</td>
<td>50 (29–71)</td>
</tr>
<tr>
<td>Inhaled corticosteroids before diagnosis</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>H1N1 infection before diagnosis</td>
<td>3 (9.7)</td>
</tr>
</tbody>
</table>
Aspergillosis in the ICU

Uncommon manifestations - Tracheobronchitis

**CxR**
- a. Aspergillus tracheobronchitis
- b. Candida tracheobronchitis
- c. Mucorales tracheobronchitis

**Bronchoscopic view**
- d. Aspergillus tracheobronchitis
- e. Candida tracheobronchitis
- f. Mucorales tracheobronchitis

**Biopsy**
- g. Septate fungal hyphae branching at a 45 angle: *Aspergillus* spp.
- h. Yeast cells/pseudohyphae: *Candida*
- i. Broad, thin-walled, non-septate hyphae,

Invasive fungal tracheobronchitis in mechanically ventilated critically ill patients: underlying conditions, diagnosis and outcomes
Aspergillosis in the ICU
Uncommon manifestations – Pericardial Aspergillosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Admission Diagnosis</th>
<th>APACHE II</th>
<th>Death</th>
<th>Involved organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>Respiratory failure</td>
<td>34</td>
<td>Yes</td>
<td>Lung, abdomen, kidney, endocardium</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>Spontaneous bacterial peritonitis</td>
<td>27</td>
<td>Yes</td>
<td>Lung, abdomen, liver, spleen, kidney, pancreas, endocardium</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>M</td>
<td>Bilateral Pneumonia post renal transplantation</td>
<td>17</td>
<td>No</td>
<td>Lung, endocardium</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>F</td>
<td>MRSA pneumonia, <em>Klebsiella spp</em> species</td>
<td>37</td>
<td>Yes</td>
<td>Lung, endocardium</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>F</td>
<td>Stevens Johnson syndrome, Respiratory failure</td>
<td>26</td>
<td>Yes</td>
<td>Lung, endocardium</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>F</td>
<td>Bilateral pneumonia</td>
<td>30</td>
<td>Yes</td>
<td>Lung, endocardium</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>M</td>
<td>Liver transplant</td>
<td>8</td>
<td>Yes</td>
<td>Lung, brain, pericardium</td>
</tr>
<tr>
<td>8</td>
<td>79</td>
<td>M</td>
<td>Bilateral pneumonia-Septic shock</td>
<td>32</td>
<td>Yes</td>
<td>Lung, abdomen, liver, kidney, endocardium, pericardium</td>
</tr>
</tbody>
</table>

F=Female, M=Male

Pathogenesis
- **Direct fungal invasion** from lungs to left atrium through pulmonary veins
- From the invaded endocardium fungi enter circulation → fungemia and mycotic embolization indicating hematogenous dissemination as a result rather than cause of endomyocardial invasion
- Pericardial involvement results either from mycotic emboli deriving from pulmonary circulation in the context of hematogenous dissemination or **directly from endocardium**

Dimopoulos G et al et al 2017 Mycoses
Aspergillosis in the ICU
Influenza associated - Aspergillosis

1st hypothesis
Severe damage of epithelial membrane because or the viral infection leading to fungal invasion.

Pathogenesis
Local and systemic effects

2nd hypothesis
Increased use of corticosteroids

Local damage
- Tracheobronchial mucosa
- Disruption of normal ciliary clearance
- Colonization
- Infection

Affect Th1/Th2 response/cytokines
- Lymphopenia

The reasons that some, but not all, patients with severe influenza infection develop aspergillosis remains unknown !!!!!!!!!!!!!!!

Aspergillosis in the ICU
Influenza associated Aspergillosis – A case
Aspergillosis in the ICU
Influenza associated Aspergillosis
Aspergillosis in the ICU
Influenza associated - Aspergillosis

Tracheobronchitis with obstruction

Tracheal stenosis
Multiple small bowel perforation revealed during emergency laparotomy.
A patient with HIV, admitted in the ICU because of coma and respiratory failure. She received empirically Amphotericin B. She died 48 hours later. Autopsy (no whole body) revealed disseminated Aspergillosis.

Aspergillosis in the ICU
Disseminated disease
Aspergillosis in the ICU

Diagnosis

**Diagnosis is difficult**

- Clinical signs and symptoms: non specific
- Radiology: halo sign and air-crescent non specific
- Biomarkers, Point Of Care $$\Leftrightarrow$$ putative aspergillosis
  - Galactomannans
  - Lateral Flow Device
- Algorithms (AspICU) $$\Leftrightarrow$$ confirm the putative aspergillosis

# Aspergillosis in the ICU

## Diagnosis - Radiology

<table>
<thead>
<tr>
<th>Radiological findings</th>
<th>N (n in proven IPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-specific infiltrates &amp; consolidation</td>
<td>42 (10)</td>
</tr>
<tr>
<td>Nodular lesions</td>
<td>25 (5)</td>
</tr>
<tr>
<td>Diffuse reticular or alveolar opacities</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Halo sign</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Air crescent sign</td>
<td>1</td>
</tr>
<tr>
<td>Cavitation</td>
<td>1</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
</tbody>
</table>

Aspergillosis in the ICU
A clinical algorithm to diagnose Aspergillosis

1. *Aspergillus (+)* LRT specimen culture (entry criterion)

2. Compatible signs / symptoms (one of the following)
   - Fever refractory to at least three days of appropriate antibiotic therapy
   - Recrudescent fever after a period of defervescence of at least 48 hours while still on antibiotics and without other apparent cause
   - Pleuritic chest pain
   - Pleuritic rub
   - Dyspnoea
   - Hemothysis
   - Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support

3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs

4. Either

   4a. Host risk factors (one of the following)
   - Neutropenia (absolute neutrophil count less than 500/mm$^3$) preceding or at the time of ICU admission
   - Underlying haematological or oncological malignancy treated with cytotoxic agents
   - Glucocorticoid treatment (prednisone or equivalent, >20 mg/day)
   - Congenital or acquired immunodeficiency

   OR

   4b. Semiquantitative *Aspergillus*-positive
   - culture of BAL fluid (+ or ++) without bacterial growth together with a positive cytological smear showing branching hyphae

$1 + 2 + 3 + \text{either 4a or 4b}$
$\leq 1 \text{ criterion} \Rightarrow \text{*Aspergillus* colonization}$
$\geq 1 \text{ criterion} \Rightarrow \text{Putative Aspergillosis}$
Aspergillosis in the ICU
Definite diagnosis requires biopsy and cultures
# Aspergillosis in the ICU

Definite diagnosis requires Autopsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Pts</th>
<th>Outcome</th>
<th>Aspergillus isolation</th>
<th>Steroid Treatment</th>
<th>Diagnosis confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tankanow</td>
<td>1988</td>
<td>1</td>
<td>NS</td>
<td>SP</td>
<td>YES</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Wiest</td>
<td>1989</td>
<td>3</td>
<td>NS</td>
<td>SP,PSB,BAL</td>
<td>YES</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Palmer</td>
<td>1991</td>
<td>1</td>
<td>NS</td>
<td>BA</td>
<td>YES</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Thommi</td>
<td>1991</td>
<td>2</td>
<td>NS</td>
<td>BAL,PSB, LB</td>
<td>YES</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Rodriguez</td>
<td>1992</td>
<td>5</td>
<td>NS</td>
<td>SP,LB</td>
<td>YES</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Crean</td>
<td>1992</td>
<td>1</td>
<td>NS</td>
<td>PSB</td>
<td>YES</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Conesa</td>
<td>1995</td>
<td>1</td>
<td>NS</td>
<td>BAL</td>
<td>YES</td>
<td>CT-scan / Autopsy</td>
</tr>
<tr>
<td>Pittet</td>
<td>1996</td>
<td>2</td>
<td>NS</td>
<td>BAL, BA</td>
<td>YES</td>
<td>CT-scan / Autopsy</td>
</tr>
<tr>
<td>Rello</td>
<td>1998</td>
<td>8</td>
<td>NS</td>
<td>BAL,PSB, BSP</td>
<td>YES</td>
<td>CT-scan / Autopsy</td>
</tr>
<tr>
<td>Dimopoulos</td>
<td>2002</td>
<td>5</td>
<td>NS</td>
<td>BAL, SP</td>
<td>YES</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Franquet</td>
<td>2003</td>
<td>9</td>
<td>NS</td>
<td>LB</td>
<td>YES</td>
<td>CT-scan / Autopsy</td>
</tr>
</tbody>
</table>
Aspergillosis in the ICU
Mode of actions of antifungal drugs

Bind to sterols, forming pores in the cell
↓
membrane permeability
↓
induces the accumulation of ROS
↓
Toxic effects on fungal cells

Reactive Oxygen Species (ROS)

Inhibit the ERG11 enzyme thereby blocking the ergosterol biosynthesis. 
ERG11 catalyses the formation of 4,4-dimethylcholesta-8,14,24-trienolfromlanosterol.
The lack of ergosterol and the subsequent accumulation of lanosterol, results in high toxicity for the cell.

Inhibit the β-1,3-glucan synthesis. As a response to the reduction of glucan content there is an increase in chitin biosynthesis.

Aspergillosis in the ICU
Treatment

Voriconazole arm* (n=144) 71%
Amphotericin B arm* (n=133) 58%

Patients Surviving (%)

0% 20% 40% 60% 80% 100%

0 2 4 6 8 10 12 Week

144 131 125 117 111 107 102 Voriconazole
133 117 99 87 84 80 77 Amphotericin B

HR: 0.59, 95% CI (.40–.88)
12.9% absolute survival benefit

$P = 0.02$

Aspergillosis in the ICU

Treatment

**Voriconazole vs. C-AMB**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Responses at week 12</th>
<th>Survival at week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B-d</td>
<td>32%</td>
<td>0</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>53%</td>
<td>71%</td>
</tr>
</tbody>
</table>

**AmBiLoad**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Responses at EOT</th>
<th>Survival at week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-AmB 10 mg/kg/day</td>
<td>46%</td>
<td>0</td>
</tr>
<tr>
<td>L-AmB 3 mg/kg/day</td>
<td>50%</td>
<td>72%</td>
</tr>
</tbody>
</table>

High proportion of neutropenia/hemocnc!

Aspergillosis in the ICU
Isavuconazole

Loading dose (6 doses)
- 200 mg every 8 h

Day 1

200 mg every 8 h
- Day 2

Maintenance dose
- 200 mg per day

Day 3 ...

- Duration of therapy should be determined by the clinical response.
- For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered.
Aspergillosis in the ICU
Isavuconazole – SECURE trial

Primary end-point: survival up to day 42 for the ITT population

Maertens JA et al. Lancet 2016; 387: 760–69
Aspergillosis in the ICU
Isavuconazole – SECURE trial / Safety
Aspergillosis in the ICU
Assessing the response to the treatment

- **Fever**
  - too long
- **CT-scan**
  - not early (lesion increases up to 1 week)
- **Ag +++**
  - related to prognosis
- **↑ GM level over baseline**
  - predictive of treatment failure
## Aspergillosis in the ICU

### ESCMID/ERS/ECMM guidelines

<table>
<thead>
<tr>
<th>Targeted therapy of pulmonary disease—first line</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td>Neutropenia (non-allo HSCT recipients)</td>
</tr>
<tr>
<td>Allo-HSCT (during neutropenia)</td>
</tr>
<tr>
<td>Allo-HSCT (w/o neutropenia) or other non-neutropenic patients</td>
</tr>
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</tr>
</tbody>
</table>

Life-threatening haemoptysis | Bridging until neutrophil recovery | Efficacy unproven

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Aspergillosis in the ICU

Conclusions

- **Epidemiology**
  a. not well known because of the difficult diagnosis
  b. Risk factors: well confirmed
  c. Rare manifestations are emerging

- **Diagnosis**
  a. Difficult because of the lack of a diagnostic method able to discriminate colonization from infection

- **Antifungal regimens**
  a. A huge number available

- **Outcome**
  a. High mortality (exceeds frequently 95%)
  b. delayed diagnosis
  c. delayed treatment as a consequence of the difficult diagnosis