Invasive Pulmonary Aspergillosis in Non-Immunocompromised Patients

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Introduction on Aspergillus

- Filamentous fungi
- Widespread in environment
- Mechanism of pathogenesis:
  - inhalation of spores or conidia
  - hematogenous spread
  → may affect any organ system
  → mostly: lung (colonization or invasive disease)
Introduction on Invasive Aspergillosis

- Exposure to *Aspergillus*...
- Healthy subjects → (generally) no problem
- CAVE: immunocompromised patients
  - Allogeneic BMT
  - Hematologic malignancy
  - Neutropenia
  - Solid organ transplants (>lung)
  - Corticosteroid therapy
  - HIV
Diagnosis of Invasive Pulmonary Aspergillosis

Problematic diagnosis

EORTC / MSG criteria

3 major categories to appreciate the likelihood of IPA

1. Proven
2. Probable
3. Possible

Based on:

1. Host factors
2. Clinical features: > medical imaging
3. Mycology
Diagnosis of Invasive Pulmonary Aspergillosis

(1) Host factors

- Recent history of neutropenia (<500 neutrophils/mm$^3$)

- Receipt of an allogeneic stem cell transplant.

- Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for 13 weeks.

- Treatment with other recognized T cell immunosuppressants or nucleoside analogues during the past 90 days.

- Inherited severe immunodeficiency
Medical imaging (on CT) suggestive for IPA

Dense, well-circumscribed lesions(s) with or without a halo sign

Cavity

Air-crescent sign
Suggestive Medical Imaging in IPA:
the « Halo sign »
Suggestive Medical Imaging in IPA:
Well shaped nodules with cavitation

Suggestive Medical Imaging in IPA:
The « Air Crescent Sign »
Diagnosis of Invasive Pulmonary Aspergillosis

(3) Mycology

Proven IPA...

Biopsy sample

→ Histopathologic, cytopathologic, direct microscopic evidence of fungal elements

AND

→ associated tissue damage
Diagnosis of Invasive Pulmonary Aspergillosis

(3) Mycology

Probable IPA...

**Direct test** (cytology, direct microscopy, or culture)

*Aspergillus* in sputum, BAL fluid, PSB, indicated by

1 of the following:  
- Positive microscopy
- Positive culture

**Indirect tests** (detection of antigen or cell-wall constituents)

Galactomannan antigen detected in plasma, serum, BAL fluid
Beta-D-glucan detected in serum
Diagnosis of Invasive Pulmonary Aspergillosis

Summary

- **Proven IPA**
  - Host factors
  - Clinical features
  - Mycology: positive on tissue

- **Probable IPA**
  - Host factors
  - Clinical features
  - Mycology: positive

- **Possible IPA**
  - Host factors
  - Clinical features
  - Mycology: negative / not done
Diagnosing IPA in Non-Immunocompromised Patients: Histopathology

« Golden standard »:

Positive lung biopsy → proven IPA

Problem:
- contra-indicated: coagulation disorders in septic patients
- chance of missing the infiltrate → false negative results
Diagnosing IPA in Non-Immunocompromised Patients: Medical Imaging

Early recognition of *Aspergillus* involvement

= ‘Halo sign’ on CT

Problem:

CT not always feasible in unstable patients

Mechanical ventilation → disturbed imaging

→ rarely *Aspergillus*-specific findings…
Diagnosing IPA in Non-Immunocompromised Patients: Medical Imaging

Radiological findings in ICU patients with IPA (n=83)

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

How to diagnose IPA in ICU patients?

• Clinical diagnostic algorithm
  (appreciation of the clinical relevance of *Aspergillus*
  in respiratory tract samples)

• Galactomannan in BAL fluid
Clinical relevance of *Aspergillus* isolation from respiratory tract samples in critically ill patients

**Definite Invasive Pulmonary Aspergillosis:**

- positive result of histological testing and positive result of culture obtained by biopsy or autopsy

- positive result of culture of a specimen obtained from a normally sterile site by use of aseptic invasive technique

Clinical relevance of *Aspergillus* isolation from respiratory tract samples in critically ill patients

Probable Invasive Pulmonary Aspergillosis:

1. Aspergillus-positive lower respiratory tract specimen culture

2. Compatible signs and symptoms
   - Fever refractory to at least 3 days of appropriate antibiotic therapy
   - Recrudescent fever after period of defervescence >48h while still on antibiotics and without other apparent cause
   - Pleuritic chest pain
   - Pleuritic rub
   - Dyspnoea
   - Hemoptysis
   - Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support

Clinical relevance of *Aspergillus* isolation from respiratory tract samples in critically ill patients

**Probable Invasive Pulmonary Aspergillosis:**

1. *Aspergillus*-positive lower respiratory tract specimen culture
2. Compatible signs and symptoms
3. Abnormal medical imaging (chest X-ray or CT)
4. Either: a. Host risk factors (one of the following):
   - Neutropenia (absolute neutrophil count <500/mm³)
   - Underlying hemato-oncological malignancy treated with cytotoxic agents
   - Glucocorticoid treatment (prednisone or equivalent, >20 mg/d)
   - Congenital or acquired immunodeficiency
   or...
   b. Semiquant. *Aspergillus*-positive culture of BAL (+/++), with a positive cytological smear

Clinical relevance of *Aspergillus* isolation from respiratory tract samples in critically ill patients

Clinical relevance of *Aspergillus* isolation from respiratory tract samples in critically ill patients

**Probable invasive pulmonary aspergillosis (n=83)**

- Histologic examination?
  - Yes: n=17
  - No

**Probable invasive pulmonary aspergillosis (n=66)**

- Clinical diagnosis confirmed?
  - Yes
  - No: n=0 (0%)

**Definite invasive aspergillosis (n=17; 100%)**

**Aspergillus colonization (n=89)**

- Histologic examination?
  - Yes: n=9
  - No

**Aspergillus colonization (n=9; 100%)**

**Unconfirmed Aspergillus colonization (n=80)**

- Clinical diagnosis confirmed?
  - Yes
  - No: n=0 (0%)

Clinical relevance of *Aspergillus* isolation from respiratory tract samples in critically ill patients

Log rank test: $p<0.001$

Diagnosing IPA in Non-Immunocompromised Patients: Galactomannan

- GM released predominantly by hyphae (less by conidia)
- GM antigen detection by ELISA
- Well studied in immunocompromised hosts (mostly neutropenic)
- Problem in non-neutropenic patients = circulating neutrophils are capable to of clearing the antigen
Galactomannan in Bronchoalveolar Lavage Fluid
A Tool for Diagnosing Aspergillosis in ICU Patients

• 110 « immunocompromised » ICU patients
  • 36 with hematologic malignancy (33%)
  • 74 other immunocompromising factors (67%)
    • Classical host factors
    • 3 additional ICU-related host factors - cirrhosis,
      - COPD,
      - steroids
  • 24 neutropenic (22%)

Galactomannan in BAL Fluid
GM and culture results in 72 pathology controlled cases

<table>
<thead>
<tr>
<th>Serum galactomannan, no.</th>
<th>Invasive Aspergillosis (n = 26)</th>
<th>No Invasive Aspergillosis (n = 46)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>11</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Negative</td>
<td>15</td>
<td>43</td>
<td>58</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>46</td>
<td>72</td>
</tr>
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<table>
<thead>
<tr>
<th>BAL galactomannan, no.</th>
<th>Invasive Aspergillosis (n = 26)</th>
<th>No Invasive Aspergillosis (n = 46)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>23</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>46</td>
<td>72</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>BAL culture, direct examination, no.</th>
<th>Invasive Aspergillosis (n = 26)</th>
<th>No Invasive Aspergillosis (n = 46)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (%)</td>
<td>15 (58)</td>
<td>14 (30)</td>
<td>29</td>
</tr>
<tr>
<td>Negative (%)</td>
<td>11 (42)</td>
<td>32 (70)</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>46</td>
<td>72</td>
</tr>
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Galactomannan in BAL Fluid

ROC curve analysis for GM detection in BAL fluid vs. serum

BAL fluid: AUC: 0.90 (95% CI: 0.81 – 0.96)
Serum: AUC: 0.76 (95% CI: 0.63 – 0.82)

Trends in invasive fungal infections

US, 1980-1997

Invasive aspergillosis in critically ill patients without malignancy

Retrospective study (2000 – 2003) in a medical ICU

127/1850 ICU admissions with evidence of *Aspergillus* (microbiological/histological)

89 patients (70%): no malignancy.

- proven IA: \( n = 30 \)
- probable IA: \( n = 37 \)
- possible IA: \( n = 2 \)
- colonization: \( n = 20 \)

Incidence of invasive aspergillosis in the MICU = 6.5%

Clinical relevance of positive *Aspergillus* respiratory tract samples in critically ill patients

Retrospective study (1997 – 2003) in a general ICU
172 patients with tracheal aspirates positive for *Aspergillus* spp.

- 89 colonization
- 83 IPA (based on criteria derived from the EORTC/MSG definitions)

Incidence:
- 0.33% all ICU patients
- 1% in medical ICU patients

Isolation of *Aspergillus spp.* from the respiratory tract in critically ill patients: risk factors, clinical presentation and outcome

Prospective multicentre study in 73 Spanish ICUs

Inclusion criteria: ICU stay >7 d.

Surveillance cultures: 1/week (tracheal aspirate, urine, oropharyngeal & gastric swab)

IPA defined as “pneumonia”

n=1756 patients → 36 positive for *Aspergillus*:  
- 16 colonization  
- 20 IPA

Incidence: \(~1.1\%\) (in patients with an ICU stay >7 days!)

Epidemiology of IPA in ICU Patients

Incidence

- In literature incidence data vary from 1% to 6%.

- Insufficient data available to have a reliable estimate

- (!) Incidence = underestimated…??

Incidence of IPA~1% > candidemia

- Incidence is strongly dependent on the presence of host factors in the population.
Epidemiology of IPA in ICU Patients

Risk Factors

• Immunocompromised patients → specific host factors
• Critically ill patients with high disease severity index
  • COPD
  • steroid use
  • cirrhosis
  • severe sepsis
Mortality in invasive aspergillosis
Review of Literature after 1995

Review of 1941 patients from 50 studies

<table>
<thead>
<tr>
<th>Category</th>
<th>Case Fatality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>50 (n=1941)</td>
</tr>
<tr>
<td>BMT (n=285)</td>
<td>90</td>
</tr>
<tr>
<td>Leuk/Lymph (n=288)</td>
<td>60</td>
</tr>
<tr>
<td>Pulmonary (n=1153)</td>
<td>50</td>
</tr>
<tr>
<td>CNS/Dissem (n=175)</td>
<td>80</td>
</tr>
</tbody>
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Mortality in invasive aspergillosis

**Figure 2.** Survival Curves for the Modified Intention-to-Treat Population According to Treatment Group.

Mortality in ICU patients with IA

- Meersseman W, et al. AJRCCM 2004

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandewoude 2006</td>
<td>76%</td>
</tr>
<tr>
<td>Garnacho-Montero 2005</td>
<td>80%</td>
</tr>
<tr>
<td>Meersseman 2004</td>
<td>90%</td>
</tr>
<tr>
<td>Janssen 1996</td>
<td>95%</td>
</tr>
</tbody>
</table>
Attributable mortality in ICU patients with IPA


- Cases with IA (n=38): 75.7%
- Matched controls (n=76): 56.8%

Attributable mortality: 18.9% (95% CI: 1.1 – 36.7)
Conclusion

• Do not discard an *Aspergillus* spp. positive respiratory tract specimen in critically ill patients

• Consider the clinical significance even in the absence of EORTC/MSG host factors

• Validation of galactomannan detection in BAL fluid

• Validation of clinical diagnostic algorithm
  → Useful to guide (pre-emptive) therapy
  → Development of criteria for pre-emptive treatment
Invitation to join the AspICU project
www.aspicu.org

• A web-based registration of *Aspergillus* in Intensive Care Units

• Objective: To collect a large series of ICU patients with evidence of either *Aspergillus* colonization or infection, in order to:
  
  1) Investigate the epidemiology of invasive aspergillosis in ICU patients
  
  2) To validate the clinical diagnostic algorithm that discriminates colonization from invasive disease
Invitation to join the AspICU project
www.aspicu.org

AspICU
Web-based surveillance of Aspergillus in Intensive Care Units

Login

username
password
Login

Objectives
To collect a large series of ICU patients with either Aspergillus colonization or invasive disease, in order to (1) investigate the epidemiology of invasive aspergillosis in ICU patients, and (2) to validate the diagnostic algorithm that discriminates colonization from invasive disease as proposed by Vandewoude et al.

Investigators
Principal investigators
- S. Blot, Intensive Care Dept., Ghent University Hospital, Ghent, Belgium
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