Aspergillosis
in the critically ill patient

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Directorate of National Health - DGS
Portugal
In the last 20 years, the probability of acquiring a mold infection has increased 50%
The rationale for an adequate antimicrobial treatment
Not just the in classical immunosuppressed patient

- Allogeneic Bone Marrow Transplant: 25%
- Hematologic Malignancy: 28%
- Solid Organ Transplant: 9%
- AIDS: 8%
- Other Immunosuppression: 6%
- Pulmonary: 9%
- Other: 6%
- None: 2%
- Autologous Bone Marrow Transplant: 7%

(595 patients)

Patterson TF, et al. Medicine, 2000;79:250-60
Not just the in classical immunossupressed patient

Steroids
COPD
Liver failure

Cornillet et al. Clin Infect Dis 2006; 43: 577-84
Aspergillus isolation and disease

Classical view

- Negative sputum samples in 70% of patients with confirmed IPA
- Positive results not always correlate with invasive disease
- Immunocompetent patients with Aspergillus in the sputum: 92% colonization and 4.5% IPA

Modern view

Classical host factors as defined by the EORTC/MSG:
- neutropenia,
- hematological malignancy,
- bone marrow transplantation,
- chronic use of corticosteroids.

Vandewoude KH et al. Crit Care 2006; 10: R31
Aspergillus isolation in the ICU: AsplICU study

- 47% of the ICU patients with a positive Aspergillus culture were classified as IA: 24% proven IA and 76% putative IA.

- **Only 40% of patients had classical host factors** as defined by the EORTC/MSG: neutropenia (6.6%), hematological malignancy (8.7%), BMT (2.7%), chronic use of corticosteroids (15.3%).

- **Co-morbid conditions or underlying diseases were:**
  - COPD 37.2%
  - ARDS 19.0%
  - Solid organ transplantation 14.2%
  - Diabetes mellitus 13.7%
  - Chronic heart failure 8.7%

- Medical imaging: with multiple abnormalities and rarely halo sign (3%) or air crescent sign (2%).

- **IA may occur in the absence of classical IA host factors and imaging**

Blot S et al. Am J Respir Crit Care Med 2012
The rationale for an adequate antimicrobial treatment

The bug

The host

Inflammatory response

Microbiology

The drugs

PK/PD
Globally, low levels of resistance, but....

- A. niger
- A. fumigatus
- A. versicolor
- A. flavus
- A. nidulans
- A. terreus

Susceptibility to amphotericin B

Aspergillus fumgatus azole resistance may be an emerging problem

- 3,788 Aspergillus isolates were screened in 22 centers from 19 countries.
- Azole-resistant *A. fumigatus* was more frequently found (3.2% prevalence) than previously acknowledged.
- TR34/L98H was the predominant mechanism of resistance (48.9%).
- Azole-resistant *A. fumigatus* caused aspergillus diseases in the patients (5.1% of cases of IA).
- Azole resistance was associated with a worsened outcome (mortality 88%).
- Surveillance studies show that, in areas to which *Aspergillus* is endemic, the environmental route of resistance selection contributes to >90% of resistance mechanisms in azole-resistant *Aspergillus* diseases.
- Azole resistance observed in patients with no recent history of azole therapy.

The rationale for an adequate antimicrobial treatment

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**Histology: necrosis and hemorrhage**

**Neutropenic:**
- coagulative necrosis,
- intraalveolar hemorrhage,
- scant mononuclear inflammatory infiltrate
- high fungal burden

**Non-neutropenic:**
- inflammatory necrosis
- scant intraalveolar hemorrhage
- neutrophilic and monocytic infiltrates
- low fungal burden
Invasive and thrombo-hemorrhagic

- **Infarction/necrosis** (nodule) of the lung tissue secondary to vascular invasion

- Subsequent **thrombosis** of small arterioles and sometimes large pulmonary vessels.

- Surrounding (in at least 75% of its perimetrum) red peripheral ring of **hemorrhage** or **hemorrhagic infarction** (halo of ground glass attenuation) and oedema
Radiology: evolutive signs

Halo sign (day 0)

Hypodense sign (day 6)

Central area of hipodensity in nodules resulting from secondary lung infarction

Precedes air crescent sign by 2-19 days

Specificity 100%; sensitivity 30%; very high PPV
The rationale for an adequate antimicrobial treatment

The bug

Microbiology

Inflammatory response

The host

PK /PD

The drugs
Difficult diagnosis: often necropsy diagnosis

1970
68% of patients with autopsy proven IA were not diagnosed antemortem

Young, Medicine 1970; 49: 147-173

1996
68% patients with autopsy proven IA received no treatment

Groll, J. Infect 1996; 33: 23-32
Cultures and invasive aspergillosis

- Blood cultures are rarely positive
- **Negative sputum samples in 70%** of patients with confirmed IPA
- Positive results not always correlate with invasive disease
- *Aspergillus* in ETA cultures in up to 2% of mechanically ventilated patients
- Positive fungal smear or culture of BAL in the neutropenic: low sensitivity (30-50%) and high specificity (97%)
- In immunocompetent patients with *Aspergillus* in the sputum: **92% colonization and 4,5% IPA**
- Invasive respiratory specimens are as effective as non-invasive for the diagnosis of IA

Biomarkers - Galactomannan

<table>
<thead>
<tr>
<th></th>
<th>GM</th>
<th>β-D-Glucan</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida sp</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aspergillus sp</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Criptococcus</td>
<td>+#</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Fusarium</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Penicillium</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Paecilomyces</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Lesser role in non-neutropenic and in solid-organ transplant recipients

False positivity: β-lactam antibiotics, severe mucositis

*Dalle F, et al. JCM 43:2929-2931
*Roiz MP et al. ECCMID 2011,P1952;
Mikulska M et al Diagn Microbiol Infect Dis 2012;
Tortorano AM, et al JCM 2012 50:1051-1053
Galactomannan; better in BAL than in blood

More galactomannan detected in BAL and earlier than in serum

Hope et al. Antimicrob Ag Chemother 2010: 54; 4879-86
Galactomannan in BALF in COPD patients: looking for the cut off.

- Compared to serum GM and LRT culture, BALF GM appears to have higher sensitivity for the diagnosis of IPA in COPD patients.
- ROC curve suggest a possible cut-off value of 0.8 for GM from BALF specimens in critically ill COPD patients.

He H et al. Crit Care 2012; 16: R138
Looking for a good cut off index of BALF-GM

- The BALF-GM is more sensitive than serum-GM and fungal cultures.
- BALF-GM has a high false-positive rate at the cut off of 0.5. Risk of overdiagnosis.
- The optimal cut off index was 1.19 for BALF-GM, and the sensitivity and specificity were 67.9% and 89.2%.

![ROC curve for BALF-GM and serum-GM](image)

**Table 2: The diagnostic values of the BALF-GM and serum-GM assays at the different cutoff indices.**

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.5</td>
<td>85.7%</td>
<td>62.4%</td>
<td>40.7%</td>
<td>93.5%</td>
</tr>
<tr>
<td>≥1</td>
<td>67.9%</td>
<td>79.6%</td>
<td>50.0%</td>
<td>89.2%</td>
</tr>
<tr>
<td>≥1.5</td>
<td>65.4%</td>
<td>92.5%</td>
<td>70.8%</td>
<td>90.5%</td>
</tr>
<tr>
<td>≥2</td>
<td>46.4%</td>
<td>96.8%</td>
<td>81.2%</td>
<td>85.7%</td>
</tr>
</tbody>
</table>

**Serum-GM**

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.5</td>
<td>67.9%</td>
<td>93.5%</td>
<td>76.0%</td>
<td>90.6%</td>
</tr>
<tr>
<td>≥1</td>
<td>50.0%</td>
<td>98.9%</td>
<td>93.3%</td>
<td>86.8%</td>
</tr>
<tr>
<td>≥1.5</td>
<td>25.0%</td>
<td>98.9%</td>
<td>87.5%</td>
<td>81.4%</td>
</tr>
<tr>
<td>≥2</td>
<td>25.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>81.6%</td>
</tr>
</tbody>
</table>

**Culture**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50.0%</td>
<td>98.9%</td>
<td>93.3%</td>
<td>86.8%</td>
</tr>
</tbody>
</table>
Early diagnosis is fundamental for success and to achieve it...

- Host factors
- Clinical features + Radiology
- Cultural & Non-cultural Mycology
- Histology

- Non-responding patients
- Lung, skin, sinus, SNC, hepatic lesions
- Pulmonary CT scan suggestive and non-cultural lab methods negative
- Atypical pulmonary CT scan alterations and non-cultural lab methods negative
Halo sign as a marker of early stage of IA

<table>
<thead>
<tr>
<th></th>
<th>Halo sign present n=143</th>
<th>Halo sign absent n=79</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive global response rate</td>
<td>52% (75/143)</td>
<td>29% (23/79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 week survival</td>
<td>71%</td>
<td>53%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The earlier the treatment the higher the success rate

Greene RE et al. CID 2007; 44: 373-9
The rationale for an adequate antimicrobial treatment

The bug

Inflammatory response

Microbiology

The host

PK /PD

The drugs
## What are intensivists using?

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Treated patients n (%)</th>
<th>Treated Colonized patients n (%)</th>
<th>Treated Putative/Proven patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampho B deoxycholate</td>
<td>53 (22.0)</td>
<td>15 (28.3)</td>
<td>38 (20.2)</td>
</tr>
<tr>
<td>Ampho B lipid ass.</td>
<td>14 (5.8)</td>
<td>4 (7.5)</td>
<td>10 (5.3)</td>
</tr>
<tr>
<td>Echinocandin</td>
<td>34 (14.1)</td>
<td>6 (11.3)</td>
<td>28 (15.0)</td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td><strong>94 (39.0)</strong></td>
<td><strong>21 (39.7)</strong></td>
<td><strong>73 (38.8)</strong></td>
</tr>
<tr>
<td>Other</td>
<td>46 (19.1)</td>
<td>7 (13.2)</td>
<td>39 (20.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>241 (100)</strong></td>
<td><strong>53 (100)</strong></td>
<td><strong>188 (100.0)</strong></td>
</tr>
</tbody>
</table>

3.4% first line combination therapy
Global Comparative Aspergillosis Study: Survival Benefit of Voriconazole

Survival and response rates at week 12:
- **Voriconazole arm**: 70.8% survival, 56.8% response
- **Amphotericin B arm**: 57.9% survival, 31% response

Hazard ratio = 0.60
95% CI (0.40, 0.89)

- Poor efficacy of AmB prior “gold standard”
- Vori recommended for primary therapy
- Importance of early therapy
- Limited success of rescue therapy

_Herbrecht R et al. NEJM 2002;347:408-15_
Effect of voriconazole use on survival in mechanically ventilated haematological patients with IPA

Guidelines for Invasive Aspergillosis

- Limited efficacy of amphotericin B deoxycholate in high risk pts

- **Recommendations for treatment of invasive aspergillosis**
  - **Voriconazole** as primary therapy in most patients
  - Liposomal amphotericin alternative therapy in some patients
  - Options for salvage therapy; dependent on prior therapy, host factors, dosing considerations;
  - potential agents: posaconazole, *combination therapy*

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**Herbrecht et al 2002**


**Maertens 2011**

**Lortholary 2011**

---

<table>
<thead>
<tr>
<th>Drugs</th>
<th>IDSA</th>
<th>ECIL</th>
<th>UK</th>
<th>Italy</th>
<th>Germany</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional AmB</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>All</td>
</tr>
<tr>
<td>L-AmB</td>
<td>Al</td>
<td>Bi</td>
<td>Al</td>
<td>Bi</td>
<td>Al</td>
<td>Bi</td>
</tr>
<tr>
<td>ABLC</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>III</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>ABCD</td>
<td>D</td>
<td>CIII</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Al</td>
<td>Al</td>
<td>Al</td>
<td>Al</td>
<td>Al</td>
<td>Al</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Al</td>
<td>Al</td>
<td>Al</td>
<td>Al</td>
<td>Al</td>
<td>Al</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>CII</td>
<td>Al</td>
<td>BII</td>
<td>BII</td>
<td>BII</td>
<td>BII</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>CII</td>
<td>Al</td>
<td>BII</td>
<td>BII</td>
<td>BII</td>
<td>BII</td>
</tr>
<tr>
<td>Micafungin</td>
<td>CII</td>
<td>Al</td>
<td>BII</td>
<td>BII</td>
<td>BII</td>
<td>BII</td>
</tr>
</tbody>
</table>

AmB, amphotericin B; L-AmB, liposomal amphotericin B; ABLC, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion.
Cerebral Aspergillosis in AsplCU population

- 79 Definitive IA and 199 Putative IPA
- 10 cerebral aspergillosis
- CT scann: either solitary and hyperdense or were multiple and randomly distributed throughout the brain. One patient with sole meningeal infestation. Often clinically silent
- Voriconazole was used as primary treatment in only one-half of the patients. Mortality was 90%.
- Diagnosis must be considered in patients at risk presenting with proven or probable/putative IPA in association with suggestive neuroradiological findings and should actively seeken for in all IA patients, namely with MRI.

Evaluation of outcome of patients with aspergillosis (definitive or proven) who experienced failure of initial therapy with amphotericin B formulations

Voriconazole (n=31) vs. voriconazole + caspofungin (n=16) for salvage therapy.

Survival rate at 3 months

Probability of death due to IA

CID 2004; 39: 797-802
Combination Antifungal Therapy for Invasive Aspergillosis
A Randomized Trial

Kieren A. Marr, MD; Hasan T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Dow, MD, MSC; Oliver A. Comely, MD; Werner J. Heinz, MD; Shyla Jagannath, PhD; Liang Pia Keh, MBBS; Dimitrios P Kontoyiannis, MD; Dong-Gun Lee, MD; Marco Nucillo, MD; Peter G. Pappas, MD; Monica A. Staliv, MD; Flovis Caumi-Teles, MD, PhD; Dominik Selke, MD; Thomas J. Walsh, MD; John R. Wiegard, MD; and Johan A. Mouton, MD, PhD

Table 4. Results of Multivariate Analysis of Baseline Factors of Prognostic Significance for Mortality at 6 wk*

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky score (unit increase = 10)</td>
<td>0.22 (0.60–0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum bronwne serum CM antigen index (unit increase = 0.5)</td>
<td>1.07 (1.02–1.13)</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline chlortet count (unit increase = 5)</td>
<td>0.95 (0.93–1.03)</td>
<td>0.026</td>
</tr>
<tr>
<td>BMI (unit increase = 5)</td>
<td>0.80 (0.61–1.00)</td>
<td>0.093</td>
</tr>
<tr>
<td>T-cell immunosuppressive vs. yes)</td>
<td>2.27 (0.64–8.14)</td>
<td>0.109</td>
</tr>
<tr>
<td>Diagnosis chlortet (probable based on CM antigen positivity vs. all other)</td>
<td>0.67 (0.33–1.35)</td>
<td>0.332</td>
</tr>
<tr>
<td>Age (unit increase = 5)</td>
<td>1.08 (0.97–1.21)</td>
<td>0.157</td>
</tr>
</tbody>
</table>

Marr K et al. Annals Int Med 2015

Figure 2. Cumulative incidence of death in the modified intention-to-treat population.
P=0.049

Figure 3. Outcomes in the positive galactomannan subgroup.

International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigatus*

Paul E. Verweij, Michelle Aranta-Rajah, David Andes, Maiken C. Arendrup, Roger J. Brittgermann, Anuradha Chowdhary, Oliver A. Cornelly, David W. Denning, Andreas H. Croll, Koichi Izumiya, Bart Jan Kuilberg, Katrien Lagrou, Johan Maertens, Jacques F. Meis, Pippa Newton, Ian Page, Seyedmohsen Seyedmohseni, Donald C. Sheppard, Claudio Vicoli, Adilia Warris, J. Peter Donnelly

Low azole resistance

Significant azole resistance

Potential azole resistance as a driver of biopsy guided diagnosis, to achieve PCR study of the sample

Need to standardize PCR-based assays, to deal with the decision on an individual, not only epidemiological basis
## Indications for surgical treatment of IPA

<table>
<thead>
<tr>
<th>Condition</th>
<th>Surgical procedure</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary lesion in proximity to great vessels or pericardium</td>
<td>Resection of pulmonary lesion</td>
<td>May prevent erosion of pulmonary lesions into great vessels and into pericardial space</td>
</tr>
<tr>
<td>Pericardial infection</td>
<td>Pericardiectomy</td>
<td>Pericardiectomy reduces organism burden around heart and prevents tamponade</td>
</tr>
<tr>
<td>Invasion of chest wall from contiguous pulmonary lesion</td>
<td>Resection of pulmonary lesion</td>
<td>Resection of lesion may relieve pain and prevent pleurocutaneous fistula</td>
</tr>
<tr>
<td>Aspergillus empyema</td>
<td>Placement of chest tube</td>
<td>Reduces burden of organism in closed space</td>
</tr>
<tr>
<td>Persistent hemoptysis from a single cavitary lesion</td>
<td>Resection of cavity</td>
<td>May prevent exsanguinating hemoptysis; other measures to reduce hemoptysis include embolization of involved blood vessel and cauterezation; however, recurrence of bleeding is possible</td>
</tr>
</tbody>
</table>
The rationale for an adequate antimicrobial treatment
Pharmacokinetic variability and exposures of fluconazole, anidulafungin, and caspofungin in intensive care unit patients: Data from multinational Defining Antibiotic Levels in Intensive care unit (DALI) patients Study

Mahipal G Sinnollareddy1,2,3, Jason A Roberts1,4*, Jeffrey Lipman1,4, Murat Akova5, Matteo Bassetti6, Jan J De Waele7, Kirs-Maija Kaukonen8, Despoina Kouenti1,9, Claude Martin10,11, Philippe Montravers12, Jordi Rello13, Andrew Rhodes14, Therese Starr4, Steven C Wallis1, George Dimopoulos9 and on behalf of the DALI Study authors

**Conclusions:** Considerable interindividual variability was observed for fluconazole, anidulafungin, and caspofungin. A large proportion of the patients (33%) receiving fluconazole did not attain the PK/PD target, which might be related to inadequate dosing.

- With the limitation of small sample size, this study illustrates that antifungal dosing in the critically ill is as complex as previously demonstrated for antibiotics. Further research is required to optimize exposures of antifungal agents in at-risk critically ill patients.
Interindividual variability of voriconazole levels

Pascual A et al. CID 2008; 46: 201-211
Keeping voriconazole trough levels inside the therapeutic range of 1.0-5.5 mg/l during the first week of therapy may prevent treatment failures (88% vs, 54%) and neurological toxicity.

Pascual A et al. CID 2008; 46: 201-211
Conclusions
Invasive Aspergillosis

- Not just in the immuno suppressed population
- Increasing but low level of azole resistance (PCR useful)
- In the non-neutropenic patient, huge inflammatory necrosis and scant intralveolar hemorrhage
- Early diagnosis is paramount: Clinical picture, microbiology with BAL-GM, CT scan and, if needed, histology
- If clinical signs, abnormal imagingology and *Aspergillus* in BAL, treat even in the absence of classic immunosuppression
- Voriconazole with TDM is the preferred therapy
- Combination therapy in severe and azole-resistant cases