Managing chronic pulmonary aspergillosis infection

Jacques Cadranel
Service de Pneumologie et Réanimation
Conflict of interest statement : J Cadranel

- Principal investigator of the VERTIGO trial on behalf of Pfizer France
- Paid for talks on behalf of Pfizer
- Travel grants from Pfizer
Aspergillosis in human
*Aspergillus fumigatus* anatomy

Reproductive mycelium
- Conidium (spores)
- Phialides
- Conidiophore (stipe)

Vegetative mycelium
(hyphae or septate filaments)

Aspergillosis in human

Summary

- Fungi (Ascomycetes) of the order of *Plectomycetes*, the family of *Aspergillacea*
- Small percentage of the fungal flora (2%)
- About 30 species pathogenic for humans
- *Aspergillus fumigatus* (AF) responsible for 90% of cases, then *A. flavus* and *A. Niger*
Aspergillosis in human

Summary

- Cosmopolitan proliferating on decaying organic matter (plants, cereals, air conditioners ...)
- Found in 50% of urban habitats
- Permanent in the atmosphere
  - with renewed automnno-winter and during demolition work
  - in the environment: 1-20 spores/m3
- Pathogenicity factors of Aspergillus, factors related to the host
Aspergillosis in human

Pathogenicity factors of Aspergillus

- Small spores (2-5μm): acute inhalation; growth at 37°C in wet
- Filament formation: embarrassment to phagocytosis
- Receptors to fibrinogen and laminin: adhesion to the matrix
- Production of proteases and toxins (fumigatoxine, fumagillin, haemolysin ...) responsible for shock, hemorrhage, necrosis and inhibition of cellular repair
- To exhaust host defenses (gliotoxin)

Aspergillosis in human
Pathogenicity factors related to the host
Immunity

Inhalation of spores

Normal

Diminished

Pre-existing cavity

Highly diminished

Invasive aspergillosis

Unsuitable?

Asymptomatic

Asthma

ABPA

PHS

Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003
Pulmonary aspergillosis

Diagnostic methods

- Mycological diagnosis samples: sputum, fibroaspiration, BAL, biopsy ...
  - Direct examination:
    - size of the filaments, number and branching angle, aspect of the head
  - Cultures:
    - Sabouraud medium, several tubes, 37°C for at least 48 hours to 15 days, special media for identification
    - results even more valuable than:
      - sample obtained on "protected" specimen
      - repeatedly positive on direct examination
      - growing rapidly in culture to the "bottom of the tube »

- Absence of other pathogens +++
Pulmonary aspergillosis

Diagnostic methods

- Biological and immunological diagnosis
  - antigenemia (invasive aspergillosis):
    - different techniques,
    - highly specific (> 90%), sensitivity 70% (interest of repeated samples);
      diagnostic value depends on the center
    - can be applied to LBA or products of secretion
  - PCR diagnosis?
  - specific IgE (RIA, ELISA):
    - indicator of an immediate hypersensitivity
    - interest of associated skin testing
  - specific IgG assay:
    - screening by indirect hemagglutination (> 1 / 160);
    - confirmed by immunoprecipitation (≥ 3 arcs catalase),
    - indicator tissue infection
    - interest of associated skin testing
Pulmonary aspergillus infection

*Diagnostic methods: depending on the situation*

<table>
<thead>
<tr>
<th></th>
<th>Aspergilloma</th>
<th>CCPA</th>
<th>CNPA</th>
<th>Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT-scan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- mycetoma</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>- pneumonia</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>- necrosis</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Direct exam</strong></td>
<td>-</td>
<td>±</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Culture</strong></td>
<td>±</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Antigenemia</strong></td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td><strong>IgG</strong></td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>
Chronic pulmonary aspergillosis

- Numerous clinical, radiological, anatomical and pathological entities
  - Simple pulmonary aspergilloma
  - Complex pulmonary aspergilloma
  - Chronic, fibrosing or pleural cavitary pulmonary aspergillosis
  - Semi-invasive pulmonary aspergillosis
  - Chronic necrotising pulmonary aspergillosis
  - Pseudomembranous tracheobronchitis caused by Asp.
  - Invasive pulmonary aspergillosis
Anatomical and clinical continuum

Inhalation of spores

Normal

- Asymptomatic
- Pre-existing cavity

Diminished

- Necrotising aspergillosis
- Cavitary aspergillosis

Highly diminished

- Invasive aspergillosis

Immunity

- Unsuitable?
- Asthma
- Bronchitis
- ABPA
- PHS

Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003
Anatomical and clinical continuum

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Immunity

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Asthma

Bronchitis

Aspergilloma

Cavitary aspergillosis

Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003
Chronic pulmonary aspergillosis

Simple aspergilloma
Complex aspergilloma
Cavitary pulmonary aspergillosis
Necrotising pulmonary aspergillosis
Invasive aspergillosis
Pseudo-membranous tracheobronchitis

Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003
Chronic pulmonary aspergillosis

Aspergilloma
- simple aspergilloma

Chronic Necrotising Pulmonary Aspergillosis
- semi-invasive aspergillosis

Chronic Cavitary Pulmonary Aspergillosis
- complex aspergilloma
- chronic fibrosing/pleural aspergillosis

Pseudo-membranous tracheobronchitis

Invasive aspergillosis

Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003
Invasive aspergillosis in COPD
A new clinical entity?
CPA, an anatomical and clinical continuum

- Underlying lung disease
  - active or sequel tuberculosis
  - bronchiectasis, COPD
  - sarcoidosis

- Comorbidities
  - smoking
  - alcohol, diabetes, malnutrition

- Prolonged exposure to steroids
  - inhaled
  - oral, small doses

Sarceno J, Chest 1997; Soubani, Chest 2002; Denning D, CID 2003
<table>
<thead>
<tr>
<th>Underlying Lung Disease</th>
<th>Underlying disease (n=237)</th>
<th>Patients (n=126)</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>21 (16.7%)</td>
<td>20 (15.9%)</td>
<td>31 to 81%</td>
</tr>
<tr>
<td>Non MTB</td>
<td>20 (15.9%)</td>
<td>18 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>COPD/emphysema</td>
<td>42 (33.3%)</td>
<td>12 (9.5%)</td>
<td>42 to 56%</td>
</tr>
<tr>
<td>Pneumothorax (± emphysema)</td>
<td>21 (16.7%)</td>
<td>12 (9.5%)</td>
<td>12 to 17%</td>
</tr>
<tr>
<td>ABPA (± asthma)</td>
<td>18 (14.3%)</td>
<td>15 (11.9%)</td>
<td>12%</td>
</tr>
<tr>
<td>Asthma (± hypersensitivity)</td>
<td>13 (10.3%)</td>
<td>3 (2.4%)</td>
<td>5.6 to 12%</td>
</tr>
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<td>Sarcoidosis</td>
<td>9 (7.1%)</td>
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<td>12 to 17%</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>5 (4%)</td>
<td>4 (3.2%)</td>
<td>2.4%</td>
</tr>
<tr>
<td>Lung cancer survivor</td>
<td>13 (10.3%)</td>
<td>12 (9.5%)</td>
<td>8 to 10%</td>
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<tr>
<td>Thoracic surgery</td>
<td>18 (14.3%)</td>
<td>6 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>28 (22.2%)</td>
<td>10 (7.9%)</td>
<td>9.2 to 12%</td>
</tr>
<tr>
<td>Others</td>
<td>19 (8.2%)</td>
<td>5 (3.2%)</td>
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Adapted from Smith NL, Eur Respir J 2010
Underlying lung disease

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Adapted from Smith NL, Eur Respir J 2010
### Lung disease, comorbidities and steroids

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<tbody>
<tr>
<td></td>
<td>CNPA (n=59)</td>
<td>CPA (n=43)</td>
<td>CNPA (n=15)</td>
<td>CNPA (n=19)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CCPA (n=9)</td>
<td>CCPA (n=22)</td>
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<tr>
<td><strong>Lung disease</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>78%</td>
<td>95%</td>
<td>100%</td>
<td>44%</td>
</tr>
<tr>
<td>Tuberculosis/mycobacteriosis</td>
<td>76%</td>
<td>14%</td>
<td>54%</td>
<td>27%</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>20%</td>
<td>93%</td>
<td>-</td>
<td>15%</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>-</td>
<td>-</td>
<td>17%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>64%</td>
<td>40%</td>
<td>33%</td>
<td>41%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17%</td>
<td>-</td>
<td>12.5%</td>
<td>10%</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>7%</td>
<td>12%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>64%</td>
<td>35%</td>
<td>-</td>
<td>BMI = 17 (13-39)</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled route</td>
<td>42%</td>
<td>-</td>
<td>50%</td>
<td>37%</td>
</tr>
<tr>
<td>Oral route</td>
<td>-</td>
<td>19%</td>
<td>-</td>
<td>29%</td>
</tr>
</tbody>
</table>

*Saraceno J, Chest 1997; Camuset J, Chest 2007; Nam HS, Int J Infect Dis 2010; Cadranel J, for the VERTIGO group, CPLF 2010*
# General symptoms and haemoptysis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergilloma (n=72)</td>
<td>18 (25%)</td>
<td>19 (79%)</td>
<td>19 (79%)</td>
<td>33 (56%)</td>
</tr>
<tr>
<td>CPA (n=43)</td>
<td>19 (79%)</td>
<td>21 (87%)</td>
<td>19 (79%)</td>
<td>26 (44%)</td>
</tr>
<tr>
<td>CNPA (n=15)</td>
<td>19 (79%)</td>
<td>21 (87%)</td>
<td>19 (79%)</td>
<td>26 (44%)</td>
</tr>
<tr>
<td>CCPA (n=9)</td>
<td></td>
<td>8 (33%)</td>
<td>8 (33%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>CNPA (n=59)</td>
<td></td>
<td>3 (4%)</td>
<td>7 (33%)</td>
<td>15 (25%)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (5.6%)</td>
<td>4 (7%)</td>
<td>4 (7%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Expectoration</td>
<td>-</td>
<td>8 (33%)</td>
<td>8 (33%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>4 (5.6%)</td>
<td>21 (87%)</td>
<td>21 (87%)</td>
<td>26 (44%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (4%)</td>
<td>8 (33%)</td>
<td>8 (33%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td><strong>Haemoptysis</strong></td>
<td>61 (91%)</td>
<td>9 (37%)</td>
<td>9 (37%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Fever (T°C ≥ 38)</td>
<td>4 (5.6%)</td>
<td>7 (29%)</td>
<td>7 (29%)</td>
<td>40 (68%)</td>
</tr>
</tbody>
</table>

Recurrent and severe haemoptysis

Farthoukh M, Respir Research 2005

n=650

* p<0.05
Therapeutic strategy

☐ Three main objectives

- To limit further destruction of lung tissue
- To prevent life-threatening haemoptysis
- To improve quality of life
Therapeutic strategy

- Treatment of underlying condition, comorbidities and haemoptysis
  - Specific treatments for underlying lung disease and comorbidities
  - Respiratory rehabilitation and re-nutrition
  - Discontinuation or reduction of corticosteroids
  - Treatment of haemoptysis by endovascular procedure

- Treatment of aspergillosis
  - Curative treatment = surgery
    - eradicate aspergillosis
    - avoid relapse?
  - Palliative treatment
    - antifungal treatment, systemic >>>> local
Endovascular treatment

- Major systemic hypervascularisation
  - Bronchial and non-bronchial
  - Erosion of pulmonary blood vessels (arteries and veins)

- Importance of CT angiography
  - Etiological diagnosis
  - Localisation of bleeding associated with bronchoscopy
  - Mapping of vessels involved in hypervascularisation
  - Pin-pointing the mechanism
    - bronchial arterial hypervascularisation = systemic arterial embolization
    - false arteriovenous aneurysm = pulmonary vaso-occlusion

Khalil A, AJR 2007
## Endovascular treatment

- Efficiency of systemic arterial embolization

<table>
<thead>
<tr>
<th>Series</th>
<th>n/N</th>
<th>1 month relapse</th>
<th>Late relapse</th>
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<tbody>
<tr>
<td>Ulfacker (1985)</td>
<td>8/64</td>
<td>0/8</td>
<td>4/8 (2 deaths)</td>
</tr>
<tr>
<td>Corr P (2006)</td>
<td>12/12</td>
<td>1/12</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/14 (2 BAE)</td>
<td></td>
</tr>
</tbody>
</table>

“n” aspergilloses/“N” haemoptyses

Surgical treatment

- Avoid haemoptysis and loco-regional extension, permanent cure, improve survival
- No randomised study
- Numerous possible procedures:
  - lobectomy, pulmonectomy, atypical resection, cavernostomy, thoracoplasty, etc.
Surgical treatment

- Mortality 1 to >15%
- Morbidity 9 to 69% !!!
  - morbidity/mortality much lower with simple aspergilloma
  - primary morbidities and late mortality more likely linked to the underlying lung disease responsible and comorbidities

- Need for strict preoperative evaluation:
  - PFT, DLCO, V/Q scintigraphy, echocardiography, VO2 max
  - depending on comorbidities and the respiratory disease responsible
Therapeutic approach, aspergilloma

- Simple aspergilloma
  - Spontaneous lysis in 7 to 10% of cases
    (BTSA, Tubercle 1970; Hammerman KJ, Chest 1973)
  - Clinical/radiological stabilisation in 25% of cases
  - No proof of efficiency of antifungal treatments by systemic route
    - Itraconazole (Campbell JH, Thorax 1991)

Therapeutic abstention…

Soubani O, Chest 2002; Judson MA, Curr Opin Investig Drugs 2001
Therapeutic approach, aspergilloma

- Simple aspergilloma
  - Loco-regional complications and intermediate forms progressing to other aspergillus diseases in 65 to 75% of cases
  - Unpredictable risk of severe (>30%) and fatal haemoptysis

Indication for surgery…

Stevens DA, Clin Infect Dis 2000
Therapeutic approach, CCPA and CNPA

- Chronic cavitary/necrotising aspergilloses
  - Therapeutic strategy not codified
  - No methodologically satisfactory study
  - Place for surgery?
  - Indication for systemic antifungal treatment? (potentially combined with surgery if it is possible)

Multidisciplinary approach…

Antifungal treatments

- **Therapeutic classes**
  - **Polyenes (IV, local?)**
    - Amphotericin B deoxycholate
    - Liposomal amphotericin B
    - Amphotericin lipid complex
  - **Echinocandins (IV)**
    - Caspofungin
    - Micafungin
  - **Triazoles (IV, oral)**
    - Itraconazole
    - Voriconazole
    - Posaconazole

*From Sanglard D. JIDIF: Optimed Ed. 2003: 29-45*

*Walsh T in IDSA Guidelines, Clin Infect Dis 2008*
Local antifungal treatment

- Injection of Ampho. B in the aspergillus cavity or in the bronchus draining the aspergilloma in inoperable patients
  - Control of haemoptysis
  - Disappearance of the aspergilloma and/or negative result on aspergillus serology in 2/3 cases

- Limits
  - Case series, single centre studies
    - non-controlled?; small number of patients?
  - Complications: pulmonary abscess and anaphylactic shock

# Systemic antifungal treatment, IV

<table>
<thead>
<tr>
<th>Studies</th>
<th>Treatment</th>
<th>Type</th>
<th>n</th>
<th>Efficiency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denning</td>
<td>amphotericin B</td>
<td>CPA</td>
<td>11</td>
<td>82%</td>
<td>Definition of efficiency ?</td>
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<tr>
<td>Case series</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nam</td>
<td>amphotericin B</td>
<td>CNPA ?</td>
<td>4</td>
<td>All dead</td>
<td></td>
</tr>
<tr>
<td>Case series</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Izumikawa</td>
<td>micafungin ± other antifungal</td>
<td>CCPA</td>
<td>9</td>
<td>78%, “success at EOT”</td>
<td>Association with other antifungals in 5/9 4-week treatment (29-96 dys)</td>
</tr>
<tr>
<td>Case series</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Kohno                       | micafungin line?                  | CPA                 | 31  | 60%, “success at EOT” | Different response criteria for CNPA and aspergilloma  
Treatment duration: 13-56 dys |
| Prospective trial          |                                   | Aspergilloma CNPA   | 22  | 55%          |                                                                          |
|                             |                                   | 9                   |     | 67%          |                                                                          |
| Khono 2                     | micafungin (vs voriconazole)      | CPA                 | 50/96 | 60% “success at 4 weeks” | Only 4-week treatment  
Very subjective criteria of evaluation |
| Prospective controlled trial|                                   |                     |     |              |                                                                          |

## Systemic antifungal treatment, oral

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<tr>
<td>De Beule</td>
<td>itraconazole</td>
<td>Aspergilla</td>
<td>42</td>
<td>30%, radiological</td>
<td>Diagnostic criteria? Dose, duration? Evaluation of efficacy? Endpoints?</td>
</tr>
<tr>
<td>Prospective trial</td>
<td>&gt;40% post ampho.</td>
<td>CNPA</td>
<td>44</td>
<td>66%, radiological</td>
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<td>Dupont</td>
<td>itraconazole</td>
<td>Aspergilla</td>
<td>14</td>
<td>14%, radiological</td>
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<td>line?</td>
<td>CNPA</td>
<td>14</td>
<td>50%, radiological</td>
<td>Treatment duration: aspergilloma=7 months (2-13); CNPA=5.7 months (2-11.5)</td>
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<td>Nam</td>
<td>itraconazole</td>
<td>CNPA</td>
<td>39</td>
<td>38%, “success after ≥ 3 mo”</td>
<td>Probably CPA rather than CNPA</td>
</tr>
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<td>Case series</td>
<td>line ?</td>
<td></td>
<td></td>
<td></td>
<td>Treatment duration: 6 months (IQR=6-12)</td>
</tr>
</tbody>
</table>

*De Beule K, Mycosis, 1988; Dupont B, J Am Acad Dermatol 1990; Nam HS, Int J Infect Dis 2010*
Systemic antifungal treatment, oral

<table>
<thead>
<tr>
<th>Studies</th>
<th>Treatment</th>
<th>Type</th>
<th>n</th>
<th>Efficiency</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Felton Case series, National Referral Centre | posaconazole 28% post itra- or voriconazole 46% after toxicity          | CPA   | 79 | 61%, “success at 6 mo.”       | Treatment duration: 7 mo. (1-11) for naive and 7.8 mo. (<1-53) for pre-treated  
≈15% of patients need dose modification after evaluation of plasma [posa.] |
## Systemic antifungal treatment, oral

<table>
<thead>
<tr>
<th>Studies</th>
<th>Treatment</th>
<th>Type</th>
<th>n</th>
<th>Efficiency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jain</td>
<td>voriconazole</td>
<td>CCPA</td>
<td>11</td>
<td>64%,</td>
<td>No radiological evaluation</td>
</tr>
<tr>
<td>Case series</td>
<td>≈100% post itra.</td>
<td></td>
<td></td>
<td>“clinical success at 3 mo.”</td>
<td></td>
</tr>
<tr>
<td>Sambatakou</td>
<td>voriconazole</td>
<td>CPA</td>
<td>15</td>
<td>67%,</td>
<td>Pos-hoc centralised review by D Denning</td>
</tr>
<tr>
<td>Prospective trial</td>
<td>27% post itra.</td>
<td></td>
<td></td>
<td>“success at EOT”</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment duration: 3.6 months (&lt;1-4)</td>
<td></td>
</tr>
<tr>
<td>Camuset</td>
<td>voriconazole</td>
<td>CPA</td>
<td>24</td>
<td>58%,</td>
<td>Centralised review by 2 investigators</td>
</tr>
<tr>
<td>Case series</td>
<td>46% post itra.</td>
<td></td>
<td></td>
<td>“success at EOT“</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNPA</td>
<td>15</td>
<td>67%</td>
<td>Very stringent diagnostic criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCPA</td>
<td>9</td>
<td>44%</td>
<td>Treatment duration: 6.5 months (4-36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P=0.04, in favor of CNPA</td>
<td></td>
</tr>
<tr>
<td>Khono 2</td>
<td>voriconazole</td>
<td>CPA</td>
<td>46/96</td>
<td>59%</td>
<td>Only 4-week treatment</td>
</tr>
<tr>
<td>Prospective controlled trial</td>
<td>(vs micofungin)</td>
<td></td>
<td></td>
<td>“success at 4 weeks“</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very subjective criteria of evaluation</td>
<td></td>
</tr>
</tbody>
</table>

Systemic antifungal treatment, oral

- Prospective, non-comparative, multicentre study
- Diagnostic criteria:
  - clinical+CT+mycological+serology
    - CNPA, n=19
    - CCPA, n=22
- No pre-treated patients
  - severe haemoptysis
  - eligible for surgery
  - prior systemic treatment
- Voriconazole
  - 200 mg x 2/d, 6 months
  - >6 months and <12 months
  - duration: 8.3 months (<1-13.5)

- Endpoints
  - clinical, radiological and mycological
  - 3 months, 6 months, end of treatment
  - centralised review by panel

- Objectives
  - primary:
    - CT improvement (>50%) + mycological eradication at 6 months > 30%
  - secondary:
    - radiological efficiency
    - quality of life and safety
    - relapse at 6 months post EOT
    - survival

Cadranel J, for the VERTIGO trial group
Systemic antifungal treatment, oral

Efficiency at different endpoints

- Global success at M3: 12/41 (29%)
- Global success at M6: 13/41 (32%)
- Global success at EOT: 18/41 (44%)

CNPA: 9% (2/22), 14% (3/22), 10% (2/22)
CCPA: 53% (10/19), 53% (10/19), 58% (11/19)

p = 0.01, p = 0.01, p = 0.09

Cadranel J, for the VERTIGO trial group
Systemic antifungal treatment, oral

- Mycological response
  All patients had mycological eradication or presumed eradication of Aspergillus spp in relevant bronchopulmonary samples at M6 and EOT

- Radiological response at ≥6-month treatment (n=31 patients)

Cadranel J, for the VERTIGO trial group
Systemic antifungal treatment, oral

Quality of Life

Cough, Dyspnea, Sputum production, Hemoptoïc sputum, Chest tightness, Nocturnal awakening, Global

Mean VAS (mm)

Baseline, M6, End of Study

Cadranel J, for the VERTIGO trial group
Systemic antifungal treatment, oral

- Safety results
  - Treatment related adverse events with a frequency greater than 5% (i.e. in at least 3 patients):
    - visual disturbances (21%),
    - photosensitivity reactions (19%),
    - blurred vision (12%),
    - constipation, vomiting, gamma-GT increased (10% each),
    - chills, decreased appetite, headache, insomnia (8% each)
    - vertigo, nausea, cholestasis, weight loss, anorexia (6% each)
  - These side effects are consistent with the known adverse event profile of voriconazole

- Overall survival (88%)
  - 5 patients died during the study from underlying disease (bacterial pneumonia, pneumothorax, chronic respiratory insufficiency, ovarian cancer, septic shock.)
    None attributable to CPA.
Systemic antifungal treatment

- According to guidelines from IDSA experts

<table>
<thead>
<tr>
<th>Type</th>
<th>Treatment</th>
<th>Options</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Invasive aspergillosis</td>
<td>voriconazole</td>
<td>amphoB, caspo., mica., posa., itra.</td>
<td></td>
</tr>
<tr>
<td>Aspergilloma</td>
<td>abstention or surgery</td>
<td>itraconazole or voriconazole</td>
<td><strong>medical treatment?</strong></td>
</tr>
<tr>
<td>Chronic necrotising aspergillos</td>
<td>voriconazole</td>
<td>amphoB, caspo., mica., posa., itra.</td>
<td>prolonged oral treatment</td>
</tr>
<tr>
<td>Chronic cavitary aspergillosis</td>
<td>itraconazole or voriconazole</td>
<td>amphoB, caspo., mica., posa.</td>
<td>prolonged oral treatment surgery?</td>
</tr>
</tbody>
</table>

*From Walsh T in IDSA Guidelines, Clin Infect Dis 2008*
Managing chronic pulmonary aspergillosis infection

- Heterogeneous clinical entities
  - comorbidities ± pulmonary disease
  - pay attention to the association between COPD and steroids
- Surgery alone rarely possible
- Most often need a multidisciplinary approach:
  - surgeon, radiologist, functionalist, pneumologist…
  - impact of “booming“ in antifungal armamentarium
  - efficiency of triazole particularly in necrotizing forms
  - therapeutic sequence to define
- Important morbidity/mortality
  - mainly due to comorbidities and underlying diseases