Cryptococcosis
A cosmopolite fungal disease caused by a sugar-coated yeast

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Pathogenic agents

The yeast

- Phylum = Basidiomycete
- Teleomorphs = *Filobasidiella neoformans* and *Filobasidiella bacillispora*
- Budding yeast
- Production of a mucopolysaccharidic capsule under host-relevant conditions
Epidemiology

The cryptococcosis global burden

- 1 million annual cases worldwide
- > 600 000 deaths per year

[Park BJ, AIDS 2009]
The cryptococcosis global burden

- First case report in 1895
- *Cosmopolite* agent
- *One of the most common opportunistic infection* among HIV/AIDS

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The cryptococcosis global burden

- **Endemic areas:**
  - Sub-Saharan Africa
  - South-East Asia

- **Rise of incidence in developed countries** [Mc Mullan, PloS One 2012]
  - Among *non-HIV immunosuppressed subjects* (↗ corticosteroid use, monoclonal Ac and anti-TNF, RTCT, transplants)
  - ...but also among immunocompetent people
    - High mortality rate (30%) due to delayed diagnosis
    - Not always underlying diseases
    - Genetic susceptibility to the pathogen ? (dysimmunity? Anti GM-CSF Ab production?)
Cryptococcal meningitis (CM): the most frequent clinical picture

- First fungal meningitis +++
- 3% of HIV-positive subjects develops CM in Sub-Saharan Africa
- Early mortality rates (2 weeks)
  - 5.6% in developed countries [Van der Horst, NEJM 1997]
  - 10-25% in Africa [Jarvis, AIDS 2007]
- Late mortality rates (3 months) = 15-25% even in developed countries
- Global mortality rates [Bicanic, CID 2007] [French, AIDS 2002] [Jarvis, CID 2009] [Perfect, CID 2010]
  - 15-75% in HIV/AIDS in middle-to-low income countries
  - 100% if no treatment

Cryptococcosis: other forms

- **Pulmonary forms** = South-East Asia

- **Infection of immunocompetents**
  - 31% of reported cases in Australia (overall incidence of 6.6 cases per million population/year)
  - Meningitis > pneumonia (ASE)
Taxonomy

Usual taxonomy: a 2-species concept

- *C. neoformans/gattii* complex comprises two species, and 5 serotypes

<table>
<thead>
<tr>
<th>Serotypes</th>
<th>Cryptococcus neoformans var. grubii</th>
<th>Cryptococcus neoformans var. neoformans</th>
<th>Cryptococcus neoformans serotype A/D hybrid*</th>
<th>Cryptococcus gattii</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>VNI (AFLP1), VNII</td>
<td>VNIIV (AFLP3)</td>
<td>VNIII</td>
<td>VGII (AFLP4), VGIII(a,b,c) (AFLP6), VGIV (AFLP7)</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B and C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climate</td>
<td>All</td>
<td>Mild to cold</td>
<td>—</td>
<td>Tropical, subtropical, mild</td>
</tr>
<tr>
<td>Distribution</td>
<td>Worldwide</td>
<td>Europe</td>
<td>Mainly Europe</td>
<td>Americas, Oceania</td>
</tr>
<tr>
<td>Specificities</td>
<td>Immunosuppressed subjects (HIV++)</td>
<td></td>
<td></td>
<td>Immunosuppressed AND immunocompetents subjects</td>
</tr>
</tbody>
</table>
New taxonomy: the seven species concept

- 7 species individualized

AFLP fingerprint analysis + phylogenetic analysis after amplification and sequencing of 11 nuclear loci of 115 isolates

C. neoformans
Ex. neoformans var. grubii

C. demeioformans
Ex. neoformans var. neoformans

Fig. 4. Diversity in the C. gattii neoformans species complex inferred from a concatenated data set of 11 loci. The clade letters are documented in the text, isolates indicated in bold were used for describing the seven species.

New taxonomy: the seven species concept

- 7 species, 8 serogenotypes, 4 hybrids

<table>
<thead>
<tr>
<th>Current species name</th>
<th>MLST Clade</th>
<th>AFLP-genotype</th>
<th>PCR fingerprint/ARFLP genotype</th>
<th>Proposed species name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcus neoformans var. grubii</td>
<td>Clade E, AFLP1</td>
<td>VNI</td>
<td>-</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Cryptococcus neoformans var. neoformans</td>
<td>Clade G, AFLP1/VNI, Clade H, AFLP18</td>
<td>VNI, VNI</td>
<td>-</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Cryptococcus gattii</td>
<td>Clade I, AFLP2</td>
<td>VNI, VNI</td>
<td>-</td>
<td>Cryptococcus gattii</td>
</tr>
<tr>
<td>Cryptococcus neoformans var. neoformans</td>
<td>Clade L, AFLP3</td>
<td>VNI</td>
<td>-</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Cryptococcus neoformans var. grubii</td>
<td>Clade D, AFLP4, Clade C, AFLP5</td>
<td>VG2, VG2</td>
<td>-</td>
<td>Cryptococcus gattii</td>
</tr>
<tr>
<td>Cryptococcus neoformans var. grubii</td>
<td>Clade A, AFLP6</td>
<td>VG2</td>
<td>-</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Cryptococcus neoformans var. grubii</td>
<td>Clade E, AFLP7</td>
<td>VG2, VG2</td>
<td>-</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Cryptococcus neoformans var. grubii</td>
<td>Clade B, AFLP10</td>
<td>VG2, VG2</td>
<td>-</td>
<td>Cryptococcus neoformans</td>
</tr>
</tbody>
</table>

*Hagen, 2015*
**Geographical distribution**

![Map showing geographical distribution of Cryptococcus neoformans, Cryptococcus deneoformans, and Cryptococcus gattii complex (5 species)]

<table>
<thead>
<tr>
<th>Region</th>
<th>Cryptococcus neoformans</th>
<th>Cryptococcus deneoformans</th>
<th>Cryptococcus gattii complex (5 species)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oceania</td>
<td>34%</td>
<td>1%</td>
<td>64%</td>
</tr>
<tr>
<td>Asia</td>
<td>82%</td>
<td>0.3%</td>
<td>5%</td>
</tr>
<tr>
<td>Africa</td>
<td>79%</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>North America</td>
<td>34%</td>
<td>5%</td>
<td>56%</td>
</tr>
<tr>
<td>South America</td>
<td>73%</td>
<td>1%</td>
<td>26%</td>
</tr>
<tr>
<td>Europe</td>
<td>59%</td>
<td>18%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Worldwide: Europe (North ++) Americas, Oceania

**C. deuterogattii outbreak**

- Since 1999: Vancouver Island, Canada  
  - [Kidd, 2007]
  - 1999 – 2007: 218 cases – VGII/AFLP6 newly C. deuterogattii

- Since 2005: Oregon & Washington, USA  
  - [Mac Dougall, 2007]
  - 2004 – 2011: 96 cases
Reservoir

- **Birds’ excreta** (pigeon droppings ++)

- **Eucalyptus and > 50 trees species** (decaying woods ++) → *C. gattii*

- In West Cameroon
  
  - 28.5% prevalence of *C. neoformans* and *C. gattii* in **pigeon droppings**
  
  (55%) and **bat’s guanos** (45%)  
  
  [Dongmo, 2016]
Pathophysiology & risk factors

Contamination

[Lin and Heitman, 2006]
Cryptococcosis: a dormant infection

- Basidiospore inhalation → unrecognized pneumonia in childhood
  - Granuloma formation and antibodies’ production
  - Dormancy of yeast cells (latent infection)
  - Reactivation in case of immunodeficiency
  - Replication within the lung and systemic dissemination with blood-brain barrier crossing ++

Titan cells: Toward Biological Evidence of Dormancy

- Particular adaptation of fungal cells to host = TITAN CELLS
  - Extraordinarily enlarged yeast cells resistant to phagocytosis
  - Playing a central role in the persistence of the infection in vivo

- DORMANT CELLS = Low metabolic activity and delayed growth

[Alanio, 2015]
Risk factors _C. neoformans_

- **Immunosuppression +++**
  - AIDS: \(77.4\%\)
  - SOT: \(2.7-8\%\)
  - Leukemia: \(5.8\%\)
  - Immune disorders: \(4\%\)

- HIV \(\rightarrow\) **Major risk if CD4\(^+\) \(\leq 100/\text{mm}^3\)** [Jarvis, 2010]

- Immunocompetents (-)

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Risk factors _C. gattii complex_

- **Immunocompetents +++**

- **Immunosuppression (-) C. tetragattii**
  - AIDS
  - Chronic alcohol abuse
  - Corticosteroids
  - Immunosuppressive therapies
  - Dysimmunity
  - Diabetes
  - Leukemia
  - LED, rheumatoid arthritis, psoriasis
  - Arthritis
  - SOT
  - Malignancy

[Chen, 2014]
Clinical pictures

Clinical forms

<table>
<thead>
<tr>
<th>Clinical Form</th>
<th>Frequency</th>
<th>Isolation site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningoencephalitis</td>
<td>21</td>
<td>CSF</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>5</td>
<td>Blood</td>
</tr>
<tr>
<td>Fungiemia</td>
<td>8</td>
<td>CSF + Blood</td>
</tr>
<tr>
<td>Pneumococcal meningitis</td>
<td>10</td>
<td>CSF + Blood</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>100</td>
</tr>
</tbody>
</table>

* Up to 47.71% of fungaemia among AIDS patients according to studies

[Aguiar, 2017]
Multicenter prospective French study from 1997 to 2001

Inclusion criteria:
- Adults HIV+ or HIV−
- With a first episode of culture-proven cryptococcosis = isolation of Cryptococcus neoformans A/D from at least one body site

Cases:
- Cryptococcal meningocryptococcalitis (positive CSF culture, positive direct examination, and/or antigen testing)
- Extrameningeal cryptococcosis
- Dissemination = at least two non-contiguous body sites infected

Following:
- Two weeks (W2) and three months (M3) after antifungal therapy
- Clinical evaluation
- Mycological evaluation = culture of initially infected body sites

Flow Chart and risk factors

[Diagram showing flow chart with patient outcomes and risk factors]

- HIV−
  - SOT (n=21)
  - Malignancies (n=21)
  - Various underlying diseases* (n=12)
  - No identified risk factor** (n=8)

- HIV+
  - Mean CD4+= 45.1/mm^3
  - Mean viral load = 4.9 log_{10} copies/ml
  - 40% under HAART

* Diabetes mellitus, cirrhosis, sarcoidosis, idiopathic CD4^+ T lymphopenia, hypogammaglobulinaemia, corticosteroid therapy

** Primary cutaneous cryptococcosis n=5
Clinical presentation

- **First notified symptoms:**
  - Headache [34%]
  - Fever [23%]
  - Altered mental status, skin lesions, and cough [9%]

- **Abnormal neurology signs** in 46% of cryptococcal meningitis
  - Altered mental status [33%]
  - Motor or cranial nerves paresis [15%]
  - Seizures [10%]

Characteristics according to HIV status

- **Mild and late meningism** especially among non-HIV patients ++
- Mean time of hospitalisation significantly higher in HIV – patients presenting with meningoencephalitis (6 weeks vs 3.3 weeks, p=0.0019)

Table 1. Baseline Clinical, Radiological, and Mycological Characteristics in 230 Adult Patients with Culture-Confirmed Cryptococcosis According to HIV Serostatus

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameter</th>
<th>HIV Positive Patients (n = 177)</th>
<th>HIV Negative Patients (n = 53)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical parameters at baseline</td>
<td>Sex ratio, M/F</td>
<td>0.1</td>
<td>2.5</td>
<td>0.100</td>
</tr>
<tr>
<td></td>
<td>Mean age in years ± SD (lower/upper)</td>
<td>39.2 ± 8.4 (177)</td>
<td>53.9 ± 17.4 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Mean body mass index ± SD (lower/upper)</td>
<td>26.6 ± 3.3 (155)</td>
<td>27.3 ± 4.1 (45)</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Body temperature °C ± % (positive/other)</td>
<td>86.1 ± 0.1 (177)</td>
<td>86.4 ± 0.1 (53)</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Mean hematocrit % ± % (positive/other)</td>
<td>65.3 ± 14.1 (177)</td>
<td>67.2 ± 12.1 (53)</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Mean WBC ± % (positive/other)</td>
<td>5.0 (1.0/177)</td>
<td>5.5 (0.5/53)</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Abnormal neurology*, % (positive/other)</td>
<td>38.6 (70/177)</td>
<td>32.3 (20/53)</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Abnormal bone imaging, % (positive/other)</td>
<td>35.1 (50/177)</td>
<td>32.3 (20/53)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Abnormal chest X ray or CT scan, % (positive/other)</td>
<td>51.3 (94/177)</td>
<td>55.1 (94/53)</td>
<td>0.62</td>
</tr>
<tr>
<td>Mycological results</td>
<td>Positive blood, % (positive/other)</td>
<td>91.1 (160/177)</td>
<td>81.9 (43/53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Positive CSF culture, % (positive/other)</td>
<td>86.0 (200/229)</td>
<td>60.9 (24/40)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Positive bone culture, % (positive/other)</td>
<td>45.3 (30/66)</td>
<td>25.0 (13/52)</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>Positive mycelia, % (positive/other)</td>
<td>76.0 (130/171)</td>
<td>60.9 (51/83)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Defined by abnormal mental status, seizures, neurological defects.

**Based on positive culture or, in case of negative culture, a positive examination or a positive antigen determination.

[Dromer, 2007]
Raised CSF opening pressure

- CSF opening pressure > 25 cmH20
- Accumulation of fungi at the arachnoid villi and subarachnoid spaces
  - Obstruction of the CSF outflow
  - Inflammatory processes and cerebral oedema
- Profound and irreversible visual and hearing losses
- Poor short-term survival
- Correlated to a high fungal burden in CSF (Pearson = 0.28; p = 0.001)*

* [Concha-Velasco, 2017]

Hydrocephalus

- Onset median time = 6 months (0 to 7 years)
- Always symptomatic
  - GSC < 14
  - Walking disorders
  - Papillar oedema
- Associated with persistent positive CSF culture
- CSF derivation ++

[Park, CID 1999]
Cutaneous forms

Squamous white macula with irregular shape (primitive lesion)

Papulo-nodular lesions (secondary lesions)

- 28 primitive lesions
- 80 secondary lesions

Pulmonary infection

- Portal of entry ++

- Sub-acute or chronic respiratory disorders:
  - Fever
  - Cough
  - Dyspnea
  - Chest pain

- TDM: pulmonary nodules ++

- Non HIV-patients: occurs on pre-existing pulmonary diseases
Cryptococcal IRIS (1)

- **Immune reconstitution inflammatory syndrome (IRIS)** following the initiation of ART in patients with subclinical or established cryptococcal disease
- Rapid but **dysregulated** pathogen-specific immune restoration → dysregulated response to residual fungus or polysaccharide Ag
- HIV and also non-HIV...
- Aseptic meningitis, fever, cerebral lesions, necrotic lymphadenopathy...

[Perfect & Bicanic 2015]
Cryptococcal IRIS (2)

- 13-39% of HIV patients in the early months on ART

- Mortality between 8 and 31% [Lawn, AIDS 2008] [Walker, CID 2012]

- In a South African study, CM IRIS was implicated in 20% of all deaths of patients within the first four months of ART initiation (more common than TB-attributable mortality!)

- Risk factors of high mortality: Early initiation of ART (within the first 15 days) +++ [Perfect, J. R. & Bicanic, T. 2015]
Mycological diagnosis

Direct examination and culture
Immunodiagnosis

Cryptococcal meningitis: a late diagnosis

- 2 to 3 weeks between the beginning of symptoms and the diagnosis of cryptococcal meningitis (both HIV-infected and SOT patients) [Bratton, 2012]

- Even worse for immunocompetents !!
CM and CSF cell count/biochemical parameters

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Cell count</th>
<th>Glucose</th>
<th>Proteins</th>
<th>Chlorures</th>
<th>Micro-organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purulent</td>
<td>PNN</td>
<td>▼</td>
<td>▼</td>
<td>N</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Clear opalescent</td>
<td>PNN/lympho</td>
<td>▼</td>
<td>▼</td>
<td>N</td>
<td>Listeria</td>
</tr>
<tr>
<td>Clear</td>
<td>Lympho</td>
<td>▼</td>
<td></td>
<td></td>
<td>TB</td>
</tr>
<tr>
<td>Clear</td>
<td>Lympho</td>
<td>N</td>
<td>▼</td>
<td>N</td>
<td>Virus</td>
</tr>
<tr>
<td>Clear</td>
<td>Lympho +/-</td>
<td>▼ ou N</td>
<td>▼</td>
<td>N</td>
<td>Cryptococcus</td>
</tr>
</tbody>
</table>

Diagnostic tools

- **Direct examination:**
  - In body fluids with India ink examination (*i.e.* Encre de Chine)
  - Histopathology of infected tissue with specific stains to identify capsule (*mucicarmine and alician blue*)

- **Culture-based methods** of fluids and/or tissues

- **Immunodiagnosis** from body fluids (serum/plasma, CSF, urines)

Gold standard methods ++
- Sensitivity
- Large quantity of sample required

- Good sensitivity
- Less time intensive than culture
Direct examination

- India ink stain
- Round to ovoid yeasts
- 3-8µm, up to 20µm (titan cells)
- Multilateral budding
- Encapsulated ++ → halo around cells

Culture and identification

- Sabouraud medium at 30-32°C under aerobic conditions during 42 days
- Usually fast growing (3 to 5 days) beige and mucous colonies
- Gender and species identification now routinely based on MALDI-TOF

By using the CBS-KNAW in-house database together with the Bruker BDAI database (3905 MSPs, v3.1.2.0) all 423 isolates (100%) of the C. gattii/C. neoformans species complex were identified by MALDI-TOF MS at the species level.

A correct identification at the species and AFLP genotype level was obtained for 415 (98.1%) out of 423 isolates.

[Hagen et al., 2014]
Species diagnosis

- **Serotyping** (monoclonal Ab)
- **Molecular identification and genotyping** (RFLP)

→ National Center of Mycosis

*Fig. 1.* Gel RFLP fingerprint showing the DNA patterns between 11 Cryptococcus strains and C. neoformans var. grubii reference strain. Lanes 1-7: C. neoformans, lanes 8-11: C. neoformans var. grubii strains A, B, C, and D. M: molecular marker (Bio-Rad D1000 ladder, 100-bp ladder).

Immunodiagnosis

- **Aim** = detection of cryptococcal antigen (**CrAg**) in body fluids = capsular glucuronoxylomannan (**GXM**)
- **Techniques** = based on anti GXM monoclonal antibodies
  - **EIA (ELISA)**
    - Premier EIA (Meridian Biosciences, Cincinnati, OH)
    - Alpha CrAg EIA (Immuno-Mycologics [IMMY], Norman, OK)
  - **Latex agglutination (LA)**
    - CALAS™ (Meridian Biosciences, Ohio, USA)
  - **Lateral flow assay (LFA)** → point of care (POC) ++
    - CrAg LFA (Immuno-Mycologics [IMMY], Norman, OK)
    - Biosynex CryptoPS (BIOSYNEX® diagnostics, Strasbourg, France)

**CrAg LFA** 20 sera testing = ~17 min compared to 50 min by Premier EIA, 60 min by the Alpha CrAg EIA, and 70 min by the LA test.
Mycological diagnosis

- **At least two body sites** in 222 [97%] of the patients

- **Cryptococcal meningoencephalitis** mostly diagnosed by:
  - **CSF culture +++** (with positive CSF + serum Ag)
  - Except in 3 patients (2 positive CSF antigen and one positive India ink)

- **Extra meningeal cryptococcosis**
  - 20% presenting with **negative serum antigen detection**

- **Disseminated infection/fungaemia**
  - Significantly higher antigen titers ($p<0.001$)

[Dromer, 2007]

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**CrAg LFA: why ?**

- **Point-of-care test (POCT) +++ → WHO ASSURED criteria**

- Intended for developed countries with a high cryptococcosis burden
  - **Affordable**
  - **Sensitive**
  - **Specific**
  - **User friendly**
  - **Rapid**
  - **Equipment free (no requirement of enzyme or heat)**
  - **Delivered to those who need**

POCTs: HBV, HIV, Malaria, Syphilis, Cholera, NTDs such as Human African Trypanosomiasis or visceral leishmaniasis
What does the literature say?

CrAg IMMY LFA performances

- Very sensitive tool when compared with the gold standard culture ++
  - Se= 100% (serum, CSF), Sp=92.9-100% (minor FP due to Trichosporon sp. infection are possible) ➔ Less false positive than with LA

- Can be used on both serum, plasma, CSF (and urines)

- Low specificity in urines ➔ PPV=22.7-42.1% but a good NPV [Magambo, 2014] [Mc Mullan, 2012] [Longley, 2016]

- Higher sensitivity than EIA or LA tests [Binnicker, 2012] [Hansen, 2013] [Longley, 2016] [Mc Mullan, 2012]

- No agreement between LFA and LA titers +++
Biosynex CryptoPS can detect the 4 serotypes

- Results within 10 min
- 2 bands:
  - T1-band is qualitative
  - T2-band is semi-quantitative → only appear with elevated CrAg titres
- 98.4% and 100% of agreement between IMMY LFA and Biosynex CryptoPS in serum and CSF respectively
- Sensitivity of 100% (= IMMY)
- Slightly better specificity than IMMY in serum (98.3 vs. 96.6%)
- No false positive in urines (= IMMY)
- T2-band associated with high serum titers → surrogate marker of CM
- T2-band allows to avoid serial dilutions in patients presenting with high titers in developing countries (expensive and time-consuming)
Asymptomatic CrAg: what does it mean?

- Prevalence of asymptomatic CrAg among HIV-positive patients with CD4 ≤ 100/mm³ between 4.3 and 7.5% according to the studies (East and South-East Africa)

- CrAg is detectable in peripheral blood by an average of 22 days prior to the onset of CM symptoms (100 days for 11% of people)

Clinical significance of asymptomatic CrAg

- Independent risk factor of mortality among patients initiating ART +++
  - Mortality increase by 18% in the first 3 months of ART initiation** [Lietchy, 2007]
  - CrAg-positive patients = 2.46 more risk of death over the first year on ART

Hazard ratio (HR) for death = 2.46; 95% confidence interval [CI], 1.13–5.36; P = .023 [Longley, 2016]

** 1 death potentially avoided per 67 people screened in a 7% prevalence area!!
Clinical significance of asymptomatic CrAg

- Independent risk factor of developing CM among patients initiating ART

- 28% of asymptomatic CrAg-positive patients developed proven CM without pre-emptive ttt [Etard, 2006]

- 40% of asymptomatic CrAg-positive patients had a positive CSF CrAg in a South-African prospective study (n=645) [Longley, 2016]

- 45.5% of asymptomatic CrAg-positive patients had meningeal involvement [Dromer, 2007]

CrAg screening and pre-emptive treatment

- Systematic screening of patients with CD4 ≤ 100/mm3 and pre-emptive ATF treatment of asymptomatic CrAg-positive patients endorsed by the WHO in 2011

- Preemptive antifungal treatment by fluconazole and timely ART initiation prevents CrAg-positive asymptomatic patients without meningeal involvement from developing CM or CM-IRIS in the first year of ART
Clinical significance of CrAg during disease

- **At the diagnosis:** > 1:512 (serum or CSF) = risk of mycological failure at two weeks

- **During therapy:**
  - Lack of correlation between titers decrease in CSF or serum and:
    - CM outcome [Antinori, 2005]
    - CFU decline in CSF culture [Antinori, 2005]
    - Not for therapeutic monitoring +++
  - Persistently elevated CSF titers = risk of relapse in HIV-infected patients and poor prognosis marker (ongoing production of viable yeasts ?)
  - CrAg remains detectable in serum and CSF for months (up to one year) following successful therapy (i.e. culture sterilization) → Not an index of cure !! [Lu, 2005] [Antinori, 2005]
Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

General principles
CM Treatment – 3 phases

**Induction phase**
- AmB - 5-FC
- 14 days
- Ideally until culture sterilization, CSF normalization, and clinical improvement

**Consolidation phase**
- Fluconazole PO
- 400 to 800 mg/d
- Minimum 8 weeks

**Secondary prophylaxis**
- Fluconazole PO
- 200 mg/d
- Minimum 12 months

The bitherapy reevaluation should not be based on CrAg kinetic but on the CSF sterilization, India Ink and biochemical normalization!

- AmB deoxycholate IV 1 mg/kg/d or LamB 3 mg/kg/d
- 5-FC IV or PO 100 mg/kg/d in 4 administrations – NFS & therapeutic monitoring +++

**Exhaustive mycological monitoring**
- Weekly CSF opening pressure
- Weekly CSF direct exam and culture (and CrAg)
- Blood and urine cultures

**CSF OP management**

- Frequent monitoring +++

- CSF drainage (20 to 30 ml) 2 to 3 times a week to maintain an OP < 25 cmH_2O

- If CSF drainage failure → **ventricular derivation**+

- Mannitol and steroids are not recommended

- High baseline CSF opening pressure (≥35 cmH_2O) associated with:
  - Failure of early mycological clearance and 10 weeks relapse
  - Headache, meningismus, papilloedema, hearing loss, and poorer long-term survival

Graybill, CID 2000
Bicanic, AIDS 2009
Baseline CSF OP as a predictive factor

<table>
<thead>
<tr>
<th>Pressure (cm H₂O)</th>
<th>&lt;19</th>
<th>19-25</th>
<th>25-35</th>
<th>&gt;35</th>
</tr>
</thead>
<tbody>
<tr>
<td>nb Patients</td>
<td>52</td>
<td>50</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>Guérison clin. à S2</td>
<td>83%</td>
<td>80%</td>
<td>80%</td>
<td>82%</td>
</tr>
<tr>
<td>LCR stérile à S2</td>
<td>69%</td>
<td>64%</td>
<td>47%</td>
<td>45%</td>
</tr>
<tr>
<td>* LCR stérile à S10</td>
<td>62%</td>
<td>60%</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>Survie (Méd. Mois)</td>
<td>11</td>
<td>10</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

* malgré antifongiques + PL évacuatrice si P>25 mmHg

Graybill, CID 2000

2 weeks-outcomes

- **6.5% of early deaths** (14/214, 3 HIV – and 11 HIV +)
  - More frequent if abnormal neurology ($p = 0.021$), abnormal brain imaging ($p = 0.007$), abnormal thoracic imaging ($p = 0.047$) and hyponatraemia ($p = 0.023$)

- **Clinical cure in 57.3%** (115/200) of cases
  - Less frequent among patients with abnormal neurology ($p < 0.001$) or meningoencephalitis ($p = 0.026$)

- **Control of sterilization**
  - Among patients considered clinically cured ➔ **28% still had one body site infected**
  - Among patients with clinical failure ➔ **53% only achieved sterilization**
    - CSF positive India Ink in 65% (70% among HIV + and 43% among HIV -, $p = 0.030$)
    - CSF culture still positive in 40%

[Dromer et al. 2007]
Predictive factors of W2 early mortality

- **No use of 5-FC** (Dromer, PLoS 2007)

- **CSF fungal Ag titer > 1:1024** (Brouwer, Lancet 2004) (Bicanic, CID 2009) [Jarvis, CID 2014] [Cabrera, WI AIDS 2011]

- **Altered mental status, GCS < 14**

- **Abnormal brain imaging** (Cabrera, 2011) [Jarvis, CID 2014] [Dromer, PLoS 2007]

- **Hyponatremia** (Dromer, PLoS 2007)

- **Slow rate of fungal clearance** (Jarvis, 2014)

Predictive factors of W2 early mycological clearance failure

- **No use of 5-FC** \( \rightarrow \) OR 3.8 [95% CI, 1.9–7.8], \( p = 0.001 \) (Dromer et al. 2007)

- **Serum Ag > 1:512** \( \rightarrow \) OR, 2.6 [95% CI, 1.3–5.4], \( p = 0.008 \) (Dromer et al. 2007)

- **Initial dissemination** \( \rightarrow \) OR, 2.4 [95% CI, 1.2–4.5], \( p = 0.015 \) (Dromer et al. 2007)

- **Monotherapy (AmB alone < AmB + fluco)** \( \rightarrow \) RR, 1.56 [95% CI, 1.14–2.14] (Concha Velasco et al., 2017)

- **High baseline CSF opening pressure (≥ 35 cmH\(_2\)O)** \( \rightarrow \) RR, 0.57 [95% CI, 0.33–0.99] (Concha Velasco et al., 2017)

- **Serotype A infection (HIV + only)** \( \rightarrow \) OR, 5.6 [95% CI, 1.6–19.8], \( p = 0.008 \) (Dromer et al. 2007)

- **High baseline fungal burden (> 4.5 log\(_{10}\) CFU/ml)** \( \rightarrow \) RR, 0.61 [95% CI, 0.38–0.95] (Concha Velasco et al., 2017)
3 month-outcomes

- **11.5% of deaths** (23/200, 7 HIV – and 16 HIV +, none IC patients)
  - More frequent if abnormal neurology ($p = 0.021$), abnormal brain imaging ($p = 0.007$), abnormal thoracic imaging ($p = 0.047$), in case of haematological malignancy ($p = 0.023$) and serotype D infection among non-HIV patients ($p=0.048$)

- **3.9% of neurological sequelae** (HIV +)

- **Mycological responses**
  - 97.1% of sterilization
  - 3 HIV + patients with positive CSF culture and 1 HIV – with BAL positive culture

Dromer et al. 2007

Predictive factors of 10 weeks CSF negativation and relapse

<table>
<thead>
<tr>
<th>10 weeks CSF negativation</th>
<th>10 weeks Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early mycological clearance = CSF negativation at 2 weeks</td>
<td>Use of <em>itraconazole</em> during the consolidation phase</td>
</tr>
<tr>
<td>Effective treatment with <em>fluconazole</em> during the consolidation phase (&gt; than <em>itraconazole</em>)</td>
<td>No use of 5-FC during the induction phase</td>
</tr>
</tbody>
</table>

Saag et al. CID 1999
Therapeutic alternatives

**Induction and consolidation phases**

- **AmB – FLC (800 mg/d) -** 14 days then FLC 800 mg/jr > 8 weeks
  - Early mortality = AmB – 5-FC
  - Long-term mortality
- **5-FC - FLC (800-1 200 mg/d) -** 6 weeks
- **Fluconazole monotherapy 1200 mg/d -** 10-12 weeks \( \rightarrow \) In settings where neither 5-FC nor AmB are available (worse survival than AmB based-regimens)

**Secondary prophylaxis**

- **Itraconazole 200 mg x 2/d**
- **AmB IV 1 mg/kg 1 to 3 times per week**

---

Treatment – Management of prophylaxis

- **Discontinuation of the prophylaxis** only if:
  - ATF ttt > 12 months
  - CD4> 100/mm\(^3\)
  - HIV viral charge < 1,6 log more than 3 months
  - > 3 months of ART
  - Serum Ag < 1:512 more than 3 months

- **Re-instauration of fluconazole** if CD4 ≤ 100/mm\(^3\) (required) and if CD4 ≤ 200/mm\(^3\) despite ART (optional)
Non meningeal cryptococcosis

Management of extrameningeal cryptococcosis

- Imperative lumbar punction +++
- Mild forms: **FCZ 400 mg/day** during 6-12 months

- **Severe forms: Idem cryptococcal meningitis**
  - Severe pneumonia (Recommended, IDSA 2010)
  - High fungal burdens **(CrAg titer in serum > 1:512)** [Dromer, 2007]
  - Fungaemia [Dromer, 2007]
  - Disseminated infection (≥ 2 non-contiguous infected body sites including urines) [Dromer, 2007]

- Severe pneumonia
- High fungal burdens
- Fungaemia
- Disseminated infection
AIDS-associated asymptomatic CrAg

Management of patients with CD4 < 100/mm$^3$ and asymptomatic positive serum CrAg

- **Pre-emptive treatment endorsed by the WHO +++**
  - Prevention of developing CM or CM-IRIS and of death due of cryptococcal disease +++
  - FLC 400 mg/day for 8 weeks and 200 mg/day for 10 weeks until CD4 > 200/mm$^3$ at month 6 and 12 (WHO, 2011)
  - HAART deferred by 4 weeks

- **Mycological assessment**
  - Blood and urine cultures ++
  - Lombar punction ++
  - If + → treatment = CM
Management of early mycological clearance failure

If non sterilization of the CSF at 2 weeks

- Extend the induction phase AMB + 5-FC
- Check for therapeutic monitoring (5FC +++)
- Watch for the absence of raised cranial OP
- Immunity restauration
Cryptococcal IRIS management & prevention

Cryptococcal IRIS management

- No clear recommendations
- Maintain antifungals
- Corticosteroids 0.5-1mg/kg/d eq prednisone 2-6 weeks
- CSF opening pressure management
Cryptococcal IRIS prevention

- ARV instauration after 4 weeks of effective antifungal treatment and no neurological sign

C. gattii complex & treatment specificities
C. gattii treatment

- Longer treatment duration ++
  - Induction therapy with AMB + 5-FC 6 weeks then FLC 400 g/d 18 months
  - Monitoring of CSF opening pressure ++++ (high frequency of intracranial hypertension)

- Pulmonary forms
  - Induction therapy with AB + 5-FC 2 weeks then FLC 400 mg/d 12 months
Susceptibility testing and resistance profiles

Susceptibility profile

- Natural resistance to echinocandins
- Susceptibility to amphotericine B, 5-FC and triazoles
- Increase of theazole resistance
- ↑ risk of fluconazole resistance if previous exposition
- Susceptibility profile varies according circulating genotype → local epidemiology of the resistances +++
- Higher MICs with non-neoformans isolates
Susceptibility testing

- Numerous surveys defining CLSI MICs for most WT isolates
- No clinical breakpoints
- Epidemiological cut-off values (ECOFFs)

ECOFF: valeur de CMI qui identifie la limite supérieure d’une population sauvage
CBP: interprétation des CMI et catégorisation des souches en S-I-R (i.e. niveau d’activité de l’ATF associé à une probabilité importante de succès ou d’échec thérapeutique)
Pas de relation formelle entre ECOFF et CBP

ECVs

- Highest WT susceptibility endpoints recently defined by Espinel-Ingroff et al., 2012
- A total of 2,985 to 5,733 CLSI MICs for C. neoformans and 705 to 975 MICs for C. gattii
- Gathered in more than 10 laboratories worldwide (Europe, USA, Canada, Argentina, Brazil, Mexico, Cuba, India, South Africa)
ECVs and species specificities

<table>
<thead>
<tr>
<th>Drug</th>
<th>C. neoformans</th>
<th>C. deneiformans</th>
<th>C. gattii</th>
<th>C. bacillisporus</th>
<th>C. deuterogattii</th>
<th>C. tetragattii</th>
<th>C. decagattii</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmB</td>
<td>0.5*/1</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>0.5**/1</td>
<td>1</td>
<td>ND***</td>
</tr>
<tr>
<td>5-FC</td>
<td>8*/16</td>
<td>16</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>4</td>
<td>ND***</td>
</tr>
<tr>
<td>Fluco</td>
<td>8*/16</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>8**/32</td>
<td>16</td>
<td>ND***</td>
</tr>
<tr>
<td>Itra</td>
<td>0.25*/0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>1</td>
<td>ND***</td>
</tr>
<tr>
<td>Posa</td>
<td>0.25</td>
<td>0.25</td>
<td>0.5</td>
<td>0.25</td>
<td>0.5</td>
<td>0.5</td>
<td>ND***</td>
</tr>
<tr>
<td>Vori</td>
<td>0.25</td>
<td>0.12</td>
<td>0.5</td>
<td>0.25</td>
<td>0.12</td>
<td>0.25</td>
<td>ND***</td>
</tr>
<tr>
<td>Isavuco</td>
<td>0.06*/0.12</td>
<td>ND</td>
<td>0.25</td>
<td>ND</td>
<td>0.25</td>
<td>0.25</td>
<td>ND***</td>
</tr>
</tbody>
</table>

* for VN1/AFLP1 genotype  
** for VNIIa/AFLP6a genotype  
*** consider C. tetragattii ECVs

FCZ ≥ 16 µg/ml  
AmB ≥ 2 µg/ml

ECVs – Triazoles

According the CLSI M27-A3 method

Species- and molecular type-specific

Higher fluco MICs among C. deuterogattii isolates

Correlations between fluconazole MICs and clinical outcomes:

- More rapid CSF sterilization and infection eradication with MICs of 4 to 8 µg/ml
- Clinical failure or recurrence with MICs of ≥16 µg/ml

Clinical data suggest that:

- Clinical susceptibility for fluconazole for MICs ≤8 µg/ml
- Clinical failure or recurrence for MICs ≥ 16 µg/ml
ECVs – 5-FC/Amb
Espinel-Ingroff et al., 2012

- According the CLSI M27-A3 method
- Species- and molecular type-specific
- AmB MICs > 2 μg/ml associated with clinical failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>ECV95 (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FC</td>
<td>4-16</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0.5-1</td>
</tr>
</tbody>
</table>

Fluconazole resistance: one issue

- Rate of fluconazole non-WT MICs higher than that of the other triazoles (> 30%) (Espinel-Ingroff, 2012)
- 72.2% of isolates with MIC ≥ 8 μg/mL (Argentina) (Cordoba, 2016)
- 31% isolates with MIC > 8 μg/mL (Uganda) (Smith, 2015)
- Increase of the MIC values within the last decade ++ (Uganda) (Smith, 2015)
- Critical issue especially in countries were 5-FC is not available
  - Avoid monotherapy (suboptimal option for treatment of cryptococcal meningitis, with 10-week survival of only ~40%)
  - Questions the low-dose preemptive therapy ⇒ selection of resistant organisms and/or ineffectiveness
Fluconazole resistance: an environmental origin?

- Environmental isolates showing multidrug resistance (Cameroon) (Dongmo et al., 2016)

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Cr var neoformans (n=10)</th>
<th>Cr var gattil (n=35)</th>
<th>Cr K594</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>Range 0.06 – 0.26</td>
<td>Mean 0.15 + 0.25</td>
<td>2</td>
</tr>
<tr>
<td>Ketocanazole</td>
<td>Range 0.06 – 0.26</td>
<td>Mean 0.15 + 0.25</td>
<td>1</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Range 0.06 – 0.26</td>
<td>Mean 0.15 + 0.25</td>
<td>2</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Range 0.125 – 0.5</td>
<td>Mean 0.31 + 0.65</td>
<td>0.65</td>
</tr>
</tbody>
</table>

- Increasing use of triazole fungicides by farmers

5-FC resistance

- **Mecanism**: Specifically linked in haploid *C. neoformans* cells to a single mutation at either the *FCY1* or the *FCY2* gene (cytosine permeases)

- **Never in monotherapy ++++

- **Combination AmB + 5-FC = synergistic in vitro** despite resistance to flucytosine ++ [Schwarz, AAC 2007]

Espinel-Ingroff et al., 2012
New drugs?

Sertraline (Zoloft®)

- Need of developing antifungals that can penetrate the CNS
  
  +++

- **Sertraline’s mechanism of action on fungi: not well known**
  
  - Inhibition of protein synthesis in fungi
  
  - Targets vesicle-mediated transport proteins?
Sertraline (Zoloft®)

- In vitro assay and murine model (Zhai et al., 2012)
  - Sertraline interacts synergistically or additively with fluconazole against Cryptococcus in vitro.
  - Sertraline alone or in combination with fluconazole displays antifungal activity in a murine model of systemic cryptococcosis.
  - Sertraline antagonizes the growth-inhibitory effect of fluconazole on many Candida strains.

- MIC\textsubscript{50} = 4 μg/ml and MIC\textsubscript{90} = 8 μg/ml
- Therapeutic levels should be obtainable in humans
  - Lower fungal burden and lower incidence of IRIS when adjunctive sertraline therapy was applied for the treatment of HIV-associated CM

Smith et al., 2015
Rhein et al., 2016
Antipsychotic drugs quetiapine and olanzapine

- Quetiapine and olanzapine do possess anti-cryptococcal activity and act in synergy with fluconazole
- By compromising fungal cell wall function
- By improving macrophage functions
  - Macrophages produce significantly ($p < 0.05$) more IFN-$\gamma$ and IL-6 when treated with respective anti-psychotic drugs,
  - Both drugs significantly ($p < 0.05$) enhance the ability of macrophages to internalize more cells
- Antifungal activity displayed at concentrations within the recommended dosage in the blood
- Need of animal models ++

Atorvastatin as a promising anticryptococcal agent

- Alteration of the yeast-polysaccharide membrane capsule and reduction of the ergosterol plasmatic membrane content
  - Inhibition of the HMG-CoA reductase
  - Ergosterol depletion affects the capsular structure
- Increase of fungicidal activity of phagocytes and reduction of the fungus' survival inside macrophages
- Combination with FLC promotes increase survival and reduces fungal burden in lugs of C. gattii challenged mice

Ogundeji et al., 2017
Ribeiro et al., 2017
Thank you for your attention
First cause of acute meningitis in Sub-Saharan countries (HIV endemic areas +++)

↗ incidence among non-HIV in developed countries

Early mortality rates (W2) between 5 to 25 %

Late mortality rates (M3) between 15 to 25 %

15% of AIDS-related mortality → second cause after TB

Cryptococcosis is possible among immunocompetent (C. gattii ++, Australia)

Species complex → C. neoformans var grubii (C. neoformans), C. neoformans var. neoformans (C. deneoformans) and 5 species in the C. gattii complex

≠ by their geographical distribution, ecological niches, antifungal susceptibility, clinical and mycological responses to treatment and virulence
Cryptococcosis can be a dormant infection

Pulmonary portal of entry and reservoir

The major risk factor is the immunosuppression

Major risk factor among HIV when CD4+ ≤ 100/mm³

*C. gattii* complex infections among immunocompetents

---

The major clinical form of cryptococcosis is the meningoencephalitis (CM)

Main clinical signs are non-specific

Abnormal neurological signs in half of CM (altered mental status, motor and cranial nerves paresis, seizure), associated with lower survival

Possible sub-acute and mild clinical pictures especially among non-HIV patients ++
**THE TAKE-HOME MESSAGE**

- Fungaemia = critical step in the development and persistence of meningocencephalitis → CNS reinfection and lack of CSF sterilization despite treatment *i.e.* mycological failure

- In CM, a high CSF OP is correlated to high fungal burdens and a lack of CSF sterilization at 2 weeks (early mycological failure)

- Need of frequent CSF OP monitoring and CSF drainage if required

---

**THE TAKE-HOME MESSAGE**

- Cryptococcal IRIS occurs in 15 to 40 % of HIV patients within the early months of HAART and is responsible of a high mortality

- Start of HAART at least after 4 weeks of an effective antifungal treatment

- Detection and treatment of all “hidden” CM and of asymptomatic cryptococcal antigen carriers by screening all CD4<100/mm3 patients before HAART introduction
CM is a late diagnosis!

The diagnosis is based on a conventional mycological procedure =
Direct examination (India ink) + culture (GOLD STANDARD)

Central role of the detection of cryptococcal antigen in body fluids →
good sensitivity, rapid diagnostic test

Two point of care tests for cryptococcal antigen detection (The FDA-approved CrAg LFA IMMY® and BioSynex CryptoPS®) (4 serotypes A, B, C, D)

Simple, equipment free and rapid tests (ASSURED)

Excellent correlation with agglutination or EIA techniques (but no agreement between titers ++)

Excellent sensitivity (100%) (low detection threshold)

Good specificity in serum (97-98%)

Low specificity and poor VPP in urines for IMMY (better for BioSynex)

BioSynex allows the rapid screening of patients with high fungal loads thanks to its T2-band
Prevalence of asymptomatic blood CrAg carriers between 5 to 8% (HIV cohorts)

Independent mortality risk factor among patients initiating HAART

Independent risk factor of developing CM among patients initiating HAART

A meningeal involvement (i.e. clinical signs, positive India ink, positive culture, positive CSF CrAg) is frequently found among CrAg blood carriers

A systematic screening of blood CrAg among CD4+ ≤ 100/mm³ HIV-patients is recommended (WHO)

A CrAg titer ≥ 1:512 in blood or CSF at the diagnosis = risk of early mycological failure at 2 weeks (i.e. non sterilization of CSF culture)

CrAg must not be used for therapeutic effectiveness monitoring

CrAg is not an index of cure !!

During treatment = a persistently elevated CSF CrAg is a marker of poor prognosis and disease relapse
3-phases sequential treatment

- Induction phase = bitherapy AmB+5-FC of at least 2 weeks
- Consolidation phase = fluconazole monotherapy during at least 8 weeks
- CSF culture and direct examination monitoring +++
- Opening pressure monitoring and drainage if required
- A high CSF OP is associated with mycological failure, neurological sequelae and poorer long-term mortality

A high fungal burden (serum Ag > 1/512, CSF Ag>1/1024), an initial dissemination, neurologic abnormalities, a high opening CSF pressure and the absence of 5-FC use are predictive factors of W2 mycological failure and W2 early mortality

The absence of use of 5-FC during the induction phase, the absence of use of fluconazole during the consolidation phase, a neglected high CSF opening pressure are predictive of 3 month- mycological failure and poorer long-term survival
Always perform a CSF analysis in case of extra-meningeal cryptococcosis or asymptomatic CrAg discovery

A preemptive treatment based on fluconazole has to be started in case of asymptomatic CrAg among patients with CD4+ < 100/mm³

HAART is introduced after 4 weeks of effective antifungal treatment and the absence of neurological signs

Among non-HIV immunosuppressed patients with cryptococcal infection, IS therapies should be lowered

Cryptococcus yeasts are naturally resistant to echinocandins

Increase of the fluconazole resistance

Never use 5-FC monotherapy

Susceptibility varies according to the serogenotypes

Higher fluconazole MICs for C. deuterogattii isolates

No clinical breakpoints defined yet

Fluconazole MIC ≥ 16 µg/ml is associated with a clinical failure/recurrence

Amphotericine B MIC ≥ 2 µg/ml is associated with a clinical failure
References


