جامعة محمد الخامس بالرباط
Université Mohammed V de Rabat

The Tunisian Society of Infectious Disease
organizes with the collaboration of
The World Health Organization

World Health Organization

1st Congress in Middle East North Africa region of Clinical Microbiology and Infectious disease

34th National congress of Tunisian Society of Infectious Disease

# Candidoses invasives:
# QUOI DE NEUF DANS LES GUIDELINES 2025


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*Clinical Infectious Diseases*

MAJOR ARTICLE

IDSA hivma

# Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

J. Peter Donnelly,[1] Sharon C. Chen,[2] Carol A. Kauffman,[3] William J. Steinbach,[4] John W. Baddley,[5] Paul E. Verweij,[6] Cornelius J. Clancy,[7] John R. Wingard,[8] Shawn R. Lockhart,[9] Andreas H. Groll,[10] Tania C. Sorrell,[11] Matteo Bassetti,[12] Hamdi Akan,[13] Barbara D. Alexander,[14] David Andes,[15] Elio Arsenley,[16] Raif Bizalek,[17] Robert W. Bradsher Jr.,[18] Stephanie Bretagne,[19] Thierry Calandra,[20] Angela M. Caliendo,[21] Elio Castagnola,[22] Marie Cruciani,[23] Manuel Cuenca-Estrella,[24] Catherine F. Decker,[25] Sujal R. Desai,[26] Brian Fisher,[27] Thomas Harrison,[28] Claus Peter Heussel,[29] Henrik E. Jensen,[30] Christopher C. Kibbler,[31] Dimitrios P. Kontoyiannis,[32] Bart-Jan Kullberg,[33] Katrina Lagrou,[34] Frédéric Lamoth,[35] Thomas Lehrnbecher,[36] Jurgen Loeffler,[37] Olivier Lortholary,[38] Johan Maertens,[39] Oscar Marchetti,[40] Kieren A. Marr,[41] Henry Masur,[42] Jacques F. Meis,[43] C. Orla Morrissey,[44] Marcio Nucci,[45] Luis Ostrosky-Zeichner,[46] Livio Pagano,[47] Thomas F. Patterson,[48] John R. Perfect,[49] Zdenek Racil,[50] Emmanuel Roilides,[51] Mariana Ruhnke,[52] Cornelia Schaefer-Prokop,[53] Shmuel Shoham,[54] Monica A. Slavin,[55] David A. Stevens,[56] George R. Thompson III,[57] Jose A. Vazquez,[58] Claudio Viscoli,[59] Thomas J. Walsh,[60] Adilia Warris,[61] L. Joseph Wheat,[62] P. Lewis White,[63] Theoklis E. Zaoutis,[64] and Peter G. Pappas[65]

*Clinical Infectious Diseases*

IDSA GUIDELINE

IDSA hivma

# Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

# Global guideline for the diagnosis and management of candidiasis: an initiative of the ECMM in cooperation with ISHAM and ASM

Oliver A Cornely, Rosanne Sprute, Matteo Bassetti, Sharon C-A Chen, Andreas H Groll, Oliver Kurzai, Cornelia Lass-Flörl, Luis Ostrosky-Zeichner, Riina Rautemaa-Richardson, Gunturu Revathi, Maria E Sobel-Leyva, P Lewis White, Ana Alastruey-Izquierdo, Malken C Arendrup, John Baddley, Aleksandra Barac, Noam Ben-Ami, Adrian J Brink, Jan H Grattan, Jesus Guinea, Ferry Hagen, Bruno Hochhegger, Martin Hoenigl, Shahid Hussain, Kauser Jabeen, Henrik E Jensen, Sudha S Kindo, Philipp Koehler, Thomas Lehrnbecher, Russell E Lewis, Jacques F Meis, M Hong Nguyen, Zoi D Pana, Peter-Michael Roth, Ilana Reinhold, Dusila Seidel, Takafumi Takazono, Donald C Vinh, Sean X Zhang, Javier Afeltra, Abdullah M S Al-Hatmi, Amir Armstehfar, Sevtap Arikan-Akdagli, Felix Bongomin, Fabianne Cortesse, Mathue Chayakulkeeree, Louis Y A Chai, Laili Chermani-Tabriz, Tom Chiller, Anuradha Chowdhary, Cornelius J Clancy, Arnaldo L Colombo, Andrea Cortegiani, Dora E Corzo-Leon, Lubos Drgona, Anna Dudakova, [illegible] Fraccari, Sara Gago, Macit Ilkit, Jeffrey D Jenks, Nikolai Klimko*, Robert Krause, Anil Kumar, Katrien Lagrou, Michail S Lionakis, Badrie E Limmouni, Michael K Mansour, Joseph Meletiadis, Sibylle C Mellinghoff, Mervyn Mer, Malgorzata Mikulska, Philippe Montravers, Chin Fen Neoh, Volkan Ozenci, Livio Pagano, Peter Pappas, Thomas F Patterson, Pedro Puerto-Alcalde, Laman Rahimli, Sebastian Rahn, Emmanuel Roilides, Coleman Rotstein, Tamara Ruegamer, Raquel Sabino, Jon Salmanton-García, Ilan S Schwartz, Esther Segal, Neeraj Sidharthan, Tanu Singhal, Janos Sinko, Rajeev Soman, Andrej Spec, Joerg Steinmann, Jannik Stemler, Saad J Taj-Aldeen, Alida Fe Talento, George R Thompson III, Christina Taubken, Hiram Villanueva-Lozano, Retno Wahyuningsih, Barbara Weinbergerová, Nathan Wiederhold, Birgit Willinger, Patrick C Y Woo, Li-Ping Zhu

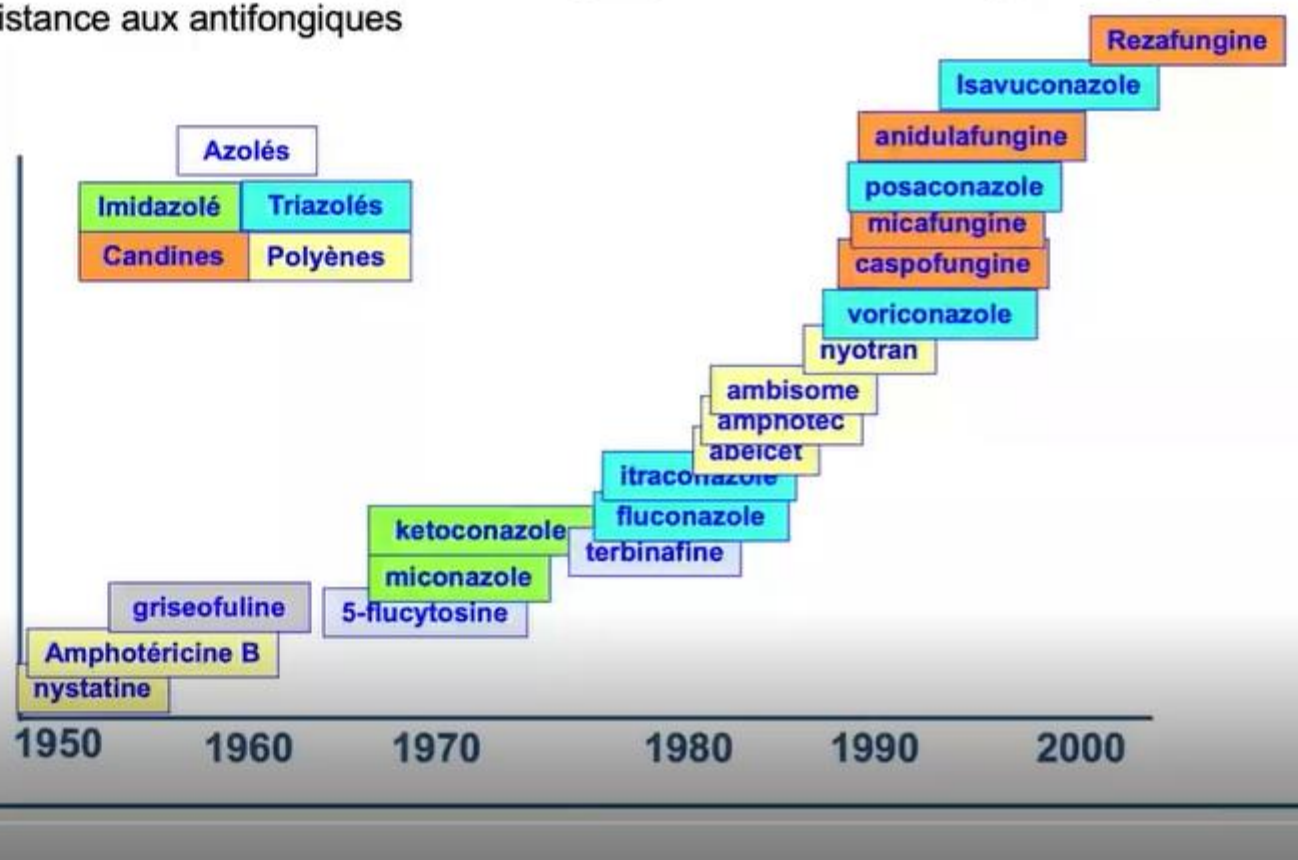
*Candida* species are the predominant cause of fungal infections in patients treated in hospital, contributing

# Candidoses invasives: contexte


- *Candida* sp: 1ère cause d'IFI (85% fongémies)→ Mortalité et morbidité ↑↑ → Fardeau économique
- 1 565 000 cas annuels (30-50% dans les USI, 30-50% de mortalité: **killer N°1**)
- **Grande diversité des espèces responsables**
- **Emergence de *Candida auris* (*Candidozyma auris*) et *Candida parapsilosis* FCZ-R → menace pour la santé mondiale**
- Diagnostic précoce difficile
- Recommandations de diagnostic : ne tiennent pas compte des différences épidémiologiques et des moyens → nécessité d'adapter à l'échelle locale

# Candidoses invasives: contexte

- Recommandations de traitement: ne tiennent pas compte des différences épidémiologiques, nécessité d'adapter à l'échelle locale
- Nombre limité de molécules pendant longtemps, nouveaux antifongiques depuis 2004
- Résistance aux antifongiques



# Country burden of invasive candidiasis

| Country | Burden | Rate/100,000 |
|---|---|---|
| Pakistan | 38,795 | 21 |
| Qatar | 288 | 15 |
| Brazil | 28,991 | 15 |
| Thailand | 8650 | 13 |
| Hungary | 1110 | 11 |
| Israel | 664 | 11 |
| Denmark | 527 | 9.4 |
| Russia | 11,840 | 8.3 |
| Spain | 3807 | 8.1 |
| United Kingdom | 5142 | 8.1 |
| Ireland | 403 | 6.3 |
| Nigeria | 9284 | 6.0 |
| Uzbekistan | 1825 | 5.9 |
| Algeria | 2020 | 5.0 |
| Bangladesh | 8100 | 5.0 |
| Belgium | 555 | 5.0 |
| Chile | 878 | 5.0 |
| Czech Republic | 526 | 5.0 |
| Dominican Republic | 504 | 5.0 |
| Ecuador | 1037 | 5.0 |

| Country | Burden | Rate/100,000 |
|---|---|---|
| Egypt | 4127 | 5.0 |
| Greece | 541 | 5.0 |
| Guatemala | 772 | 5.0 |
| Jamaica | 136 | 5.0 |
| Kenya | 1990 | 5.0 |
| Mexico | 5617 | 5.0 |
| Peru | 1557 | 5.0 |
| Tanzania | 2181 | 5.0 |
| Trinidad and Tobago | 87 | 5.0 |
| Ukraine | 752 | 5.0 |
| Vietnam | 4540 | 5.0 |
| Germany | 3712 | 4.6 |
| Korea | 1976 | 4.1 |
| France | 2370 | 3.6 |
| Canada | 1034 | 2.9 |
| Austria | 209 | 2.6 |
| Sri Lanka | 507 | 2.5 |
| Portugal | 231 | 2.2 |
| Philippines | 1968 | 2.0 |

Table from Bongomin *et al J. Fungi* 2017, *3* (4), 57

Journal of Fungi

MDPI

*Article*

# Estimated Incidence and Prevalence of Serious Fungal Infections in Morocco

Badre Eddine Lmimouni [1], Christophe Hennequin [2,3], Richard O. S. Penney [4] and David W. Denning [4,5,*]

**Table 1.** The estimated annual caseload (incidence or prevalence) of serious fungal infections in Morocco and number per 100,000 people.

| Fungal Infection | Predominant Groups at Risk | Rate Per 100,000 | Estimated Number of Cases |
|---|---|---|---|
| Cryptococcal meningitis | AIDS | 0.43 | 160 |
| PCP | AIDS | 0.53 | 195 |
| IA | Haematological malignancy, lung cancer and 1.3% of COPD admissions to hospital | 4.1 | 1500 |
| CPA | Tuberculosis patients and other respiratory disorders | 52.8 | 19,290 |
| ABPA * | Adult asthma patients | 71.0 | 25,950 |
| SAFS * | Adult asthma patients | 93.7 | 34,260 |
| Candidaemia | Hospitalised patients | 5.00 | 1830 |
| Candida peritonitis | Post-surgical patients | 0.75 | 275 |
| Oesophageal candidiasis | HIV infection | 3.7 | 1346 |
| Recurrent vaginal candidiasis # | Adult women | 2794 | 510,740 |
| Mucormycosis | Multiple, especially diabetes | 0.20 | 73 |
| Fungal keratitis | Corneal injury, contact lens | 14.0 | 5120 |
| Tinea capitis | 4–14-year-old children | 7285 | 2,664,000 |
| **Total burden estimated** | | | **3,305,100** |

PCP, pneumocystis pneumonia; IA, invasive aspergillosis; CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitisation. * Duplication between ABPA and SAFS is likely as both are sensitised to *Aspergillus*. The total number of fungal asthma cases is around 42,150 (115.3/100,000). # rate per 100,000 females only.

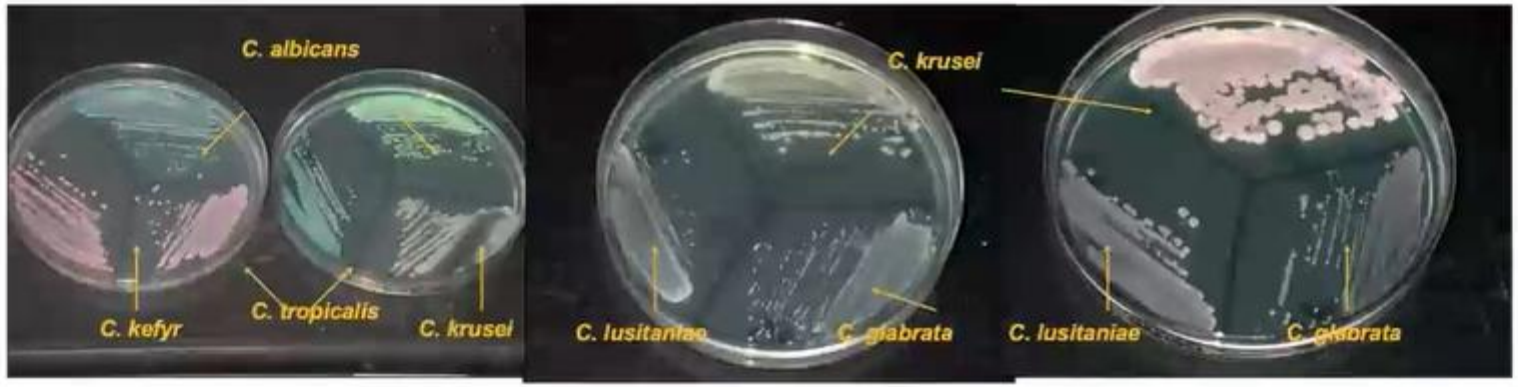
# Nouvelles tendances épidémiologiques

**Historiquement :**

- *Candida albicans :* espèce pathogène la plus fréquemment rencontrée
- *Candida albicans* : espèce classiquement sensible aux antifongiques

**Plus récemment**

- Prédominance des ***Candida non albicans***
- Importance des phénomènes de **résistance**

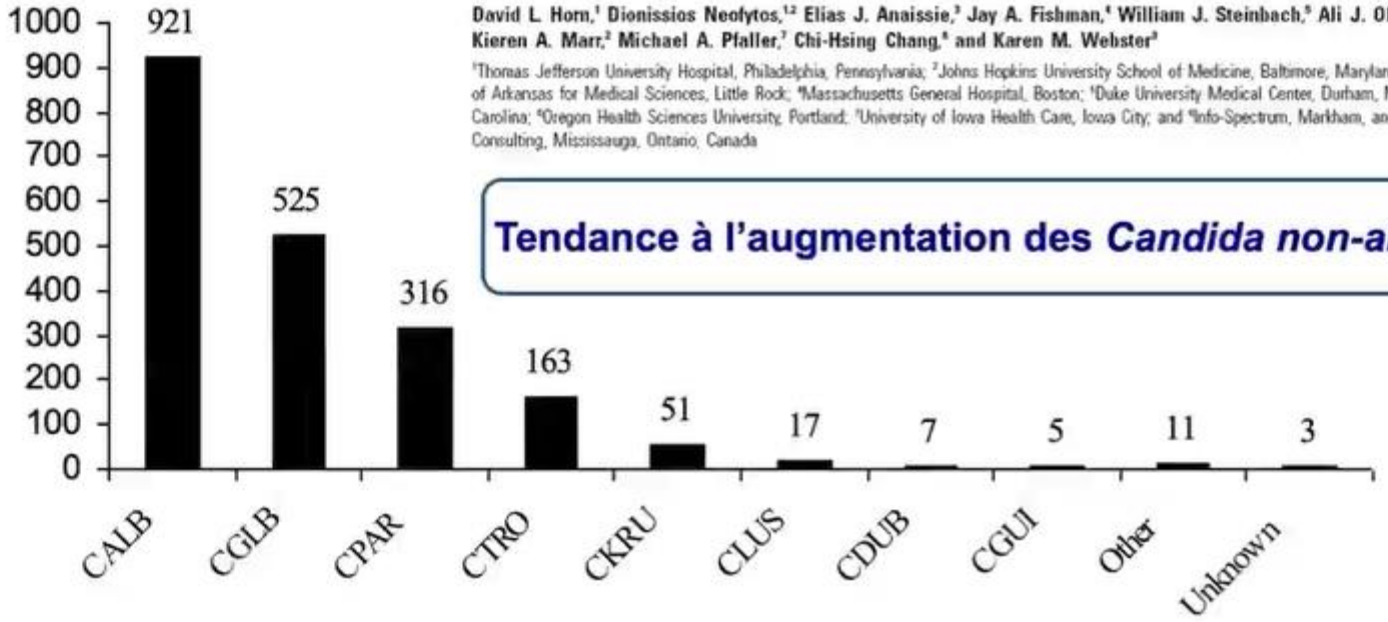



Samaranayake LP et al. Dermatologic Ther 2002 ; Pappas P. G. et al., Clin Infect Dis. 2004 ; Ruhnke M, Curr Drug Targets, 2006 ; Blyth etal., 2007

# Epidemiology and Outcomes of Candidemia in 2019 Patients: Data from the Prospective Antifungal Therapy Alliance Registry

David L. Horn,[1] Dionissios Neofytos,[1,2] Elias J. Anaissie,[3] Jay A. Fishman,[4] William J. Steinbach,[5] Ali J. Olyaei,[6] Kieren A. Marr,[2] Michael A. Pfaller,[7] Chi-Hsing Chang,[8] and Karen M. Webster[9]

[1]Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; [2]Johns Hopkins University School of Medicine, Baltimore, Maryland; [3]University of Arkansas for Medical Sciences, Little Rock; [4]Massachusetts General Hospital, Boston; [5]Duke University Medical Center, Durham, North Carolina; [6]Oregon Health Sciences University, Portland; [7]University of Iowa Health Care, Iowa City; and [8]Info-Spectrum, Markham, and [9]EBM Consulting, Mississauga, Ontario, Canada




**Tendance à l'augmentation des *Candida non-albicans***

**Clin Inf Dis 2019, *48* (12): 1695-703**

# Sensibilité des souches de *Candida* isolées aux agents antifongiques


Original Research

## Invasive Candidiasis in Critically Ill Patients: A Prospective Cohort Study in Two Tertiary Care Centers

Journal of Intensive Care Medicine
2020, Vol. 35(6) 542-553
© The Author(s) 2018
SAGE

Hasan M. Al-Dorzi, MD[1], Hussam Sakkijha, MD[2], Raymond Khan, MD[1], Tarek Aldabbagh, MD[1], Aron Toledo, BSN[3], Pendo Ntinika, BSN[4], Sameera M. Al Johani, MD[5], and Yaseen M. Arabi, MD, FCCP, FCCM[1]

Facteurs de risque spécifiques aux espèces non *albicans*?


Lortholary O et al. Intensive Care Med 2017

**Table 2.** Antifungal Susceptibility and Minimal Inhibitory Concentrations for Isolated *Candida*.

| | All Patients, N = 162 | *Albicans*,[a] n = 62 | Non-*albicans*,[a] n = 91 | *P* Value |
|---|---|---|---|---|
| Susceptibility to antifungal agents, n (%) | | | | |
| Amphotericin B | 93/96 (96.9) | 26/28 (92.9) | 67/68 (98.5) | .20 |
| Caspofungin | 99/102 (97.0) | 27/28 (96.4) | 72/74 (95.9) | 1.0 |
| Anidulafungin | 4/4 (100) | 1/1 (100) | 3/3 (100) | - |
| 5-Flucytosine | 85/104 (81.7) | 24/30 (80.0) | 61/73 (83.6) | .67 |
| Fluconazole | 80/111 (72.1) | 25/30 (83.3) | 55/81 (67.9) | .15 |
| Itraconazole | 60/93 (64.5) | 21/26 (80.8) | 39/67 (58.2) | .04 |
| Voriconazole | 91/99 (91.9) | 25/29 (86.2) | 66/70 (94.3) | .23 |

# Chez *Candida*

Alexander CID 2013
Bailly J Infect 2015


- Modification de l'écologie des services **suivant leur consommation**
- Modification répartition espèces isolées avec plus d'espèces fluco-R
  - Baisse de la sensibilité pour le fluconazole due à son utilisation accrue en première intention dans les Candidémies.
- **Augmentation des CMI aux azolés et candines chez des patients pré exposés aux AF**


**Marr K.A.,White T.C.,Van Burik J.A. et Al. Development of fluconazole resistance in *Candida albicans* causing disseminated infection in a patient undergoing marrow transplantation. *Clin Infect Dis* 1997; 25: 908–910.**

**Sanglard D., Odds F.C. Resistance of *Candida* species to antifungal agents: molecular mechanisms and clinical consequences. *Lancet Infect. Dis* 2002; 2: 73–85.**

- Importance des ttt antifongiques antérieurs pour la prise en charge des patients : modification de la répartition de espèces

**Pas de préexposition à un antifongique** | **Préexposition au fluconazole** | **Préexposition à la caspofungine**

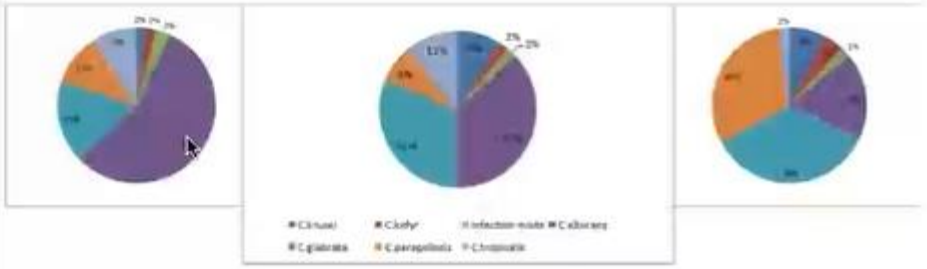
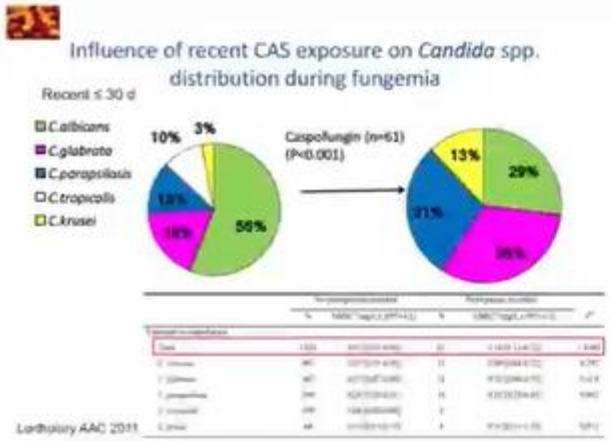
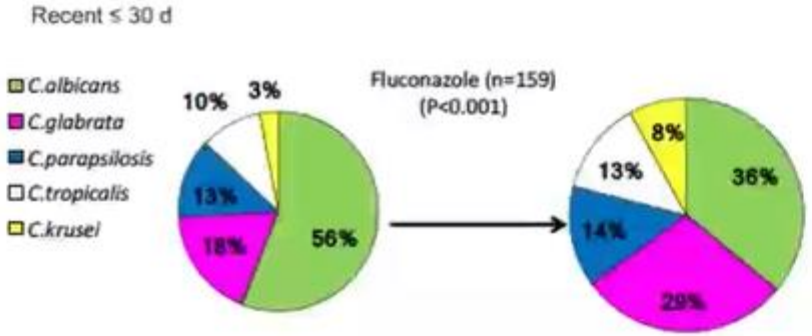


Figure: Répartition des espèces de Candida non rares responsables d'un premier épisode de fongémie, selon l'exposition dans les 30 jours précédents au fluconazole(n=135), à la caspofungine(n=53) ou à aucun antifongique(n=2383), Observatoire des levures d'Île-de-France, octobre 2002-septembre 2010




## Influence de l'exposition récente au FCZ sur la distribution des espèces




2618 isolats sur 7 ans

Lortholary AAC 2011

# Biodiversité des *Candida* : Nouvelles données moléculaires


⇒ **Prendre en compte l'évolution de la classification**

**Démembrement de *C. glabrata***

- ***Candida glabrata***
- ***Candida nivariensis***
- ***Candida bracarensis***

⇒ **Différences de sensibilité aux antifongiques !!**

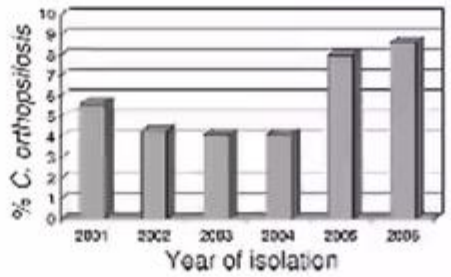
**Lockhart et al., J Clin Microbiol, 2009**

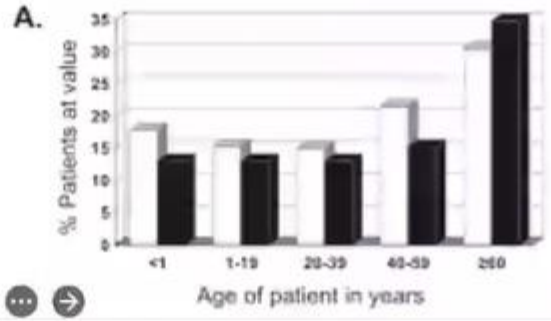
URNAL OF CLINICAL MICROBIOLOGY, Aug. 2008, p. 2659–2664 Vol. 46, No. 8
95-1137/08/$08.00+0 doi:10.1128/JCM.00803-08

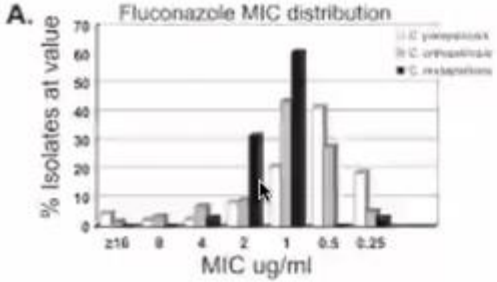

# Geographic Distribution and Antifungal Susceptibility of the Newly Described Species *Candida orthopsilosis* and *Candida metapsilosis* in Comparison to the Closely Related Species *Candida parapsilosis*[V]

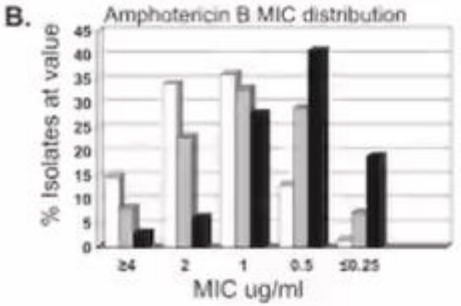
Shawn R. Lockhart,[1]* Shawn A. Messer,[1] Michael A. Pfaller,[1] and Daniel J. Diekema[1]

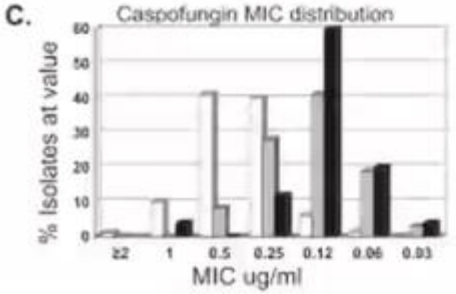
*Departments of Pathology[1] and Internal Medicine,[2] University of Iowa Carver College of Medicine, University o Iowa Hospitals and Clinics, Iowa City, Iowa*



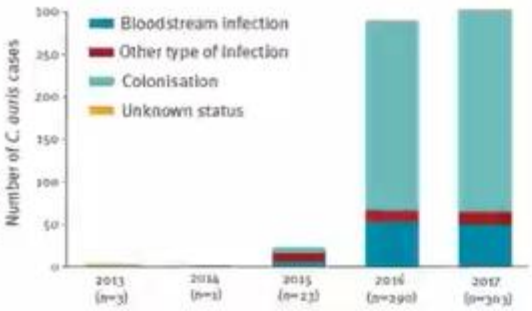



# Emergence de *Candida auris (Candidozyma auris)*

- **Découvert en 2009**
  - Identification difficile (Maldi-tof/Vitek)
- **2015:** CDC investigue une épidémie de Candidémies au Pakistan puis Inde, Afrique du Sud et Venezuela
- **Délai avant diagnostic: 19j, DC 59%**
- **Enquête ECDC janvier 2018**
  - 620 cas rapportés
- **Résistances:** 93% FCZ / 35% AmB / 7% Candines

- **Epidémie hôpital universitaire de Valence (Espagne)**
  - Avril 2016 à janvier 2017
  - 140 porteurs dont 41 Candidémies
  - **Mortalité à J30: 41,4%**
- **Gestion épidémie**
  - Isolement contacts / 3 dépistages hebdo
  - Prélèvements soignants (mains et canal auditif)
  - Toilettes patients à la chlorhexidine, bionettoyage 3/j environnement patient au dioxyde de chlore + désinfection UV à la sortie




Kohlenberg, Eurosurveillance 2018

Ruiz-Gaitan Mycoses 2018

# DIAGNOSTIC MYCOLOGIQUE

- **Précoce:** retard de 12 à 48h à l'administration des ATF associé à une augmentation de la mortalité (Garey K, CID 2006; Labelle A, Crit Care Med 2008)
- **Précis:** patients ayant reçu un traitement ATF adéquat: augmentation de la survie (Morell M, AAC 2005; Parkins M, JAC 2007)

**La documentation de l'IFI permet d'utiliser d'emblée un traitement ATF adapté et efficace ➔ Facteur pronostic essentiel**

**Documentation de nombreuses IFI toujours insuffisante**

Distribution des espèces d'*Aspergillus* isolées chez des patients AI après greffe de moelle (HSCT) ou transplantation (SOG)

| Aspergillus spp. | HSCT (N=149) | SOT (N= 128) |
|---|---|---|
| A. fumigatus | 36.9 | 61.7 |
| A. flavus | 3.4 | 10. 2 |
| A. niger | 3.4 | 10.2 |
| A. terreus | 0.6 | 3.1 |
| other spp. | 3.4 | 7.8 |
| unknown spp.* | 52.3 | 7 |

* Obtenu par histopathologie ou par détection de marqueurs sériques

D. Neofytos et al,,CID 2009



# DIAGNOSTIC MYCOLOGIQUE


HISTOPATHOLOGIE

IMAGERIE

**TOUTES LES PROCEDURES ONT DES LIMITES → COMBINAISONS**

**Séquençage d'ADN**
**Identification 24 h**

ED/CULTURE

DIAGNOSTIC INDIRECT

24----------48 h

24----------48 h

**SM MALDI-TOF**
**Identification ¼ h**

# Adapter les outils diagnostiques



3 à 5 jours

**Culture**

24----------48 h


**Identification**

24----------48 h

**Sensibilité in vitro**

**Alternatives :**

- **Identification moléculaire**
- **Spectrométrie de masse**

**24 h**

\+ **Séquençage d'ADN**
**Identification 24 h**

**48 h**

\+ **SM MALDI-TOF**
**Identification ¼ h**

**24 h**

**Lamoth, JCM 2010 ; Lau, JCM 2008 ; Ferroni, JCM 2010**

# Adapter les outils diagnostiques



3 à 5 jours

**Culture**

24----------48 h


**Identification**

24----------48 h

**Sensibilité in vitro**

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**48 h**

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**Identification ¼ h**

**24 h**

**Lamoth, JCM 2010 ; Lau, JCM 2008 ; Ferroni, JCM 2010**

## Détection de pathogènes fongiques à partir d'hémocultures positives (Maldi-Tof)


- Supérieure aux techniques conventionnelles
- Permet de discriminer les espèces de *Candida* au sein des complexes et d'identifier les espèces rares non identifiables par les techniques conventionnelles
- Un vrai progrès dans la prise en charge thérapeutique des Candidémies
- Impact direct sur la bonne adéquation des traitements antifongiques et sur le pronostic des patients

# Critères diagnostiques des IFI

- Difficultés diagnostiques
- Consensus international
- EORTC et mycoses study group
  - **IFI prouvée**
  - **IFI probable**
  - **IFI possible**

Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group

Bee De Pauw,* Thomas J. Walsh,* J. Peter Donnelly,* David A. Stevens, John E. Edwards, Thierry Calandra, Peter G. Pappas, Johan Maertens, Olivier Lortholary, Carol A. Kauffman, David W. Denning, Thomas F. Patterson, Georg Maschmeyer, Jacques Bille, William E. Dismukes, Raoul Herbrecht, William W. Hope, Christopher C. Kibbler, Bart Jan Kullberg, Kieren A. Marr, Patricia Muñoz, Frank C. Odds, John R. Perfect, Angela Restrepo, Markus Ruhnke, Brahm H. Segal, Jack D. Sobel, Tania C. Sorrell, Claudio Viscoli, John R. Wingard, Theoklis Zaoutis, and John E. Bennett*



*Clinical Infectious Diseases*

MAJOR ARTICLE

Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

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De Pauw, CID 2008
Donnelly JP, CID 2020

# Critères diagnostiques des IFI


- 1 critère d'hôte — TTT prophylactique

+

- 1 critère « clinique »

+

- 1 critère mycologique fort (Histologie ou site stérile ou Ag crypto dans LCR) = IFI prouvée: TTT documenté

- 1 critère mycologique moyen (ED, Culture, GM, BDG)= IFI probable: TTT préemptif

- Aucun critère mycologique = IFI possible: TTT probabiliste / empirique

EORTC/MSG, De Pauw, CID 2008

# IFI Prouvée

| Fungus | Microscopic Analysis: Sterile Material | Culture: Sterile Material | Blood | Serology | Tissue Nucleic Acid Diagnosis |
|---|---|---|---|---|---|
| Molds[a] | Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage | Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding BAL fluid, a paranasal or mastoid sinus cavity specimen, and urine | Blood culture that yields a mold[c] (eg, *Fusarium* species) in the context of a compatible infectious disease process | Not applicable | Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue |
| Yeasts[a] | Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells, for example, *Cryptococcus* species indicating encapsulated budding yeasts or *Candida* species showing pseudohyphae or true hyphae[d] | Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 hours ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process | Blood culture that yields yeast (eg, *Cryptococcus* or *Candida* species) or yeast-like fungi (eg, *Trichosporon* species) | Cryptococcal antigen in cerebrospinal fluid or blood confirms cryptococcosis | Amplification of fungal DNA by PCR combined with DNA sequencing when yeasts are seen in formalin-fixed paraffin-embedded tissue |
| Pneumocystis | Detection of the organism microscopically in tissue, BAL fluid, expectorated sputum using conventional or immunofluorescence staining | Not applicable | Not applicable | Not applicable | Not applicable |
| Endemic mycoses | Histopathology or direct microscopy of specimens obtained from an affected site showing the distinctive form of the fungus | Recovery by culture of the fungus from specimens from an affected site | Blood culture that yields the fungus | Not applicable | Not applicable |

Abbreviations: BAL, bronchoalveolar lavage; PCR, polymerase chain reaction.

[a] If culture is available, append the identification at the genus or species level from the culture results.

[b] Tissue and cells submitted for histopathologic or cytopathologic studies should be stained using Grocott-Gomori methenamine silver stain or periodic acid Schiff stain to facilitate inspection of fungal structures. Whenever possible, wet mounts of specimens from foci related to invasive fungal disease should be stained with a fluorescent dye (eg, calcofluor or blankophor).

[c] Recovery of *Aspergillus* species from blood cultures rarely indicates endovascular disease and almost always represents contamination.

[d] *Trichosporon* and yeast-like *Geotrichum* species and *Blastoschizomyces capitatus* may also form pseudohyphae or true hyphae.

Donnelly JP, CID 2020

**Volume sang HC:**
**- 20 mL: 12 à 36 kg**
**- 6 mL: 2 à 12 kg**
**- 2-4 mL: moins de 2 kg**



# Probable IFI


**Candidiasis**

*Host factors*

Recent history of neutropenia (<0.5 × $10^9$ neutrophils/L (<500 neutrophils/mm$^3$) for ≥10 days) temporally related to the onset of invasive fungal disease

Hematologic malignancy

Receipt of an allogeneic stem cell transplant

Solid organ transplant recipient

Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg prednisone equivalent for ≥3 weeks in the past 60 days

Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-α blockers, lymphocyte-specific monoclonal antibodies, antimetabolites, or purine analogues during the past 90 days

Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, CARD9 deficiency, STAT-1 gain of function, or severe combined immunodeficiency)

Acute graft-vs-host disease grade III or IV involving the gut, lungs, or liver refractory to first-line treatment with steroids

*Clinical features*

At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:

Small, target-like abscesses in liver or spleen (bull's-eye lesions) or in the brain, ie, meningeal enhancement

Progressive retinal exudates or vitreal opacities on ophthalmologic examination

*Mycological evidence*

(1,3)-β-D-glucan (value ≥80 ng/L (pg/mL)) detected in at least 2 consecutive serum samples provided that other etiologies have been excluded

Positive T2Candida[a]

**Cryptococcosis**

*Host factors*[a]

Human immunodeficiency virus infection

Solid organ or stem cell transplant recipient

Hematologic malignancy

Antibody deficiency (eg, common variable immunoglobulin deficiency)

Immunosuppressive therapy (including monoclonal antibodies)

End-stage liver or renal disease

Idiopathic CD4 lymphocytopenia

*Clinical features*

Meningeal inflammation

Radiological lesion consistent with cryptococcal disease

*Mycological evidence*

Recovery of Cryptococcus from a specimen obtained from any nonsterile site

**Pneumocystosis**[a]

*Host factors*

Low CD4 lymphocyte counts <200 cells/mm$^3$ (200 × $10^6$ cells/L) for any reason

Exposure to medication (antineoplastic therapy, anti-inflammatory, or immunosuppressive treatment) associated with T-cell dysfunction

Use of therapeutic doses of ≥0.3 mg/kg prednisone equivalent for ≥2 weeks in the past 60 days

Solid organ transplant

*Clinical features*

Any consistent radiographic features particularly bilateral ground glass opacities, consolidations, small nodules or unilateral infiltrates hilar infiltrate, nodular infiltrate with or without cavitation; multifocal infiltrates, miliary pattern.[a]

Respiratory symptoms with cough, dyspnea, and hypoxemia accompanying radiographic abnormalities including consolidations, small nodules, unilateral infiltrates, pleural effusions, or cystic lesions on chest X-ray or computed tomography scan

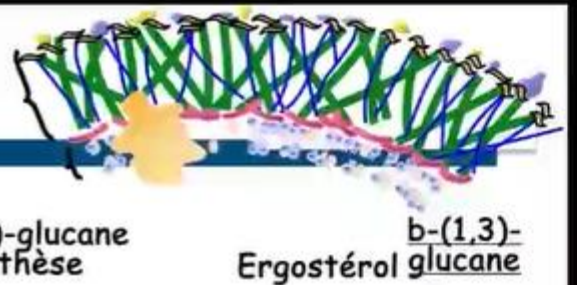
**Biomarqueurs**

**Donnelly JP, CID 2020**

# Les moyens diagnostiques


- **Diagnostic direct**
  - **Mise en évidence du champignon:** cytologie, ED
  - Culture: diagnostic d'espèce (48h)
  - Antifongigramme (48h)
  - Histologie
- **Diagnostic indirect**
  - **Polysaccharides de l'enveloppe (paroi, capsule)**
  - **Détection d'antigènes spécifiques**
    - Ag mannane → (***Candida***)
  - **Détection antigène « pan fongique »** Bêta (1-3) D-glucane (sérum) → (***Aspergillus*** et ***Candida***)
  - **Détection anticorps:** Ac anti-mannanes

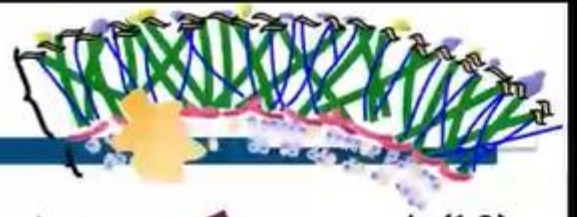
# β1-3 D Glucane (BDG)




**Critères diagnostiques IFI probables**
**(critères EORTC révisés 2008, De Pauw B. et coll, CID 2008)**

- **Origine ?**
  - **Composant pariétal majeur d'un grand nombre d'espèces fongiques**
  - **Test Fungitell®**
- **Quelles infections ?**
  - ***Candida sp, Aspergillus sp, Pneumocystis jirovecii, Fusarium sp, Paecilomyces sp, Scedosporium sp, Trichosporon sp, Histoplasma capsulatum***
- **Comment l'utiliser, quand le prescrire ?**
  - **Screening bi-hebdomadaire en absence de fièvre, quotidien: aplasie fébrile**
  - **Surveillance des patients à haut risque**

# β1-3 D Glucane (BDG)




**Critères diagnostiques IFI probables**
**(critères EORTC révisés 2008, De Pauw B. et coll, CID 200**

- **Origine ?**
  - **Composant pariétal m… …and nombre d'espèces fongiques**
  - **Test Fungite…**
- **Quelles in…**
  - ***C… Aspergillus sp, Pneumocystis jirovecii, … sp, Paecilomyces sp, Scedosporium sp, …nosporon sp, Histoplasma capsulatum***
- **…omment l'utiliser, quand le prescrire ?**
  - **Screening bi-hebdomadaire en absence de fièvre, quotidien: aplasie fébrile**
  - **Surveillance des patients à haut risque**

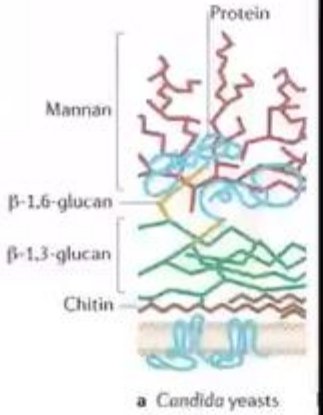
**Ce test ne permet pas de faire la différence entre infections à levures ou à champignons filamenteux**

# Mannanes

- **Marqueurs spécifiques: Ag mannanes, Ac anti-mannanes**
  - Combinaison des 2 tests (Platelia Candida®)
  - Diagnostic des candidémies (ESCMID II; ECIL CIII) et des candidoses chroniques disséminées (ESCMID II, ECIL BIII)
  - **Seuil: 0,5 ng/ml Ag et 10 U/ml Ac**
  - Se = 83%, Sp = 86%, VPN > 85%
  - Se meilleure pour *C.albicans, C.glabrata et C.tropicalis*
  - Positif en médiane 6j avant les hémocultures
  - Pas de problème de détection des Ac chez l'immunodéprimé sévère (sous chimiothérapie, corticoïdes, neutropénique, greffé)
  - Coût ?

Mikulsa, Crti Care 2010; Held, JCM 2013; Clancy, JCM 2008

Cuenca-.-Estrella, CMI 2012; Yera, Eur J Clin Microbiol Infect Dis 2001; Marchev Bone Marrow Transplant, 2012_ECIL




- **PCR *Candida***
  - Testée dans le sérum/sang total.
  - Positive plus précocement, suivi de l'infection possible si quantitative
  - Pas de standardisation, pas de recommandations

| Assay | Invasive Candidiasis (n = 55) | Candidemia[a] (n = 22) | Deep-Seated Candidiasis[a,b] (n = 38) | Intra-abdominal Candidiasis (n = 34) |
|---|---|---|---|---|
| PCR[c] | | | | |
| Sensitivity | 80% (44/55) | 59% (13/22) | 89% (34/38) | 88% (30/34) |
| Specificity | 70% (51/73) | | | |
| BDG (positive ≥80 pmol/mL) | | | | |
| Sensitivity | 56% (31/55) | 68% (15/22) | 53% (20/38) | 56% (19/34) |
| Specificity | 73% (53/73) | | | |
| BDG (positive ≥60 pmol/mL) | | | | |
| Sensitivity | 69% (38/55) | 81% (18/22) | 66% (25/38) | 65% (22/34) |
| Specificity | 63% (46/73) | | | |
| *P* value[d] | | | | |
| PCR vs BDG (positive ≥80 pmol/mL) | .03 | .77 | .004 | .0015 |
| PCR vs BDG (positive ≥60 pmol/mL) | .31 | .23 | .04 | .06 |

Avni, JCM 2011; Lucignano, JCM 2011; Pappas, CID 2015; Nguyen et al, CID 2012

| Case definition | Se | Sp | HC + |
|---|---|---|---|
| Candidemia | 0.95 | 0.92 | 100% |
| Proven/probable IC | 0.93 | 0.95 | 38% |
| Proven/probable/ possible IC | 0.73 | 0.91 | 29% |


## Quelles indications de l'antifongigramme pour les levures ?

**Systématique dans les candidoses invasives**
=> Tester au minimum le fluconazole et une échinocandine

**Candidoses localisées et superficielles**
Pas en systématique, si pertinence clinique, le fluconazole peut suffire dans la majorité des cas

**Autres situations**, en cas :
- d' échec thérapeutique
- d' études épidémiologiques pour quantifier le niveau de résistance

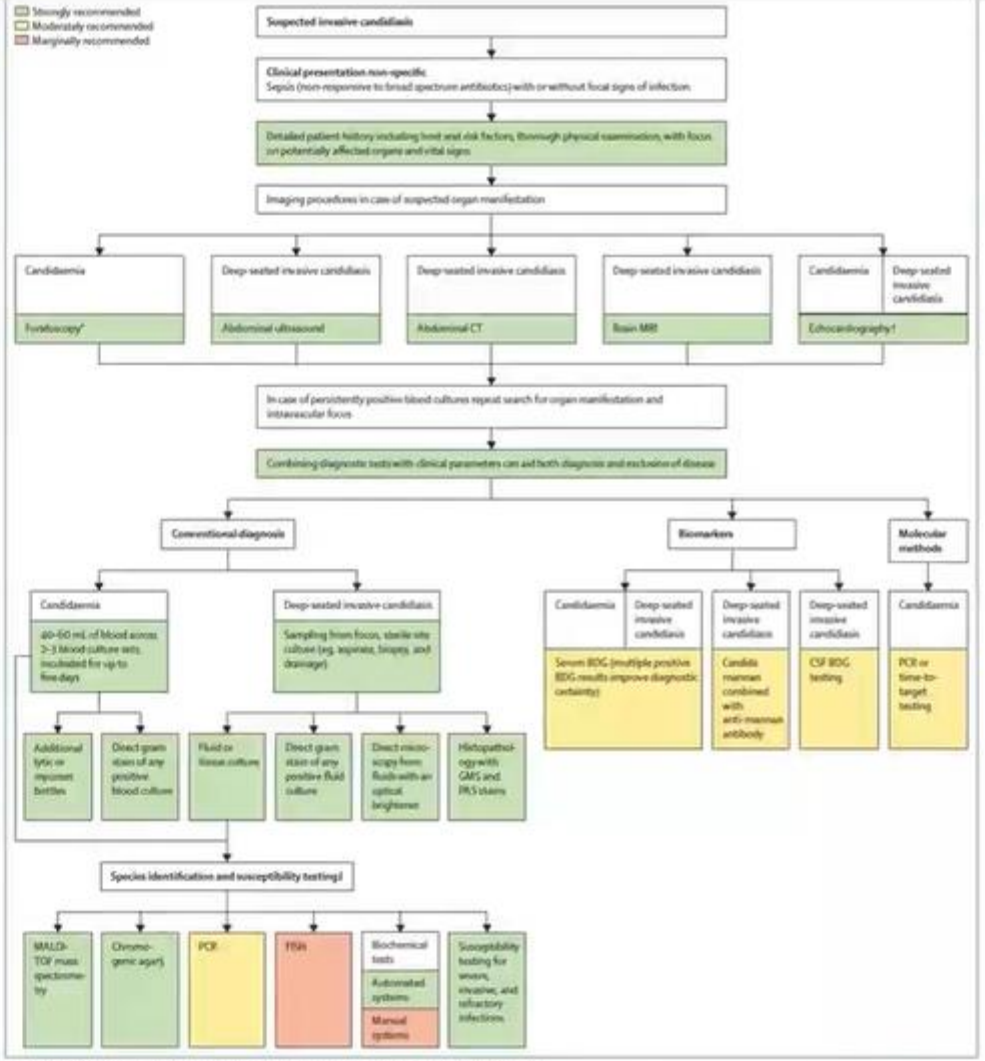



**Figure 1: Optimal diagnostic pathway for the diagnosis of candidaemia and invasive candidiasis in adults**

BDG=β-D-glucan. CSF=cerebrospinal fluid. FISH=fluorescence in situ hybridisation. GMS=Grocott-Gomori methenamine silver. MALDI-TOF=matrix-assisted laser desorption-time of flight. PAS=periodic acid-Schiff. *For patients with ocular symptoms, persistent candidaemia, immunosuppression, and those who are not able to verbalise complaints. †For patients with suspected endocarditis (including clinical signs such as skin lesions or new murmur), persistent candidaemia, presence of valve disease, and those with a cardiac implantable device. ‡Not all methods can identify every species of *Candida*. §For preliminary identification in mixed infection; confirmation needed by another method.

# Ablation du CVC : un consensus ?

IDSA GUIDELINES

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David Andes,[3] Daniel K. Benjamin, Jr.,[4] Thierry F. Calandra,[5] John E. Edwards, Jr.,[6] Scott G. Filler,[7] John F. Fisher,[8] Bart-Jan Kullberg,[9] Luis Ostrosky-Zeichner,[10] Annette C. Reboli,[11] John H. Rex,[12] Thomas J. Walsh,[13] and Jack D. Sobel[14]

**NONNEUTROPENIC PATIENTS**

8. Intravenous catheter removal is strongly recommended for nonneutropenic patients with candidemia (A-II).

**NEUTROPENIC PATIENTS**

14. Intravenous catheter removal should be considered (B-III).

Pappas, P.G. *et al* 2009 Clin Infect Dis

## Recommandations européennes

ESCMID PUBLICATIONS

**ESCMID® guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients**

*Recommendations.* In candidaemia, removal of indwelling intravascular catheters is strongly recommended. When catheter removal is not possible, lipid-based amphotericin B formulation or an echinocandin is preferable. For detailed recommendations, refer to Table 7.

Cornely, O.A. *et al* 2012 Clin Microbiol Infect

30




00:08

# Traitement des Candidémies

organisée conjointement par
la SFAR, la SPILF et la SRLF

Prise en charge des candidoses
et aspergilloses invasives de l'adulte

avec la participation de la Société Française d'Hématologie
de la Société Française de Mycologie Médicale
et de la Société Française de Greffe de Moelle

13 mai 2004
Paris, Institut Pasteur

## 1ère Etape

APRES isolement d'une levure et AVANT identification de l'espèce de *Candida* sp.

**Créatininémie**

| < 1,5 fois la normale | | ≥ 1,5 fois la normale | |
|---|---|---|---|
| **Neutropénique** | **Non-Neutropénique** | **Non-Neutropénique** | **Neutropénique** |
| Recevant ≥ 2 traitements néphrotoxiques ? | Traitement antérieur par un azolé ? | Traitement antérieur par un azolé? | |
| OUI / NON | OUI / NON | NON / OUI | |
| AmB IV (1 mg/kg/j) | AmB IV (1 mg/kg/j) OU fluconazole IV (12 mg/kg/j) | fluconazole IV (12 mg/kg/j) | |

caspofungine IV (70 mg J1 puis 50 mg/j)
OU
ABLp IV (3mg/kg/j)

AmB = amphotéricine B désoxycholate
ABLp = amphotéricine B liposomale


MIMOUNI Badre Eddine

22:32

00:06



00:08


organisée conjointement par
la SFAR, la SPILF et la SRLF

Prise en charge des candidoses et aspergilloses invasives de l'adulte

avec la participation de la Société Française d'Hématologie, de la Société Française de Mycologie Médicale et de la Société Française de Greffe de Moelle

13 mai 2004
Paris, Institut Pasteur

## 2ème Etape

APRES isolement d'une levure et APRES identification de l'espèce de *Candida* sp.

### Candida fluconazole - S

Neutropénique
ou
non

**fluconazole IV**
(6 mg/kg/j)
Relais *per os* dès que possible

### Candida fluconazole - R ou - SDD

**Créatininémie**
**< 1,5 fois la normale**

Non- Neutropénique

Neutropénique
recevant ≥ 2 traitements néphrotoxiques ?

NON

**AmB IV**
(1 mg/kg/ j)

**Créatininémie**
**≥ 1,5 fois la normale**

Neutropénique
ou
non

OUI

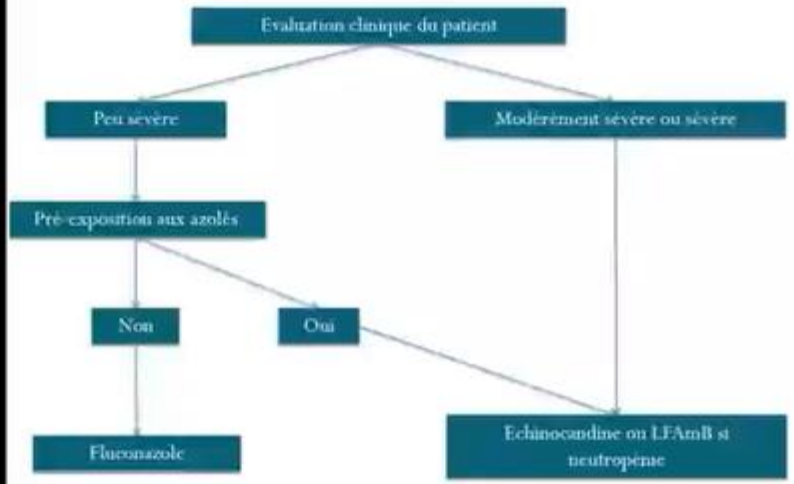
**caspofungine IV** (70 mg J1 puis 50 mg/j)
OU **ABLp IV** (3 mg/kg/j)
OU si *C. krusei*
**voriconazole** (12 mg/kg J1 puis 8 mg/kg/j)

Relais par **voriconazole oral** si infection contrôlée

AmB = amphotéricine B désoxycholate
ABLp = amphotéricine B liposomale

# Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

## Candidémie: tt initial (non neutropénique)




**Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part II. Treatment**


Benoît P. Goury
Mathew C. Arendrup
Georg Auzinger
Elie Azoulay
Márcia Borges Sá
Elizabeth M. Johnson
Eckhard Müller
Christian Pæresen
Coleman Rotstein
Gabriele Sganga
Mario Venditti
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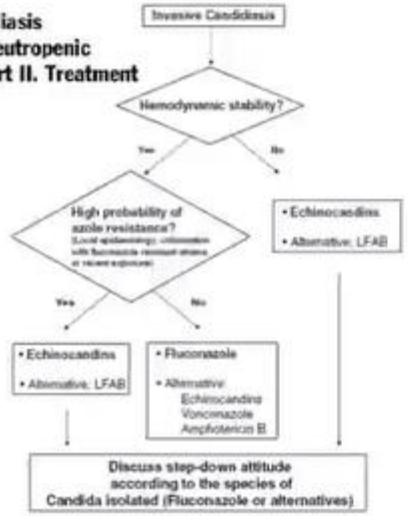
Bart Jan Kullberg



Intensive Care Med
DOI 10.1007/s00134-010-1839-6


***Pappas et al. Clinical Infectious Diseases 2009; 48:503–35***

# Traitement curatif des candidémies chez le neutropénique : résumé

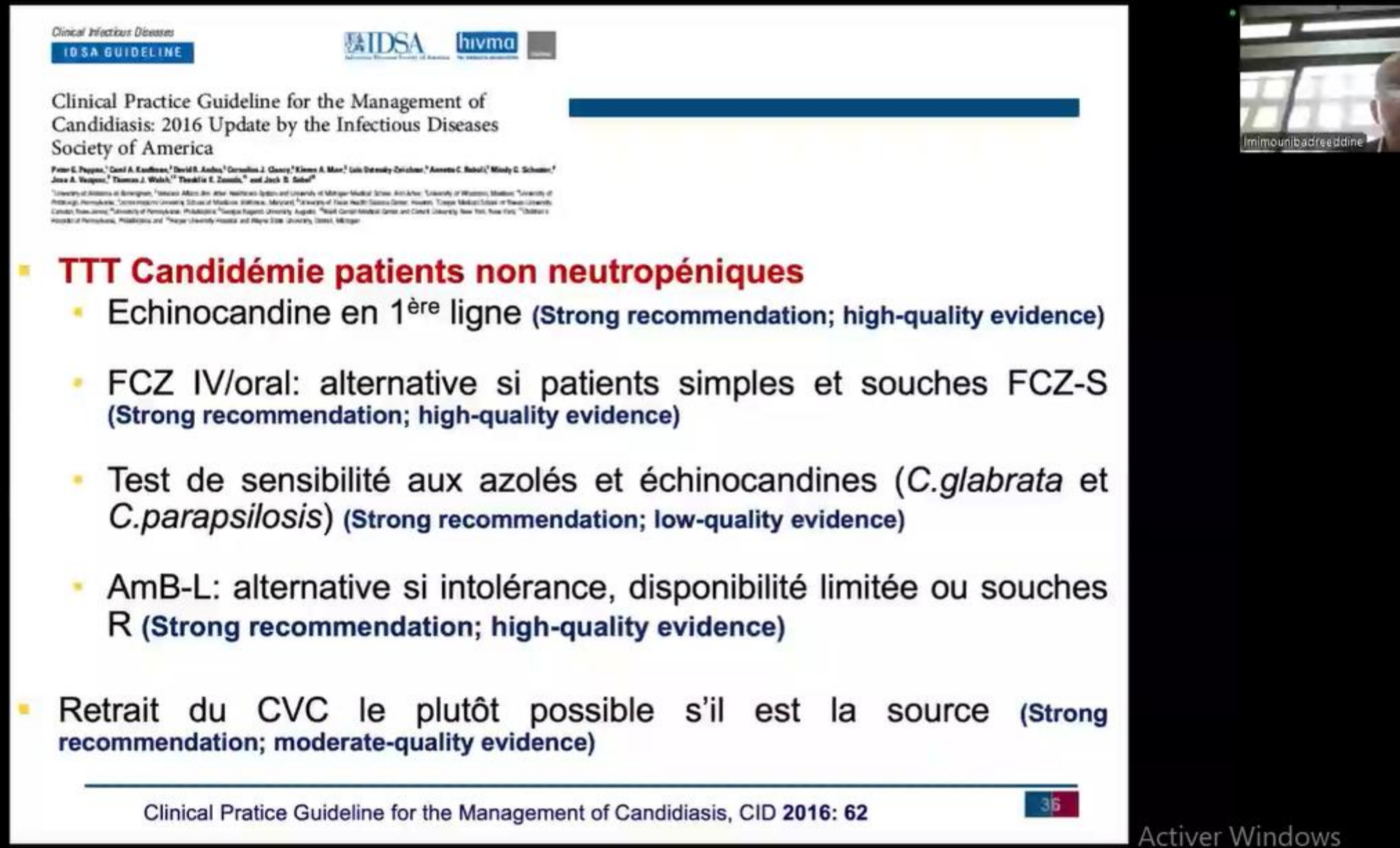
- **Avant identification**
  - Candines — A2 (caspo/mica) A3 (anidula)
  - Ampho B lipidique — A2
  - Fluconazole — B3 (Peu sévère et pas d'expo)
  - Voriconazole — B3 (id & besoin couvrir moisissures)
- **Après identification**
  - *C. glabrata*: candine: B3
    Ampho B lipidique 2ème choix B3
    Si tt initial efficace par azolés: continuer: B3
  - *C. parapsilosis*: Fluconazole: B3
    Ampho B lipidique B3
    Si tt initial efficace par candines: continuer: B3
  - *C. krusei*: Candine, ampho B lipidique ou vorico B3

*Pappas et al. Clinical Infectious Diseases 2009; 48:503–35*

# Traitement antifongique curatif des candidoses documentées bien codifié


- Candidémies
  - Débuter par une candine
  - Désescalader si possible
  - Enlever un cathéter s'il est la source de l'infection
  - Faire un fond d'oeil (+/- ETO et echodoppler)
  - Contrôler la négativité des hémocultures
  - Traiter 14j après négativation des Hc hors localisation secondaire

Pappas CID **2016**
Cornely CMI **2012**




Clinical Infectious Diseases

IDSA GUIDELINE

IDSA hivma

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Europe 2012: pas de recommandations claires

- **TTT empirique patients non neutropéniques**
  - Le plutôt possible si fièvre + FdR + signes de choc septique + biomarqueurs et/ou colonisation **(Strong recommendation; moderate-quality evidence)**
  - Echinocandine en 1ère ligne **(Strong recommendation; moderate-quality evidence)**
  - FCZ : alternative acceptable si pas d'exposition préalable au FCZ et pas de souches FCZ-R **(Strong recommendation; moderate-quality evidenc)**
  - AmB-L: alternative **(Strong recommendation; moderate-quality evidence)**
  - Arrêt si pas de réponse clinique après 4-5 j **(Strong recommendation; low-quality evidence)**

Clinical Pratice Guideline for the Management of Candidiasis, CID **2016: 62**

3B

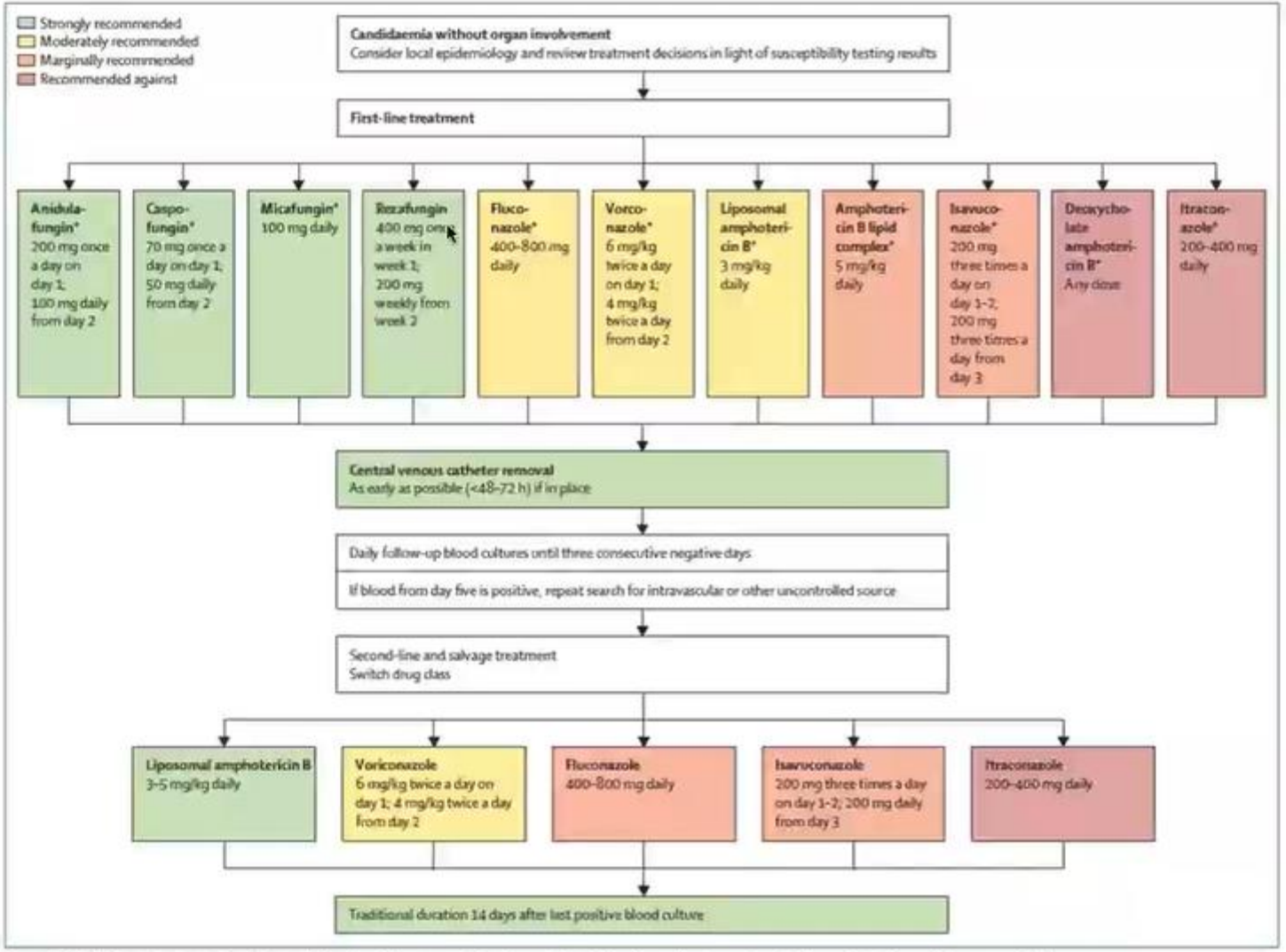



**Figure 2: Optimal treatment pathway for candidaemia without organ involvement in adults when all treatment modalities and antifungal drugs are available**

*After 5 days of first-line treatment, consider switch to oral treatment if all six prerequisites are fulfilled: haemodynamically stable; documented clearance of *Candida* from the bloodstream; non-neutropenic; source control; oral azole tolerated; and susceptibility confirmed. If blood cultures from day 5 are still positive, repeat search for an intravascular or other uncontrolled source.

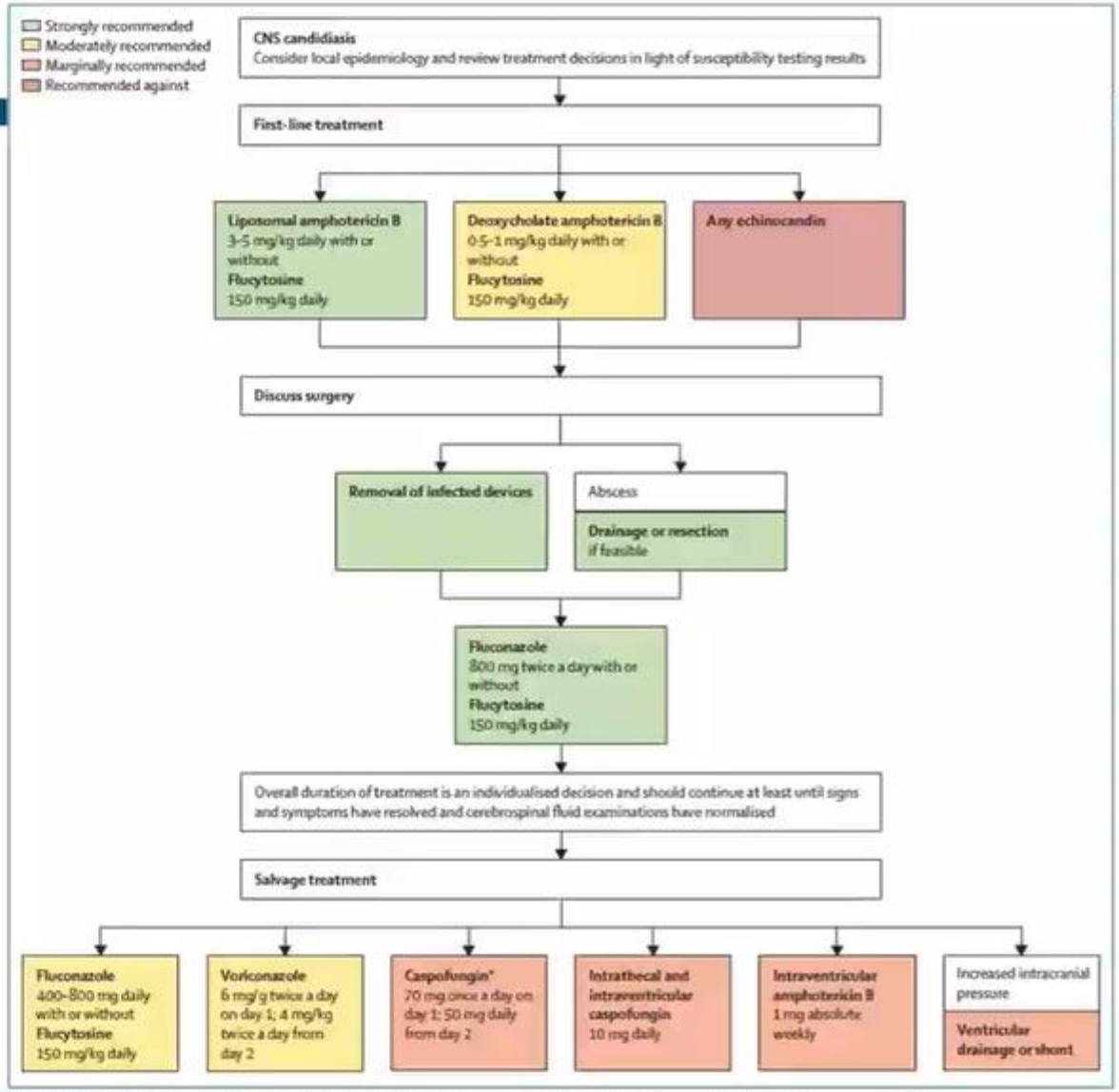



*Figure 3*: **Optimal treatment pathway for CNS candidiasis in adults when all treatment modalities and antifungal drugs are available**
*Echinocandins can be interchangeable, yet published literature only reported use of caspofungin in this setting.



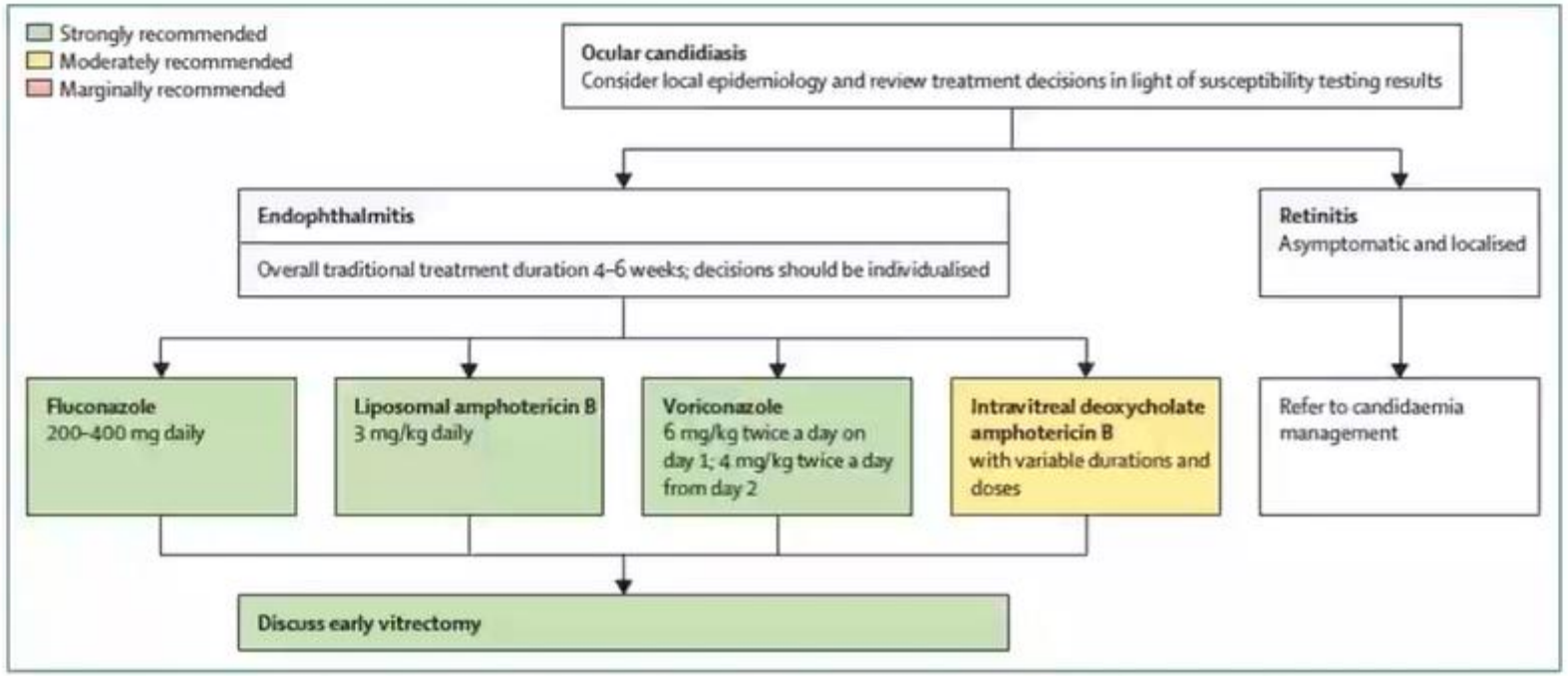



*Figure 4:* **Optimal treatment pathway for ocular candidiasis in adults when all treatment modalities and antifungal drugs are available**

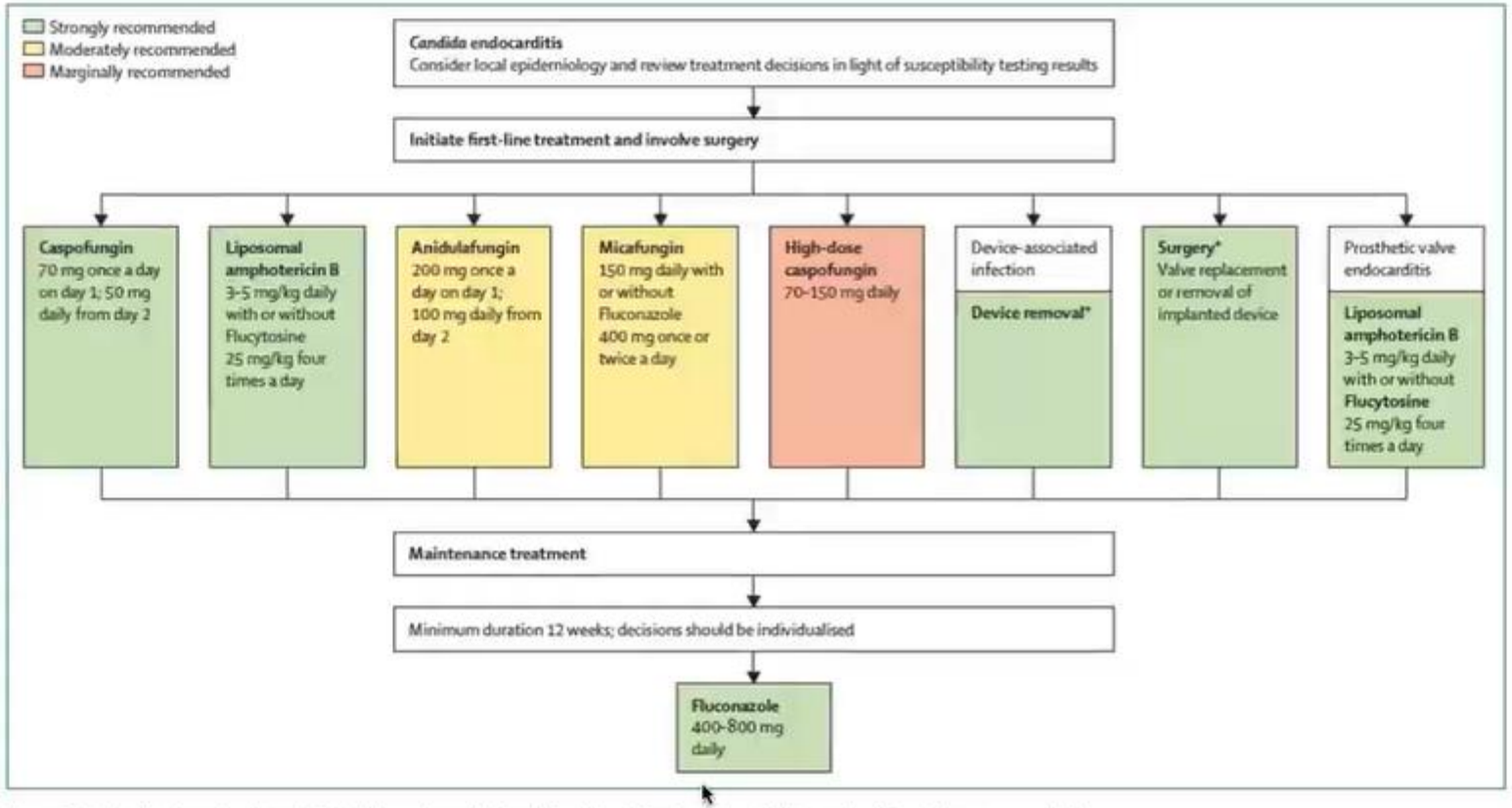



*Figure 5:* **Optimal treatment pathway for *Candida* endocarditis in adults when all treatment modalities and antifungal drugs are available**
*If surgery is not possible or implanted material cannot be removed, consider lifelong suppression with fluconazole (400–800 mg daily).

# Key messages

## Épidémiologie en pleine évolution

- Candida sp: 1ère cause d'IFI
- Emergence d'espèces résistantes Candida auris
- Méthodes conventionnelles de diagnostic: Microscopie et cultures ++++
- Biomarqueurs et PCR: aide au diagnostic
- Echinocandines: TTT de 1ère ligne pour toutes les formes
- Alternatives: AmB liposomale avec ou sans 5FC