
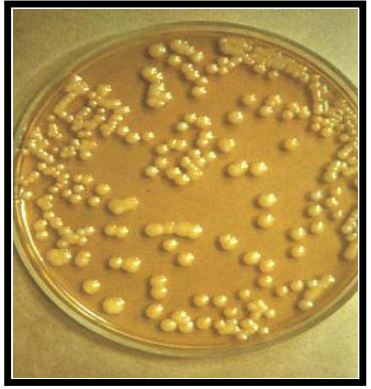
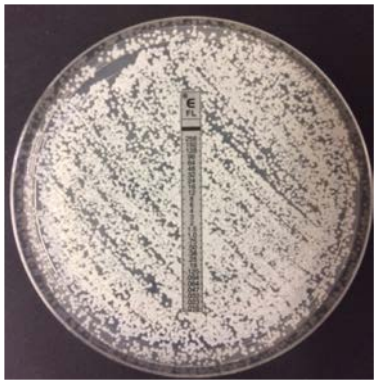

# *Yeasts infections in ICU: 2020-2021*


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**CNRS UMR 2000, Institut Pasteur, Paris, France.**


***Lyon; 25 novembre 2021***

# Conflicts of interest

Speaker for Astellas, MSD, Pfizer, Gilead Sciences

Consultant for Neteos, F2G, Gilead Sciences

# Risk factors for candidemia (& death) in ICU

6 teaching hosp; matched case-control

Candidemia

| Risk factors | Whole population[1, 2] (N = 567) | | | Intensive care[1, 2] (N = 250) | | | Non-Intensive care[1, 2] (N = 322) | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | p | OR | 95% CI | p | OR | 95% CI | p |
| Central venous catheter[4] | 6.74 | 2.96–15.4 | < 0.001 | | | | 9.77 | 3.72–25.7 | < 0.001 |
| Total parenteral nutrition[4] | 3.92 | 2.28–6.73 | < 0.001 | 6.75 | 2.89–15.7 | < 0.001 | 3.29 | 1.52–7.13 | 0.003 |
| Previous septic shock | 2.29 | 1.33–3.96 | 0.003 | 2.39 | 1.14–5.01 | 0.02 | | | |
| Acute kidney injury | | | | 4.77 | 1.94–11.8 | < 0.001 | | | |
| Heart disease | 1.78 | 0.96–3.33 | 0.07 | 3.78 | 1.09–13.1 | 0.006 | | | |
| Renal replacement therapy | 2.16 | 1.11–4.21 | 0.02 | | | | | | |
| Glycopeptides[5, 6] | | | | | | | 3.31 | 1.33–8.23 | 0.01 |
| Nitroimidazoles[5, 6] | 2.16 | 1.05–4.45 | 0.04 | | | | 3.12 | 1.07–9.11 | 0.04 |
| Aminoglycosides[5, 6] | | | | 2.28 | 1.01–5.13 | 0.05 | | | |

Poissy, Crit Care 2020

Candida colonization predicts invasive candidiasis in non-neutropenic ICU pts
OR 3.32:95%CI 1.68-6.58

Alenazy IJID, 2021

Death

| Risk factors | Whole population[1] (N = 191) | | | Intensive care unit[1, 2] (N = 83) | | | Non-ICU[1] (N = 108) | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95%CI | p | OR | 95%CI | p | OR | 95%CI | p |
| Age[2] | 1.03 | 1.00–1.06 | 0.06 | | | | | | |
| Acute kidney injury | 5.62 | 2.44–12.9 | < 0.001 | 3.45 | 1.21–9.90 | 0.02 | 11.9 | 2.47–57.7 | 0.002 |
| Septic shock concomitant to candidemia | 6.80 | 2.93–15.8 | < 0.001 | 4.09 | 1.72–14.0 | 0.003 | 8.70 | 2.26–33.5 | 0.002 |
| Number of antibiotics[3] | 1.43 | 1.16–1.77 | < 0.001 | 1.37 | 1.06–1.77 | 0.01 | | | |

Poissy, Crit Care 2020

# Risk factors for septic shock & death during candidemia in ICU

Seoul, 2009-2018; 126 adults with candidemia, 32 pts (25.4%) had septic shock.

Chronic liver disease associated with septic shock (OR 3.372, 95% CI 1.057 − 10.057)
(multivariate logistic regression analysis)

**Risk factors for death :**

malignancy (OR 8.251, 95% CI 2.227 − 30.573),

chronic liver disease (OR 3.605, 95% CI 0.913 − 14.227),

haemodialysis (OR 8.479, 95% CI 1.801 − 39.924),

mycological failure (OR 29.675, 95% CI 7.012 − 125.578),

septic shock (OR 3.980, 95% CI 1.238 − 12.796).

Suh, Infect Dis 2021

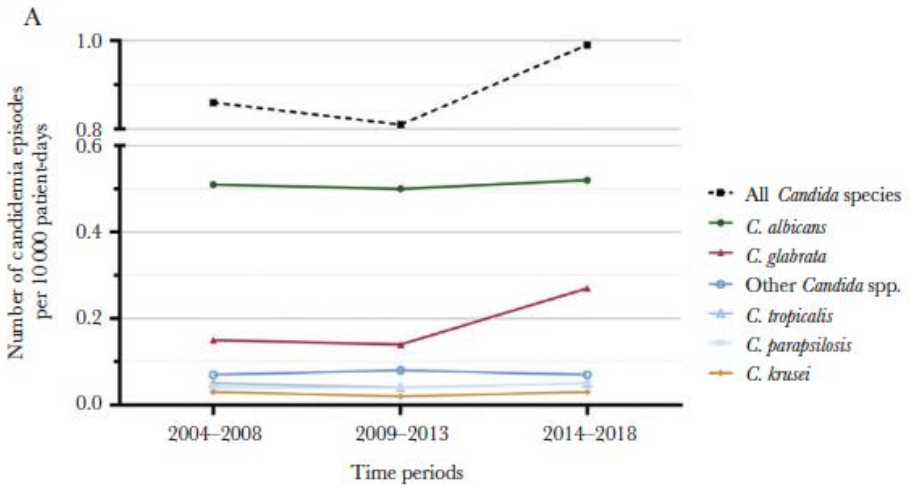
# Trends in the epidemiology of candidemia in ICU (Paris, 2004-2017)

| | Total ($n$= 3,092) | ICU ($n$ = 1,444) | No ICU ($n$ = 1,648) | $p$ |
|---|---|---|---|---|
| **Median age (IQR)** | **61.0 (23.8)** | **61.2 (22.6)** | **60.8 (24.9)** | 0.702 |
| **Sex ratio (M:F)** | **1.56:1** | **1.66:1** | **1.47:1** | 0.095 |
| **Hematology, *n* (%)** | **618 (20.0%)** | **196 (13.6%)** | **422 (25.6%)** | <0.0001 |
| Lymphoma | 225 (36.4%) | 78 (39.8%) | 147 (34.8%) | 0.107 |
| Acute leukemia | 249 (40.3%) | 67 (34.2%) | 182 (43.1%) | |
| Other | 144 (23.3%) | 51 (26.0% | 93 (22.0%) | |
| **Oncology, *n* (%)** | **988 (32.0%)** | **298 (20.6%)** | **690 (41.9%)** | 0.823 |
| Digestive tract | 472 (47.8%) | 138 (46.3%) | 334 (48.4%) | <0.0001 |
| Genital tract | 112 (11.3%) | 22 (7.4%) | 90 (113.0%) | |
| Urinary tract | 105 (10.6%) | 39 (13.1%) | 66 (9.6%) | |
| ENT | 78 (7.9%) | 22 (7.4%) | 56 (8.1%) | |
| Diverse | 221 (22.4%) | 77 (25.8%) | 144 (20.9%) | |
| **No malignancy, *n* (%)** | **1,486 (48.0%)** | **950 (65.8%)** | **536 (32.5%)** | <0.0001 |
| **Recent surgery, *n* (%)** | **560 (37.7%)** | **352 (37.0%)** | **208 (38.8%)** | 0.787 |
| Digestive tract | 244 (43.6%) | 167 (47.4%) | 77 (37.0%) | <0.0001 |
| Urinary tract | 29 (5.2%) | 9 (2.6%) | 20 (9.6%) | |
| Heart + vascular | 113 (20.2%) | 89 (25.3%) | 24 (11.5%) | |
| Orthopedic | 108 (19.3%) | 47 (13.4%) | 61 (29.3%) | |
| Diverse | 66 (11.8%) | 40 (11.4%) | 26 (12.5%) | |
| **Organ transplantation, *n* (%)** | **149 (10.0%)** | **104 (11.0%)** | **45 (8.4%)** | 0.116 |
| Kidney | 42 (28.2%) | 22 (21.2%) | 20 (44.4%) | 0.001 |
| Liver | 77 (51.7%) | 53 (51.0%) | 24 (53.3%) | |
| Heart | 15 (10.1%) | 156 (14.4%) | - | |
| Other | 15 (10.1%) | 14 (13.5%) | 1 (2.2%) | |
| **Bacterial infection, *n* (%)** | **331 (22.3%)** | **231 (24.3%)** | **100 (18.7%)** | 0.012 |
| **HIV infection, *n* (%)** | **29 (2.0%)** | **16 (1.7%)** | **13 (2.4%)** | 0.321 |
| **Intravenous drug addiction, *n* (%)** | **19 (1.3%)** | **7 (0.7%)** | **12 (2.2%)** | 0.013 |
| **Corticosteroid therapy, *n* (%)** | **38 (2.6%)** | **21 (2.2%)** | **17 (3.2%)** | 0.260 |
| **Severe burns, *n* (%)** | **26 (1.8%)** | **26 (2.7%)** | **-** | <0.0001 |
| **Central venous catheter as the only reported risk factor, *n* (%)*** | **197 (13.3%)** | **144 (15.2%)** | **53 (9.9%)** | 0.004 |
| **No reported risk factor, *n* (%)** | **176 (11.8%)** | **132 (13.9%)** | **44 (8.2%)** | 0.001 |

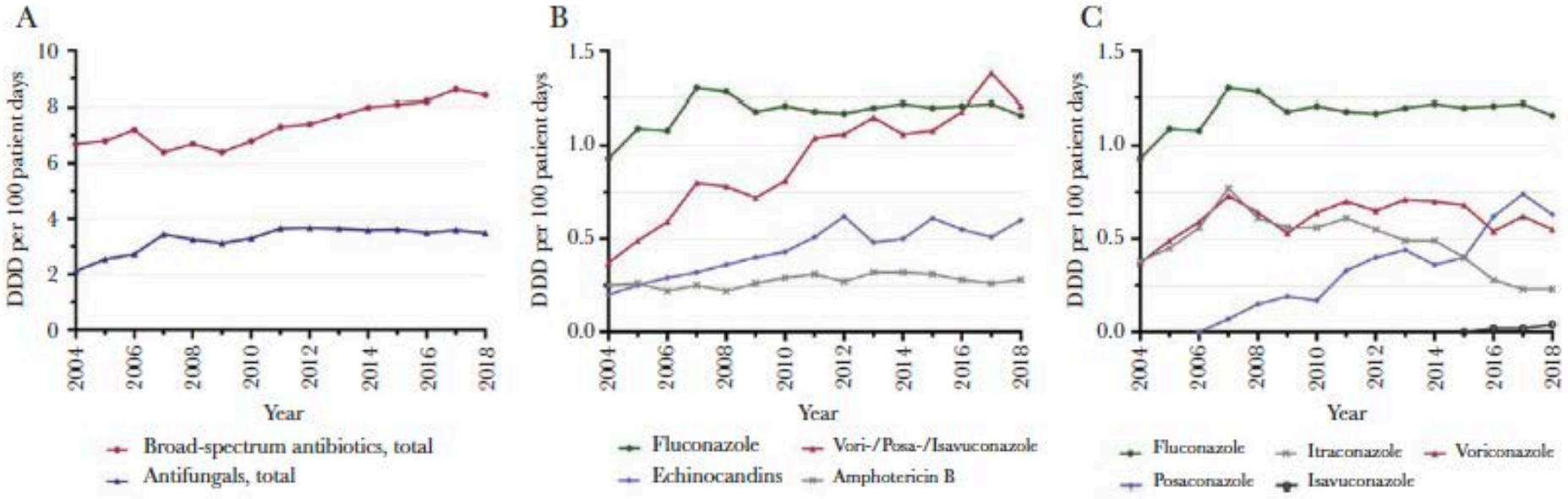
Bretagne, Front Med 2021

# Trends in the epidemiology of candidemia in ICU

**Switzerland, 2004-2018**




n = 2273




Adam, OFID 2021

# Candidemia in ICU: South America & Asia

## French Guyana; 2013-2019

2353 admissions

28,627 days hospitalization

ICU-acquired BSI= 182 cases

Enterobacteries: 67.7%

*Candida* spp.: 4.5%

Kallel, Am J Trop Med Hyg 2020

## Korea, 2006-2017 (n=2,248)

**Candida spp. n°1 since 2013**

*C. albicans* (39.9%)

*Candida tropicalis* (20.2%)

Candida parapsilosis (18.2%).

Significant increase:

proportion *C. glabrata*

proportion by year in hospitals with organ transplant wards,

<500 beds,

in surgical ICUs Kim, Front Med 2020

# Candidemia in surgical patients

RESSIF NETWORK (2012-2018; 29 centers; 15/18 regions,; France)

10,886 episodes of IFD: 5345 fungemia; 1926 with recent surgery (36.1%)

- 48.8% : abdominal surgery
- 14.6%:  vascular surgery
- Unchanged mortality between 2012 and 2018

NRCMA, Unpublished data 2021

# Effect of HIV infection on death rates during candidemia

**Table 3.** Random-effects multivariable logistic regression analysis of the effect of HIV on in-hospital death by sentinel site, simultaneously adjusted for potential confounders, among 907 persons with candidemia, South Africa, 2012–2017*

| Variable | Summary aOR for death (95% CI) | Wald p value |
|---|---|---|
| HIV status | | |
| Seronegative | Referent | |
| Seropositive | 1.89 (1.38–2.60) | <0.001 |
| Age group, y | | |
| <18 | Referent | |
| 18–44 | 2.55 (1.66–3.93) | <0.001 |
| 45–64 | 3.48 (2.21–5.49) | <0.001 |
| ≥65 | 6.47 (3.61–11.61) | <0.001 |
| Sex | | |
| F | Referent | |
| M | 1.27 (0.95–1.70) | 0.11 |
| Year | | |
| 2012 | Referent | |
| 2013 | 1.26 (0.72–2.19) | 0.42 |
| 2014 | 1.34 (0.67–2.68) | 0.40 |
| 2015 | 1.17 (0.58–2.33) | 0.66 |
| 2016 | 1.08 (0.63–1.86) | 0.77 |
| 2017 | 1.53 (0.90–2.61) | 0.12 |
| ICU admission | | |
| No | Referent | |
| Yes | 1.70 (1.23–2.36) | 0.001 |
| Receipt of systemic antifungal treatment | | |
| No | Referent | |
| Yes | 0.35 (0.25–0.48) | <0.001 |
| *Candida* species | | |
| *C. albicans* | Referent | |
| Other *Candida* spp. | 0.66 (0.49–0.89) | 0.006 |

*aOR, adjusted odds ratio; ICU, intensive care unit. Intra-cluster correlation coefficient = 0.03; likelihood ratio test for $\rho = 0$; p value = 0.003.

HIV prevalence = 41%

Govender, EID 2021

# FDG-PET/CT in ICU patients with candidemia

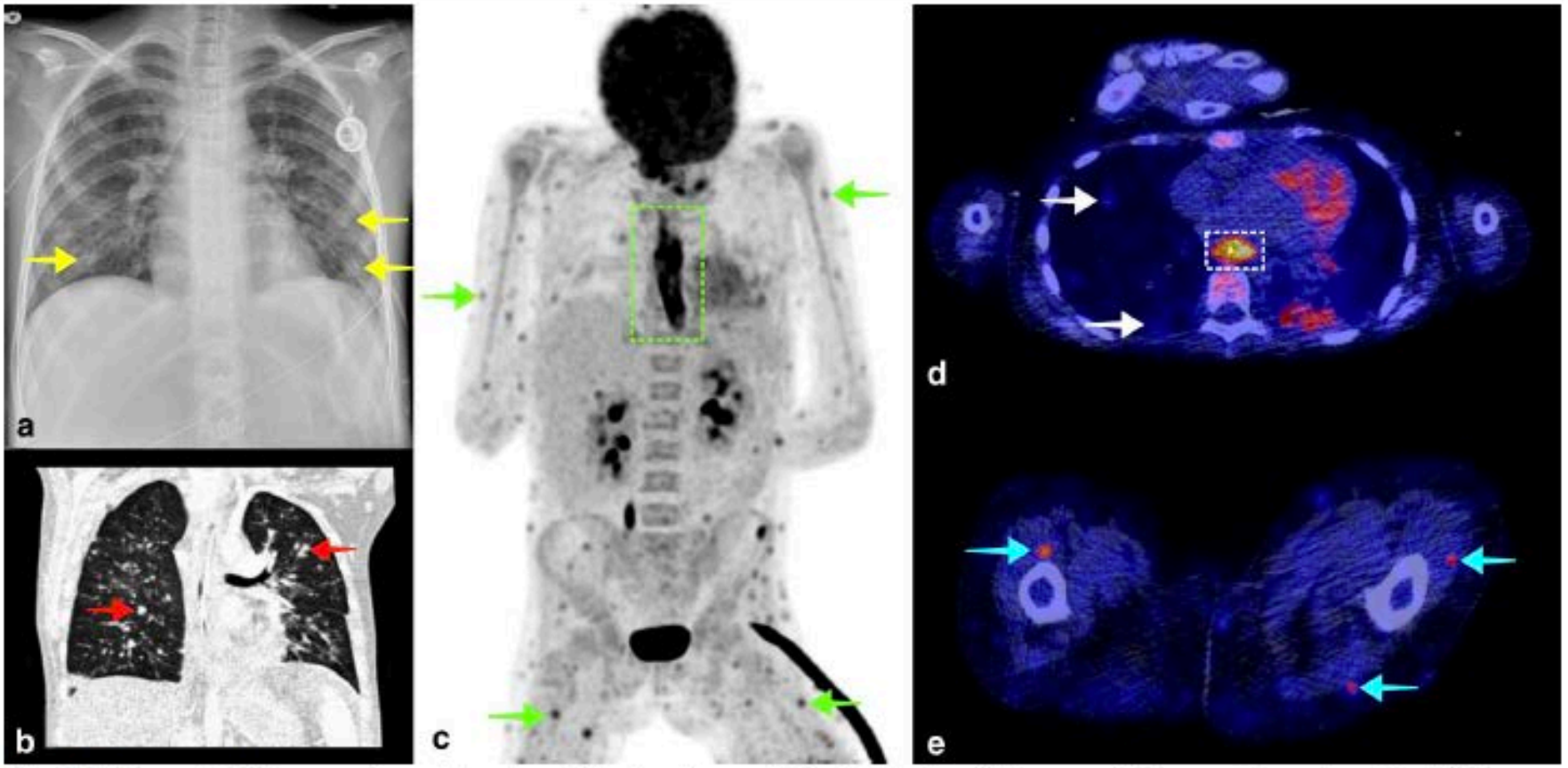
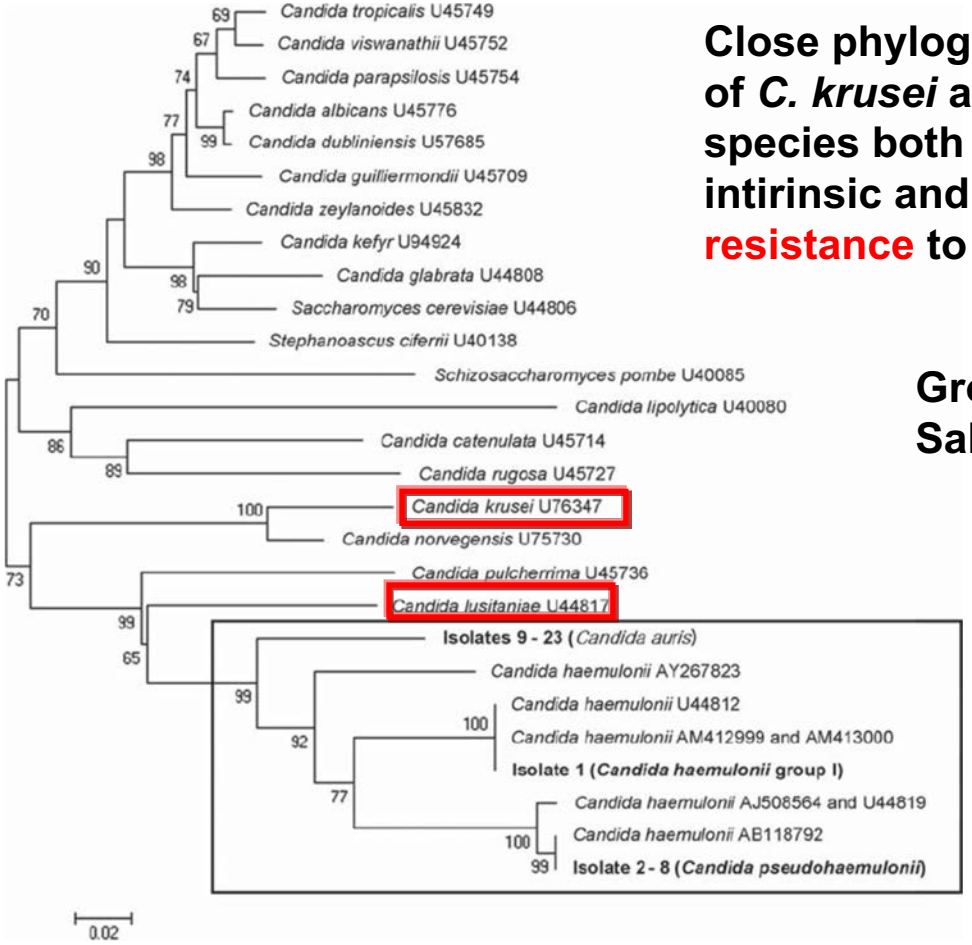



**Fig. 2** A 10-year-old girl known with acute lymphocytic leukemia was admitted to the hospital because of fatigue and general malaise. During admission, the patient also developed fever, for which blood cultures were taken and cefuroxime was started. Blood cultures were positive for *Candida albicans*. A thoracic X-ray showed small bilateral pulmonary consolidations (**a**, yellow arrows), and thoracic CT showed multifocal opacities as well (**b**, red arrows), supporting the diagnosis of pulmonary candidiasis. Voriconazole and caspofungin were started, and a venous access point of the patient was removed because of potential colonization. Despite antifungal treatment, the patient remained febrile, with a CRP level of 61 mg/L and leukocyte count of 23.6 x $10^9$/L. FDG-PET/CT was performed to evaluate other potential foci of infection. Coronal maximum intensity projection FDG-PET showed multiple small subcutaneous and intramuscular FDG avid foci (C, green arrows), and diffuse high FDG uptake in the esophagus (**c**, dashed green rectangle), suggestive of generalized candidiasis. Small FDG avid pulmonary consolidations were also visible on fused FDG-PET/CT (D, white arrows) as well as high FDG uptake in the esophagus (**d**, dashed white rectangle), and small subcutaneous and intramuscular FDG avid foci (E, blue arrows). Intensive antifungal therapy was continued, and the patient slowly recovered. The patient was discharged from the hospital 6 weeks after FDG-PET/CT

Pijl, Crit Care 2021

# *Candida auris* is an ascomycete yeast from the order *Saccharomycetales*



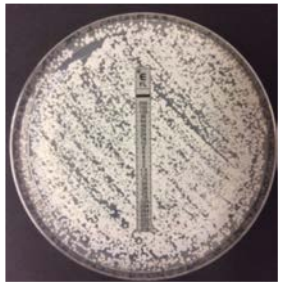

**Close phylogenetic relative of *C. krusei* and *C. lusitaniae* species both notable for their intirinsic and inducible resistance to antifungal agents**

**Grows well at 42ºC**
**Salt tolerant**

***Candida haemulonii* complex (*Metchnikowiaceae*)**
**Often resistant to amphotericin B**

**From: Biofilm formation and genotyping of *Candida haemulonii, Candida pseudohaemulonii*, and a proposed new species (*Candida auris*) isolates from Korea. Oh*et al*. 2011 Med Mycol. 2011;49(1):98-102. doi:10.3109/13693786.2010.493563**

# Why should we worry about *Candida auris ?*



1. Difficult to identify
2. Usually fluconazole resistant, some multi-drug resistant strains
3. High crude mortality reported from some outbreaks
4. Propensity for nosocomial spread patient to patient in high risk settings
5. Persists in the hospital environment
6. Often fails to respond to normal infection control procedures
7. Global spread with simultaneous emergence on at least three continents
8. Now documented from five continents since recognition in 2009

# *Candida auris* : global emergence

Simultaneous emergence on 3 continents

- 2009 Japanese - ear discharge
- Chronic otitis media S. Korea
- Nosocomial blood stream infection Korea , Japan, Malaysia

- Mutiple hard to control outbreaks reported from India and Pakistan
- High mortality rates (60%)

- S. Africa/Kenya ongoing nosocomial spread many hospitals
- Several thousand patients
- 70-80 per month

- Venezuela large multi-centre outbreaks
- 38% mortality, neonatal unit 28%
- Columbia 35% mortality

**Large outbreaks with imported strains**

Spain

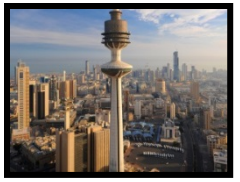
UK

USA

**Sporadic introductions**

Israel

Norway



Kuwait

Belgium

Oman

Austria

Germany

China

France

Russia

# Case–Case Comparison of *Candida auris* vs. Other *Candida* spp. fungemia

Outbreak in Colombia, 1/2015-9/2016, all pts in ICU n=40 vs.50

**Factors independently associated with *C. auris* fungemia :**

≥ 15 days of pre-infection ICU stay (OR: 5.62, CI: 2.04–15.5)

severe sepsis (OR: 3.70, CI 1.19–11.48)

diabetes mellitus (OR 5.69, CI 1.01–31.9)

Caceres, Mycopathologia 2020

# Countries where *Candida auris* has been notified (Feb 15th, 2021)

# Fungemia due to *Candida haemulonii* cx

**Complex phylogenetically related to *C. auris***

Yeasts of the complex: *C. haemulonii*, *C. duobushhaemuloni*, *C. haemulonii var. vulnera*

80 cases reported in the literature, mostly from tropical regions

**19 Reported cases in France between 2002 and 2021**

70% reported in the French West Indies and French Guyana

60% male, average age 60 years, 60% in ICU, 60% with central venous catheter

Resistance to antifungal drugs :

- Especially Amphotericin B and Fluconazole
- The susceptibility to echinochandins is preserved

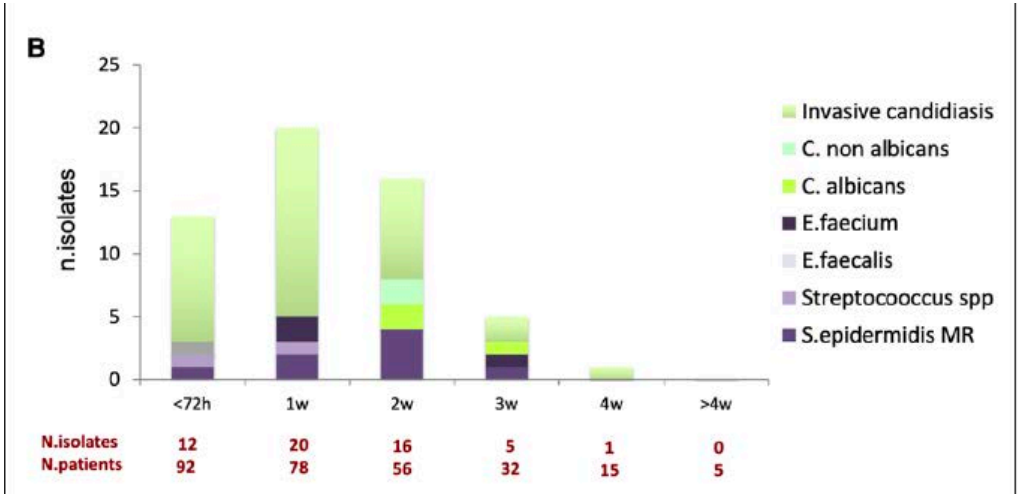
Mortality at D28: 25%.

Françoise U, ECCMID 2022

# Superinfections in critically ill patients with COVID-19

**Brescia, Italy, Feb-May 2020**

- 92 pts: 21.7% of superinfection at admission;
- 41 invasive candidiasis :36 probable




| Variables | No Superinfection ($n = 39$) | Superinfection ($n = 53$) | Total ($n = 92$) | $p$ |
|---|---|---|---|---|
| ICU length of stay (d), median (IQR) | 5.00 (2.0–8.0) | 15.00 (9.5–20.5) | 10.00 (4–16) | < 0.001 |
| Hospital length of stay (d), median (IQR) | 21.00 (14.0–28.0) | 27.00 (16.0–38.0) | 23.50 (15.5–31.6) | 0.199 |
| ICU mortality, *n* (%) | 4 (10.3) | 24 (45.3) | 28 (30.4) | < 0.001 |
| 28-d mortality, *n* (%) | 6 (15.4) | 26 (49.1) | 32 (50.9) | 0.001 |

Signorini, Critical Care Explorations 2021

# COVID-19-associated candidiasis

| Study | Country | N | ICU Only Y/N | MV % | Incidence (%) | Incidence Rate[a] | Incidence Density | Isolates | C. albicans % |
|---|---|---|---|---|---|---|---|---|---|
| Cataldo[b] [10] | Italy | 5 | Y | NR | 8.8 | NR | NR | 6 | 33 |
| Giacobbe[b] [11] | Italy | 3 | Y | NR | 3.8 | NR | NR | 3 | 33 |
| Bonazzetti[b] [12] | Italy | 3 | Y | NR | 3.4 | NR | NR | 3 | 100 |
| Antinori [13] | Italy | 3 | N | NR | NR | NR | NR | 3 | 33 |
| Al-Hatmi [14] | Oman | 4 | Y | 100 | NR | NR | NR | 5 | 60 |
| Chowdhary [15] | India | 15 | Y | 53 | 2.5 | NR | NR | 15 | 20[c] |
| White[d] [16] | UK | 5 | Y | 91 | 3.7 | NR | NR | 6 | 83 |
| Mastrangelo [6] | Italy | 21 | N | NR | NR | NR | 82[aa] | 21 | 67 |
| Riche [17] | Brazil | 11 | N | NR | NR | NR | 10-12[bb,cc] | 11 | 73 |
| Bishburg [18] | USA | 8 | Y | NR | 8.9 | NR | NR | 8 | 25 |
| Nucci [19] | Brazil | 9 | N | 100 | 1.5 | 15 | NR | 9 | 56 |
| Current | USA | 12 | Y | 92 | 5.1 | 51 | NR | 13 | 31 |

Adapted from Macaulay Mycoses 2021

# COVID-19-associated candidiasis

## Doha, Qatar March 2020- April 2021

80 patients with COVID-19-associated candidemia in an ICU matched 1:2 with those without candidemia. Multivariate conditional logistic regression analysis

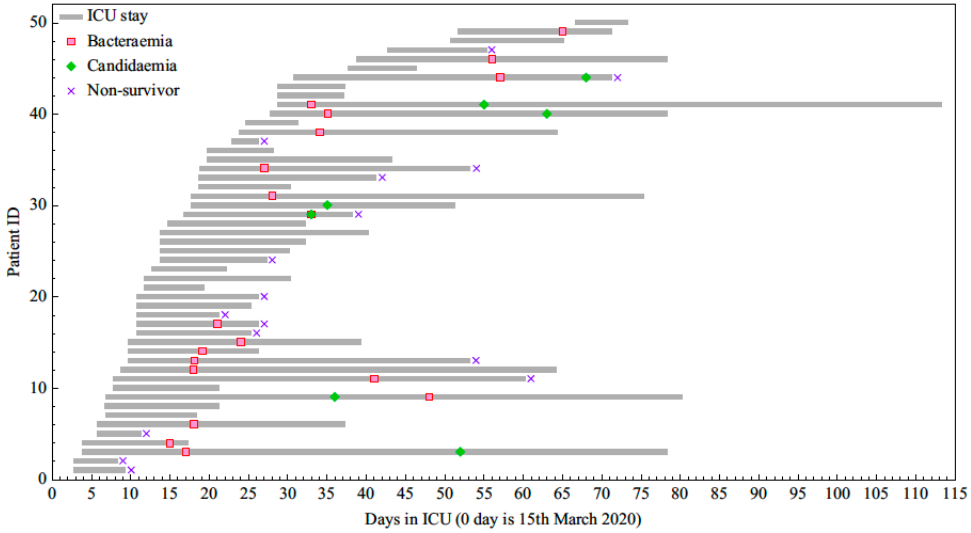
CAC incidence: 2.34 per 1000 ICU days

Age (p=0.001) and sequential organ failure assessment score (p=0.046) independently associated with CAC

Tocilizumab and corticosteroids not independently associated with candidemia

Omrani, Med Mycol 2021

## Athens, March-May 2020



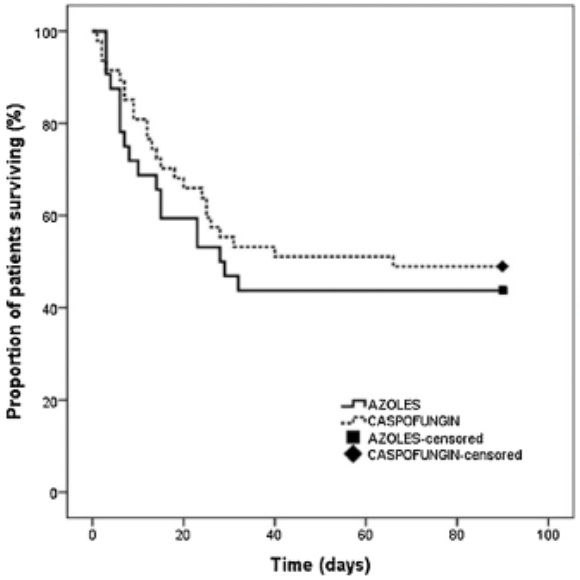

Kokkoris, J Hosp Infect 2021

# Evaluation of first-line treatment of candidemia in ICU

Azoles as a suitable alternative to echinocandins in ICU?

Retrospective multicentric cohort study in Lyon ICUs (2015-2017):

79 pts with candidemia treated by an echinocandin (47) or azoles (32)




Multivariable analysis of risk factors for 90-day mortality.

| Risk factor | Adjusted odds ratio | 95%CI | *P* |
|---|---|---|---|
| Solid organ transplantation | 0.251 | 0.037–1.624 | 0.147 |
| SOFA on the day of candidemia | 1.363 | 1.214–1.530 | <0.001 |
| Time elapsed to treatment initiation | 0.564 | 0.406–0.783 | <0.001 |
| Adequate *Candida* source control | 0.048 | 0.011–0.211 | <0.001 |
| Azoles first-line therapy | 1.898 | 0.719–5.006 | 0.196 |

Bienvenu, Int J Infect Dis 2020

# Sepsis due to uncommon or rare yeasts

Basidiomycetes : *Geotrichum, Saprochaete, Magnusiomyces, Trichosporon*

Ascomycetes: *Kodamaea, Malassezia, Pseudozyma, Rhodotorula, Saccharomyces, Sporobolomyces*

## Messages:

- on the rise (hematology)
- allmost 10% of yeasts fungemia (Paris)
- role of prior echinocandin therapy
- echinocandin ± multiply resistant
- outbreaks in ICU/hematology wards [whole genome sequencing]
- complex management: multidisciplinary approach

THE LANCET
Infectious Diseases



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

Prof Sharon C-A Chen, PhD • Prof John Perfect, MD • Prof Arnaldo L Colombo, MD • Prof Oliver A Cornely, MD • Prof Andreas H Groll, MD • Danila Seidel, PhD • Kerstin Albus, PhD • João Nobrega de Almeida Jr, MD • Prof Guillermo Garcia-Effron, PhD • Nicole Gilroy, MBBS • Prof Cornelia Lass-Flörl, MD • Prof Luis Ostrosky-Zeichner, MD • Prof Livio Pagano, MD • Prof Tamas Papp, DSc • Riina Rautemaa-Richardson, FRCPath • Jon Salmanton-García, PhD • Andrej Spec, MD • Prof Joerg Steinmann, MD • Prof Sevtap Arikan-Akdagli, MD • Dorothee E Arenz, PhD • Rosanne Sprute, MD • Luisa Duran-Graeff, MD • Prof Tomas Freiberger, MD • Corrado Girmenia, MD • Michelle Harris • Prof Souha S Kanj, MD • Maryam Roudbary, PhD • Prof Olivier Lortholary, MD • Joseph Meletiadis, PhD • Prof Esther Segal, PhD • Prof Felipe Francisco Tuon, PhD • Prof Nathan Wiederhold, PharmD • Tihana Bicanic, MD • Prof Jagdish Chander, MD • Prof Yee-Chun Chen, MD • Prof Po-Ren Hsueh, MD • Prof Margaret Ip, MD • Prof Patricia Munoz, MD • Prof Isabel Spriet, MD • Elvis Temfack, MD • Prof Luis Thompson, MD • Prof Anna Maria Tortorano, PhD • Aristea Velegraki, PhD • Prof Nelesh P Govender, MBBCh • Show less • Show footnotes


# The Phase 3 Ambition-cm trial

Single high-dose liposomal amphotericin based treatment for HIV-associated cryptococcal meningitis

Institut Pasteur

EDCTP

Sida

UKaid

MRC Medical Research Council

wellcome

# Background

- HIV-associated cryptococcal meningitis remains the second leading cause of AIDS-related mortality[1]
- Conventional treatment with amphotericin B (AmB) is associated with significant drug-related toxicities[2]
- ACTA trial demonstrated shorter, 7 day courses of AmB can be given with flucytosine (5FC)[3]
- Liposomal amphotericin (AmBisome, LAmB) is less toxic, has a long half-life and effectively penetrates the central nervous system[4]
- Phase 2 study demonstrated that a single, high dose of LAmB (10mg/kg) was non-inferior to 14 daily doses (3mg/kg) at clearing *Cryptococcus* from the cerebrospinal fluid and was well tolerated[5]

[1]Rajasingham R, Lancet Infect Dis, 2017. [2]Bicanic T, Antimicrob Agents Chemother, 2015. [3]Molloy S, N Eng J Med, 2018.
[4]Groll AH, Clin Infect Dis, 2019. [5]Jarvis J, Clin Infect Dis, 2018

**AmBisome**

10mg/kg LAmB single dose
AND
5FC 100mg/kg/day for 14 days
AND
FLU 1200mg/day for 14 days

**Control**

1mg/kg AmB for 7 days
AND
5FC 100mg/kg/day for 7 days
THEN
FLU 1200mg/day for 7 days

## Primary outcome

- All-cause mortality at 10 weeks (non-inferiority)

## Secondary outcomes

- All-cause mortality at 2, 4 and 16 weeks (non-inferiority)
- All-cause mortality at 10 weeks (superiority)
- Early fungicidal activity
- Safety
- Relapse and IRIS
- Cost-effectiveness
- PK/PD

AMBISOME THERAPY

AMBIsome Therapy Induction OptimizatioN

**Kampala, Uganda**
Infectious Diseases Institute

**Lilongwe, Malawi**
UNC Project

**Blantyre, Malawi**
Malawi Liverpool Wellcome Trust Clinical Research Programme

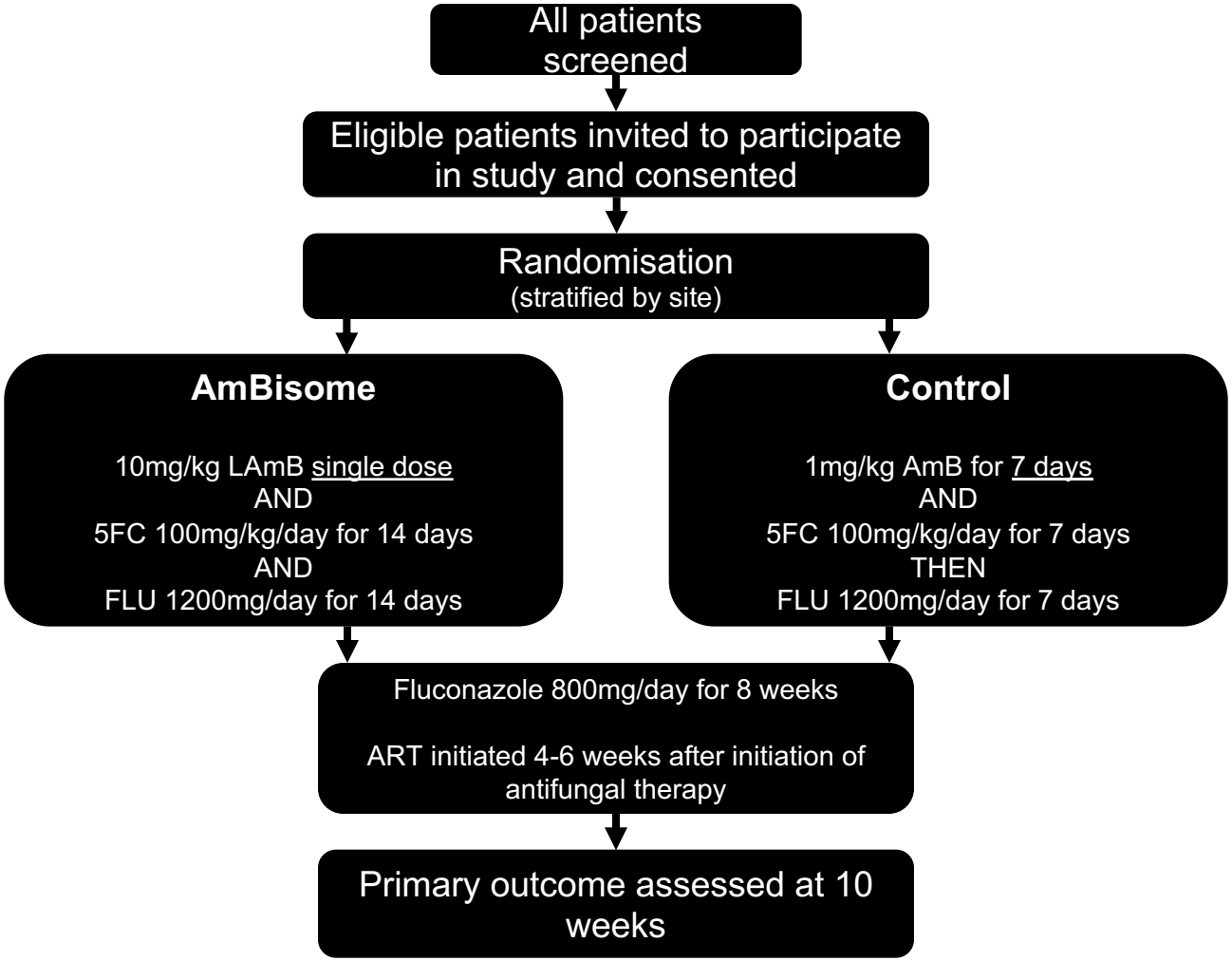
**Harare, Zimbabwe**
University of Zimbabwe

**Gaborone, Botswana**
Botswana-Harvard Partnership and University of Botswana

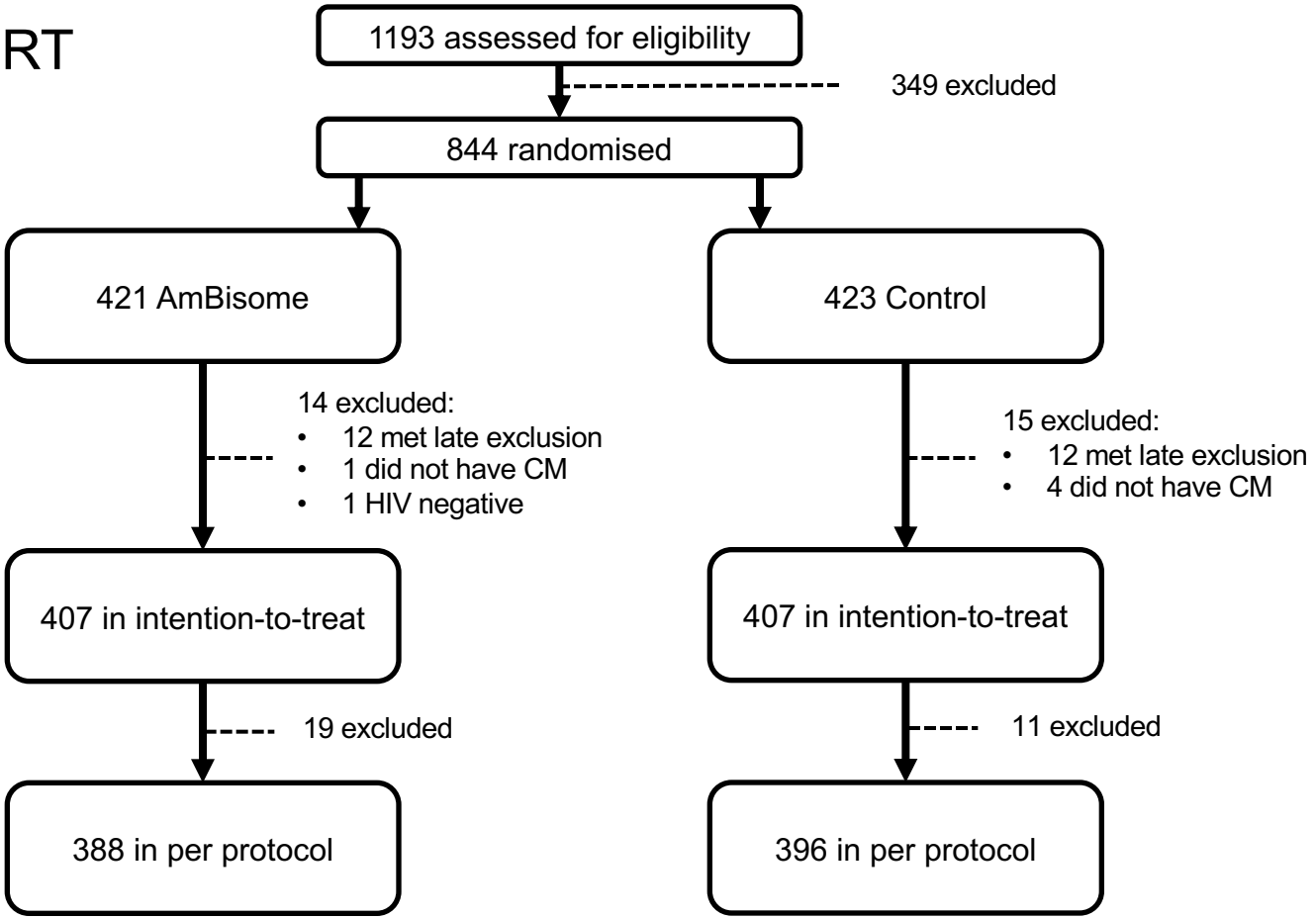
**Cape Town, South Africa**
University of Cape Town

LSHTM / SGUL
Pr Tom Harrison
Pr Joe Jarvis
Dr David Lawrence

**Institut Pasteur, Unité de Mycologie Moléculaire**
Pr Olivier Lortholary
Pr Françoise Dromer
Dr Alexandre Alanio
Dr Timothée Boyer Chammard
Aude Sturny-Leclère


All patients screened
Eligible patients invited to participate in study and consented
Randomisation
(stratified by site)
AmBisome
10mg/kg LAmB single dose
AND
5FC 100mg/kg/day for 14 days
AND
FLU 1200mg/day for 14 days
Control
1mg/kg AmB for 7 days
AND
5FC 100mg/kg/day for 7 days
THEN
FLU 1200mg/day for 7 days
Fluconazole 800mg/day for 8 weeks
ART initiated 4-6 weeks after initiation of antifungal therapy
Primary outcome assessed at 10 weeks

# CONSORT


1193 assessed for eligibility
349 excluded
844 randomised
421 AmBisome
423 Control
14 excluded:
• 12 met late exclusion
• 1 did not have CM
• 1 HIV negative
15 excluded:
• 12 met late exclusion
• 4 did not have CM
407 in intention-to-treat
407 in intention-to-treat
19 excluded
11 excluded
388 in per protocol
396 in per protocol

# Baseline characteristics

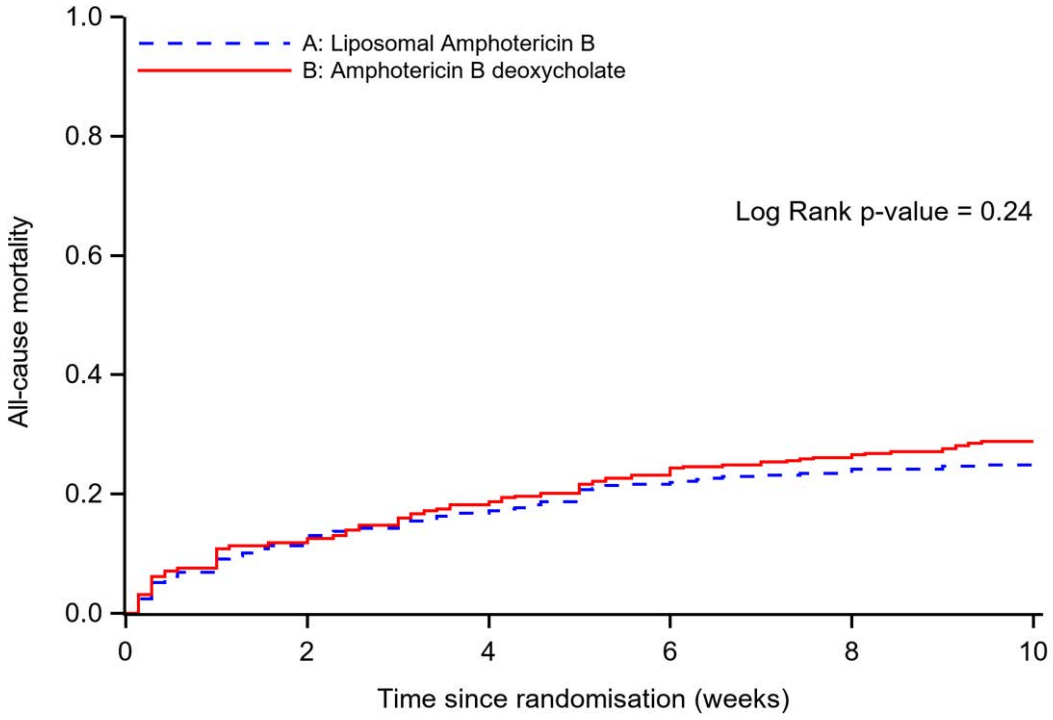
| Characteristic | AmBisome (N=407) | Control (N=407) |
|---|---|---|
| **Sex** – % male | 60% | 60% |
| **Median age** – years (IQR) | 37 (32-44) | 37 (32-43) |
| **Prior ART use** | 63% | 65% |
| **Median weight** – kg (IQR) | 53 (47-60) | 53 (48-60) |
| **Glasgow Coma Scale score** <15 | 28% | 29% |
| **Median CSF fungal count** – CFU/ml (IQR) | 48,500 (300-420,000) | 42,000 (585-365,000) |
| **CSF opening pressure** >25cm | 41% | 40% |
| **Median CSF white-cell count** – cells/$mm^3$ (IQR) | 6 (4-75) | 5 (3-52) |
| **Median CD4+ count** – cells/$mm^3$ (IQR) | 26 (9-56) | 28 (11-59) |

# All-cause mortality at 10 weeks: Non-inferiority, unadjusted analysis

| | AmBisome (N=407) | Control (N=407) | Risk difference (%) |
|---|---|---|---|
| **Intention-to-treat** | | | |
| No. of deaths | 101 | 117 | |
| | **24.8%** | **28.7%** | **-3.93%** |
| | (95% CI 20.7 to 29.3) | (95% CI 24.4 to 33.4) | (90% CI -9.0 to 1.2) |
| **Per protocol** | | | |
| No. of deaths | 95 | 113 | |
| | **24.5%** | **28.5%** | **-4.05%** |
| | (95% CI 20.3 to 29.1) | (95% CI 24.1 to 33.3) | (90% CI -9.3 to 1.1) |

95% CI
ITT: -10.0 to 2.2
PP: -10.2 to 2.1

# Kaplan-Meier Survival Curves




No. of patients at risk

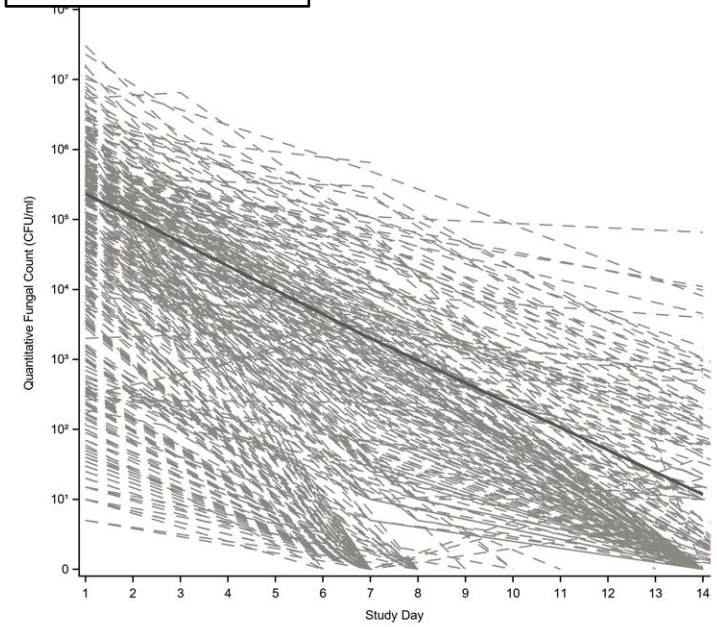
| | | | | | | |
|---|---|---|---|---|---|---|
| A | 407 | 360 | 337 | 317 | 310 | 304 |
| B | 407 | 359 | 332 | 311 | 299 | 288 |

# All-cause mortality at 2, 4 & 16 weeks: ITT, unadjusted analysis

| | AmBisome (N=407) | Control (N=407) | Risk difference (%) |
|---|---|---|---|
| **Mortality at 2 weeks** | | | |
| No. of deaths | 53 | 51 | |
| | **13.0%** | **12.5%** | **0.49%** |
| | (95% CI 9.0 to 16.7) | (95% CI 9.5 to 16.1) | (90% CI -3.4 to 4.4) |
| **Mortality at 4 weeks** | | | |
| No. of deaths | 70 | 76 | |
| | **17.2%** | **18.7%** | **-1.47%** |
| | (95% CI 13.7 to 21.1) | (95% CI 15.0 to 22.8) | (90% CI -5.9 to 3.0) |
| **Mortality at 16 weeks** | | | |
| No. of deaths | 115 | 119 | |
| | **28.2%** | **29.2%** | **-0.98%** |
| | (95% CI 23.9 to 32.9) | (95% CI 24.8 to 33.9) | (90% CI -6.2 to 4.2) |

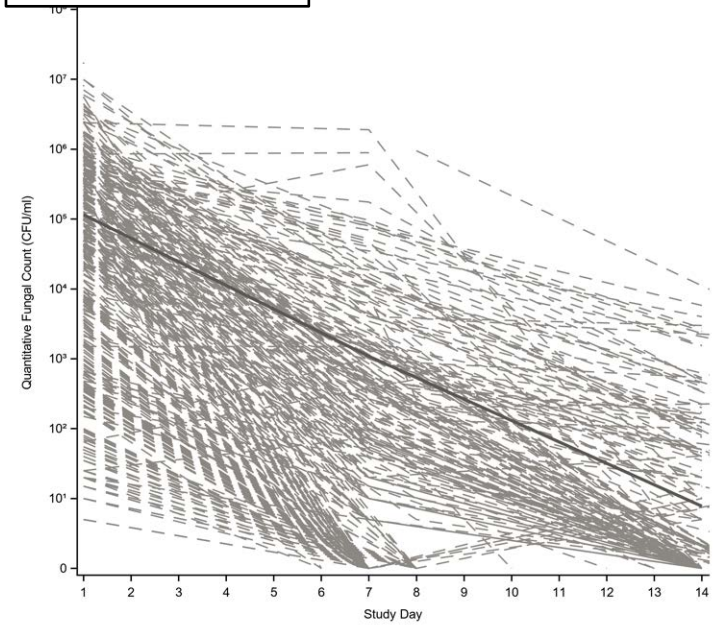
# Early Fungicidal Activity

AmBisome




EFA (SD)
n=363
-0.40 (0.13)

Control




EFA (SD)
n=381
-0.42 (0.13)

# Safety: Safety population

| Safety Parameter | AmBisome (N=420) | Control (N=422) | P value |
|---|---|---|---|
| **Total number of Grade 3 or 4 adverse events** | 382 | 579 | <0.001 |
| **Any adverse event – no. of participants (%)** | | | |
| Grade 3 | 173 (41%) | 225 (53%) | <0.001 |
| Grade 4 | 91 (22%) | 127 (30%) | 0.005 |
| **Anemia – no. of participants (%)** | | | |
| Grade 3 | 44 (10%) | 108 (26%) | <0.001 |
| Grade 4 | 12 (3%) | 62 (15%) | <0.001 |
| **Mean change in haemoglobin level to day 7 – g/dl** | -0.3 | -1.9 | <0.001 |
| **Received a blood transfusion – no. of participants (%)** | 32 (8%) | 76 (18%) | <0.001 |
| **Creatinine increase – no. of participants (%)** | | | |
| Grade 3 | 17 (4%) | 22 (5%) | 0.42 |
| Grade 4 | 5 (1%) | 3 (1%) | 0.505 |
| **Mean % change in creatinine level to day 7** | 20.2% | 49.7% | <0.001 |
| **Hypokalaemia – no. of participants (%)** | | | |
| Grade 3 | 6 (2%) | 27 (6%) | <0.001 |
| Grade 4 | 0 (0%) | 3 (1%) | 0.25 |
| **Thrombophlebitis requiring antibiotics - no. of participants (%)** | 8 (2%) | 28 (7%) | <0.001 |
| **Neutropenia – no. of participants (%)** | | | |
| Grade 3 | 27 (6%) | 21 (5%) | 0.36 |
| Grade 4 | 20 (5%) | 16 (4%) | 0.49 |
| **Thrombocytopenia– no. of participants (%)** | | | |
| Grade 3 | 9 (2%) | 17 (4%) | 0.11 |
| Grade 4 | 4 (1%) | 6 (1%) | 0.75 |
| **Elevated ALT – no. of participants (%)** | | | |
| Grade 3 | 6 (1%) | 4 (1%) | 0.52 |
| Grade 4 | 1 (0.2%) | 1 (0.2%) | 1.0 |

# Conclusion

- Single, high-dose AmBisome given with flucytosine and fluconazole was non-inferior to the current WHO recommended standard of care for HIV-associated cryptococcal meningitis.

- The AmBisome regimen was associated with a significant reduction in adverse events including significantly lower rates of anaemia, a reduced need for blood transfusions and a significantly smaller increase in creatinine.

- This regimen offers a practical, easier-to-administer and better tolerated treatment for HIV-associated cryptococcal meningitis in Africa.

- There is an urgent need to broaden access to AmBisome and flucytosine.

## ACKNOWLEDGEMENTS

**ALL PARTICIPANTS AND CAREGIVERS**

**ALL ROUTINE CARE STAFF**

**GILEAD SCIENCES INC**

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