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# FIXED DOSING OF LIPOSOMAL AMPHOTERICIN B IN MORBIDLY OBESE INDIVIDUALS

*Clinical Infectious Diseases, 2019 September 7; Epub ahead of print*

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**BACKGROUND & AIM:** Liposomal (L) amphotericin B (AmB), is widely used to treat invasive fungal diseases, typically at a dose of 3 mg/kg. However, little is known about its pharmacokinetics in obese patients. Moreover, toxicity could be a problem with very high body-weight–derived doses. The aim of this study was to evaluate the pharmacokinetics of L-AmB in morbidly obese subjects, to determine the effect of obesity on the clearance of L-AmB and hence guide dosing.

**STUDY DESIGN:** Pharmacokinetic study.

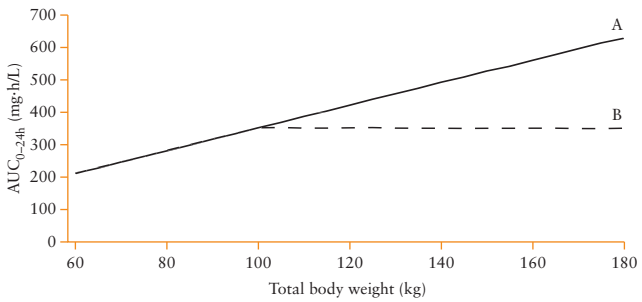
**ENDPOINTS:** Central volume of distribution ($V_c$); area under the curve ($AUC_{0–24h}$) and maximum concentration ($C_{max}$) at steady-state.

**METHOD:** Sixteen morbidly obese (body mass index, BMI, >40 kg/m$^2$) but otherwise healthy adults, were randomized to receive a single intravenous infusion of L-AmB of 1 mg/kg over 45 minutes or 2 mg/kg over 90 minutes. Blood samples were taken at intervals up to 48 hours post-infusion, for quantification of AmB concentrations. Concentration–time data were modelled, and relationships with covariates including total body weight (TBW), lean body weight, BMI, ideal body weight, body surface area, age and sex were investigated. $AUC_{0–24h}$ and $C_{max}$ were simulated for virtual patients of different weights receiving daily L-AmB 3 mg/kg over 1 hour or, for some patients weighing ≥100 kg, a fixed dose of 300 mg.

**RESULTS:** The median (range) TBW was 137 (104–177) kg, and BMI was 45.9 (40.2–52.1) kg/m$^2$. There was no relationship between TBW or other covariates and clearance of plasma AmB. $V_c$ increased linearly with TBW ($p$<0.01), but was relatively small in obese patients (probably due to AmB having limited disposition in adipose tissue). $AUC_{0–24h}$ (figure) and $C_{max}$ increased linearly in patients dosed on a per-kilogram basis. Administering a fixed dose to patients weighing ≥100 kg restricted the increase in $AUC_{0–24h}$ (figure) and lowered $C_{max}$ (due to the increase in $V_c$ with weight).

**CONCLUSION:** These results suggest that obese patients should receive L-AmB at the licensed dose of 3 or 5 mg/kg, capped at a maximum bodyweight of 100 kg to result in a 300- or 500-mg fixed dose for patients above this weight.

Simulated steady-state area under the curve from 0–24 hours for liposomal amphotericin B with (A) body-weight–derived dosing (3 mg/kg) and (B) with dose-capping at ≥100 kg bodyweight (300-mg fixed dose)



# FUNGAL BIOFILM MORPHOLOGY IMPACTS HYPOXIA FITNESS AND DISEASE PROGRESSION

*Nature Microbiology, 2019 December; 4(12):2430–41*

AUTHORS: Kowalski CH, Kerkaert JD, Liu KW, Bond MC, Hartmann R, Nadell CD, Stajich JE, Cramer RA
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**BACKGROUND & AIMS:** Populations of microbes organize into intricate macroscopic colonies with diverse morphologies. The functions of these colony morphology variants are not fully understood. Fungal colonies isolated from clinical and environmental samples have been shown to exhibit abundant intraspecies morphological diversity. For example, the filamentous fungi *Aspergillus fumigatus* shows different colony morphology at low-oxygen compared with normal-oxygen partial pressures. However, it remains unclear how this diversity affects fungal fitness and disease progression. The aims of this study were to explore how the low-oxygen colony morphology variant affects *A. fumigatus* pathogenesis and disease progression, and to identify genetic factors involved in colony morphology diversity.

**STUDY DESIGN:** Laboratory and *in vivo* study.

**ENDPOINTS:** Morphological and genetic variations, and the effect on virulence and disease progression.

**METHOD:** The macroscopic morphology of colonies of *A. fumigatus* at different oxygen tensions were compared by growing spores on culture plates for 72–96 hours at normal (21%) or hypoxic (0.2%) oxygen partial pressures. Fungal biofilms and cell walls were examined using fluorescent and electron microscopy. Genetic differences between strains were examined using various techniques including RNA sequencing and quantitative polymerase chain reaction. Finally, a murine model of invasive aspergillosis was used to assess how the different morphological types affected disease progression and mortality *in vivo*.

**RESULTS:** Oxygen partial pressure had a significant effect on the macroscopic and biofilm morphotypes of *A. fumigatus*. The hypoxia-typic morphotype that thrived at 0.2% oxygen had more abundant furrowing, a higher percentage of vegetative mycelia, and altered biofilm architecture compared with morphotypes that thrived at 21% oxygen. At the genetic level, the hypoxia-typic morphotype was generated by expression of a subtelomeric gene cluster regulated by the *hrmA* gene. The subtelomeric gene cluster contains genes, such as *cgnA*, that modify the hyphal surface, reduce the thickness of the cell wall and alter interhyphal interactions, leading to disruption of the biofilm architecture and infection-site morphologies. In the murine model of invasive aspergillosis, the hypoxia-typic morphotype led to increased host inflammation, rapid disease progression and mortality.

**CONCLUSIONS:** Oxygen tension affected macroscopic and biofilm morphotypes of *A. fumigatus*, with a subsequent impact on fungal–host interactions. *A. fumigatus* biofilm morphology should therefore be considered when assessing isolated strains for virulence and disease progression.

# UPDATES ON THE TAXONOMY OF MUCORALES WITH AN EMPHASIS ON CLINICALLY IMPORTANT TAXA

*Journal of Fungi, 2019 November 14; 5(4):E106*

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**BACKGROUND & AIM:** Fungi of the order Mucorales are a permanent part of the human environment, colonizing wet, organic materials. They are plant parasites and cause rot and spoilage, as well as being economically important as fermenting agents for soybean products and for producing a broad spectrum of enzymes used in biotechnology. Several species within this order are responsible for life-threatening infections (mucormycosis), predominantly in immunocompromised patients. Unresolved taxonomy has limited the understanding of Mucorales biology; however, significant progress has been made in recent years. The aim of this review was to summarize the main changes in the taxonomy of the Mucorales, with an emphasis on medically relevant taxa.

**ARTICLE TYPE:** Review.

**FINDINGS:** The order Mucorales has now been assigned to the phylum Mucoromycota. It consists of 261 species in 55 genera, with 38 of the species known to cause infections in humans. Studies of molecular phylogenetics has led to changes in the taxonomy of the Mucorales, with characteristics such as the shape of the suspensors, homothallism and the formation of sporangiola no longer considered to be taxonomically relevant. Sequencing of the internal transcribed spacer region is currently the preferred method for identifying species of Mucorales, as it has been shown to reliably distinguish species.

There have been amendments to several genera, including *Absidia*, *Backusella*, *Circinella*, *Mucor* and *Rhizomucor*. For example, based on molecular data, all mesophilic species of *Rhizomucor* have been transferred to *Mucor*, and *Rhizomucor* now consists purely of thermophilic species. Recent changes have also affected other medically important species, such as *Lichtheimia corymbifera*, *Mucor circinelloides* and *Rhizopus microsporus*. For example, phylogenetic analyses have now reduced the varieties of *Rhizopus microsporus* to synonyms, whereas *Lichtheimia corymbifera* has been identified as a separate species from *Lichtheimia ramose* rather than a synonym.

The Mucorales are a highly diverse group ecologically, but current data are insufficient to accurately determine the ecological role and geographical distribution of most species. Very few studies have directly investigated the natural habitats of Mucorales and a better understanding of their natural niches, reservoirs, dispersal and geographical distribution is needed in order to understand the route of acquisition and consequently how to prevent infections.

**CONCLUSION:** Molecular phylogenetic studies have led to changes in the taxonomy of Mucorales, with updates in the classification of various genera and species, including some medically relevant species.

# ANTI-COTH3 ANTIBODIES PROTECT MICE FROM MUCORMYCOSIS BY PREVENTION OF INVASION AND AUGMENTING OPSONOPHAGOCYTOSIS

*Science Advances, 2019 June 12; 5(6):eaaw1327*

AUTHORS: Gebremariam T, Alkhazraji S, Soliman SS, Gu Y, Jeon HH, Zhang L, French SW, Stevens DA, Edwards JE Jr, Filler SG, Uppuluri P, Ibrahim AS
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**BACKGROUND & AIM:** Mucormycosis is a fungal infection caused by Mucorales fungal pathogens, most commonly *Rhizopus*, which can cause angioinvasive infections in immunocompromised hosts with haematological malignancy or stem-cell transplantation, as well as in immunocompetent individuals suffering from severe trauma. *In vitro*, *Rhizopus* strains have been shown to invade endothelial cells by binding of the cell-surface protein CotH3 to the glucose-regulated protein 78 (GRP78) receptor on the endothelial cell surface. Repression of CotH3 expression limits invasion of the fungus and reduces its virulence. Antibodies against CotH3 have therefore been developed, and the aim of this study was to investigate their use as an immunotherapy against Mucorales fungi in mice.

**STUDY DESIGN:** *In vitro* and animal experiments.

**ENDPOINT:** Development of mucormycosis.

**METHOD:** Rabbit polyclonal antibodies were generated against two antigenic peptides of *Rhizopus delemar* CotH3 that reside in the binding sites of the host GRP78 protein. The protective effect of these antibodies was assessed in neutropenic mice infected with R. *delemar* and then treated intraperitoneally with a single dose of 30, 100 or 300 µg of antibody, or isotope-matched immunoglobulin G from preimmune serum as a control. The lower dose of antibody was also tested in diabetic ketoacidotic mice with pulmonary mucormycosis. Experiments investigating whether polyclonal anti-CotH3 antibodies enhanced polymorphonuclear leucocyte (PMN)-mediated killing of *R. delemar* were conducted *in vivo*. Other experiments investigated whether mouse monoclonal antibodies against a 16-mer peptide of CotH3 also protected against mucormycosis, and whether these monoclonal antibodies were synergistic with antifungal drugs.

**RESULTS:** Polyclonal antibodies against *R. delemar* CotH3 protected neutropenic mice from pulmonary mucormycosis caused by *R. delemar,* as well as that caused by other Mucorales, and prevented dissemination of infection from the lungs to the brain. The polyclonal antibodies also protected against pulmonary mucormycosis in diabetic ketoacidotic mice, and were found to enhance the PMN-mediated damage of *R. delemar* via opsonophagocytosis. Monoclonal antibodies against CotH3 also protected immunocompromised mice against pulmonary mucormycosis, and were shown to act synergistically with antifungal drugs to protect diabetic ketoacidotic mice from *R. delemar* infection.

**CONCLUSION:** Anti-CotH3 antibodies are a promising new therapeutic strategy for the treatment of mucormycosis.

# CLINICAL SIGNIFICANCE OF LOW SERUM CRYPTOCOCCAL ANTIGEN TITERS BY LATERAL FLOW ASSAY IN IMMUNOCOMPROMISED PATIENTS:

## A RETROSPECTIVE CASE CONTROL STUDY

*Journal of Clinical Microbiology, 2020 January 28; 58(2):e01648–19*

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**BACKGROUND & AIM:** *Cryptococcus* species can be associated with invasive infections of the skin, bone, lymph nodes and central nervous system, particularly in patients who are immunocompromised due to a condition such as HIV/AIDS or an organ transplantation. Cryptococcal disease is commonly diagnosed by detection of cryptococcal antigen (CrAg) by lateral flow assay (LFA). However, given the high sensitivity of this method, the clinical significance of low CrAg titres by LFA is not clear. The aim of the current study was therefore to investigate the association between low CrAg titres by LFA and the presence of cryptococcal disease in immunocompromised patients.

**STUDY DESIGN:** Retrospective case–control study.

**ENDPOINT:** Cryptococcal disease.

**METHOD:** The study included 96 patients who were tested for CrAg by LFA in serum or cerebrospinal fluid at one of two medical centres over a 52-month period. These individuals included 32 patients with first-time positive CrAg results and low serum titres (≤1:10), 32 age-matched controls with positive results and high serum titres (≥1:20), and 32 age-matched controls with negative titres. Participants' medical records were reviewed for clinical, radiological and laboratory data relevant to the occurrence of cryptococcal disease.

**RESULTS:** Most of the participants (95%) had one or more immunocompromising conditions, such as HIV infection (45%), solid organ transplantation (26%) or cirrhosis (22%). There was no significant difference in the incidence of pulmonary cryptococcus between patients with low serum CrAg titres and those with high titres (28% versus 25%, $p$=1.00). Among those with low titres, pulmonary cryptococcus was more likely in non-HIV immunocompromised patients than in HIV-positive patients (47% versus 0%, $p$=0.004). Although disseminated cryptococcus was more common in patients with high CrAg titres compared with those with low titres, the difference was not statistically significant (47% versus 22%, $p$=0.064). Positive CrAg results were due to isolated (asymptomatic) antigenaemia more often in HIV-positive than in HIV-negative immunocompromised patients ($p$<0.001). Among patients with low CrAg titres, the clinical response rate to antifungal therapy was 81%.

**CONCLUSION:** A considerable proportion of immunocompromised patients with low serum CrAg titres by LFA had clinical cryptococcal disease, particularly among non-HIV patients.

# INVASIVE PULMONARY ASPERGILLOSIS IN CRITICALLY ILL PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

*Intensive Care Medicine, 2019 December; 45(12):1732–41*

AUTHORS: Pardo E, Lemiale V, Mokart D, Stoclin A, Moreau AS, Kerhuel L, Calvet L, Valade S, De Jong A, Darmon M, Azoulay E
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**BACKGROUND & AIM:** Invasive pulmonary aspergillosis (IPA) is a major cause of death in critically ill patients with haematological malignancies admitted to the intensive care unit (ICU) with acute respiratory failure. In recent years there have been advances in ICU management, including the use of non-invasive diagnostic tests and better ventilation strategies, and more effective prophylaxis and treatments for IPA have been developed. The aim of this study was to evaluate whether these advances have resulted in better outcomes in patients with IPA.

**STUDY DESIGN:** Multicentre, retrospective, cohort study.

**ENDPOINT:** 90-day survival.

**METHOD:** Data on patients with haematological malignancies admitted to an ICU with acute respiratory failure due to IPA between 1998 and 2017 were extracted from hospital records for 17 French centres. Univariate and multivariate regression analyses were employed to identify factors affecting 90-day survival.

**RESULTS:** Data were available for 219 patients (63% men, median age 55 years). Of these, 30.1% had acute myeloid leukaemia, 22.8% had non-Hodgkin lymphoma and 24.2% had undergone allogeneic stem-cell transplantation; 62% were neutropenic on admission. Patients were admitted to ICU a median of 4.5 days after the onset of symptoms; IPA had been diagnosed before ICU admission in 61% of patients. Those admitted to ICU <5 days after symptom onset were diagnosed with IPA earlier than those admitted >5 days (3 versus 11 days, $p<0.001$). The overall rates of ICU mortality and day-90 mortality during the study period were 58.4% and 75.2%, respectively, with no significant improvement seen over the 20 years. In multivariate analysis, 90-day survival was greater among patients given voriconazole (hazard ratio for death 0.49, 95% confidence interval 0.34–0.73, $p<0.001$) and those admitted from 2010 onwards (HR 0.67, 95% CI 0.45–0.99, $p=0.042$), but was markedly worse among those with a diffuse radiological lung pattern (HR 2.07, 95% CI 1.33–3.24, $p=0.001$) and those needing first-line invasive mechanical ventilation (HR 3.16, 95% CI 1.46–6.82, $p=0.003$). ICU admission >5 days after symptom onset also impaired survival (HR 1.51, 95% CI 1.05–2.16, $p=0.026$).

**CONCLUSIONS:** Treatment with voriconazole improved the chance of survival for patients with IPA. However, mortality has declined only moderately over the last 20 years, perhaps reflecting a simultaneous trend towards admission of older and more immunocompromised patients. Delayed ICU admission, a need for invasive mechanical ventilation and the presence of a diffuse radiological pattern were associated with reduced survival.

# USING ROUTINE BLOOD PARAMETERS TO ANTICIPATE CLINICAL OUTCOMES IN INVASIVE ASPERGILLOSIS

*Clinical Microbiology and Infection, 2019 October 24; Epub ahead of print*

AUTHORS: Pang L, Zhao X, Dickens BL, Lim JT, Cook AR, Netea MG, Donnelly JP, Herbrecht R, Johnson EM, Maertens JA, Kullberg BJ, Troke PF, Marr KA, Chai LY
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**BACKGROUND & AIM:** Monitoring the effect of antifungal treatment in immunosuppressed patients with invasive aspergillosis (IA) is difficult. Sequential measurement of the galactomannan index (GMI) has been suggested as a biomarker, but it is not always available in clinical practice. The aim of this study was to evaluate routine blood counts, creatinine level and C-reactive protein (CRP) level as predictors of treatment response and outcome in patients with IA.

**STUDY DESIGN:** Post hoc analyses of two randomized controlled trials.

**ENDPOINTS:** Clinical response at week 6 or 12 and survival at week 12.

**METHOD:** Initial analysis was conducted on 123 patients with proven or probable IA from the Global Comparative Aspergillosis (GCA) study, for whom platelet, creatinine and CRP levels at weeks 0–4 and response and survival data at week 12 were available. Factors identified by univariate and multivariate regression analyses as affecting response and/or survival in this discovery cohort were validated by multivariate analysis of 251 patients from the Combination Antifungal Study (CAS). The latter study assessed response at week 6 and survival at week 12, but did not measure CRP levels.

**RESULTS:** In multivariate regression analysis of the GCA cohort, platelet levels at weeks 0, 2 and 4 and CRP levels at weeks 1 and 2 were significant predictors of week 12 survival (table). GMI values did not correlate with survival and none of these parameters correlated with response at week 12. Blood creatinine level was not identified as a discerning biomarker. In multivariate analyses of the CAS cohort, GMI value at week 0 was a better predictor of week 6 response than was platelet level, and both GMI and platelet levels at weeks 0, 1 and 2 were strong predictors of week 12 survival (table). Kaplan-Meier analysis of pooled study data found that a platelet count >30 x $10^9$/L at treatment start was associated with a >75% probability of survival to 12 weeks.

**CONCLUSIONS:** In patients with IA, platelet counts were predictive of 12-week survival and GMI was predictive of 6-week antifungal treatment response.

**Significant predictors of week 6 response and week 12 survival in multivariate analyses**

| | Timepoint | Predictor, odds ratio[a] (*p*-value) | |
|---|---|---|---|
| **GCA cohort** | | **Platelets** | **C-reactive protein** |
| Week 12 survival | Week 0 | 1.14 (*p*=0.01) | NS |
| | Week 1 | NS | 0.87 (*p*=0.01) |
| | Week 2 | 1.06 (*p*=0.02) | 0.87 (*p*=0.01) |
| | Week 4 | 1.18 (*p*=0.01) | NS |
| **CAS cohort** | | **Platelets** | **Galactomannan index** |
| Week 6 response | Week 0 | NS | 0.97 (*p*<0.01) |
| | Week 2 | 1.03 (*p*=0.02) | NS |
| Week 12 survival | Week 0 | 1.15 (*p*<0.01) | 0.97 (*p*<0.01) |
| | Week 1 | 1.07 (*p*<0.01) | 0.97 (*p*<0.01) |
| | Week 2 | 1.10 (*p*<0.01) | 0.96 (*p*<0.01) |

[a] Odds ratio per 10x$10^9$/L increase in platelets, per 10 mg/L increase in C-reactive protein or per 0.1 increase in galactomannan index. GCA = Global Comparative Aspergillosis study; CAS = Combination Antifungal Study. NS = not significant.

# *CANDIDA AURIS*: A REVIEW OF RECOMMENDATIONS FOR DETECTION AND CONTROL IN HEALTHCARE SETTINGS

*Journal of Fungi*, 2019 November 28; 5(4):E111

AUTHORS: Caceres DH, Forsberg K, Welsh RM, Sexton DJ, Lockhart SR, Jackson BR, Chiller T
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**BACKGROUND & AIM:** *Candida auris* is a multidrug-resistant fungus responsible for multiple outbreaks of invasive infections affecting critically ill hospitalized patients, with a high rate of mortality. Risk factors include major surgery, diabetes, long-term hospitalization, and the use of broad-spectrum antibiotics and devices such as breathing tubes and central venous catheters. Early detection of the fungus and the use of infection control practices can help prevent its spread. Based on published literature and the experiences of the staff of the US Centers for Disease Control and Prevention, this article reviews recommendations on the detection and control of *C. auris* in healthcare settings.

**ARTICLE TYPE:** Review.

**FINDINGS:** It can be difficult to identify *C. auris* isolates because many conventional methods misidentify it. However, the situation has improved recently with the development of a high-salt, high-temperature enrichment culture-based method, and the use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Where the latter technique is not available, DNA sequencing is a reliable alternative. Promising culture-independent methods for the detection of *C. auris* have also been developed.

Infection control practices are essential for controlling *C. auris* outbreaks. The precautions are the same whether a patient has infection or colonization. The first step is to identify the species of *Candida* isolated from sterile sites. Isolates from non-sterile body sites should also be identified when clinically indicated, when the facility already has a case of *C. auris*, or when the patient has stayed overnight in a healthcare facility in another country. Screening can be considered if patients have been in contact with an infected individual or have spent a night in an overseas facility.

Frequent hand hygiene is essential for all healthcare personnel (with monitoring of adherence). Affected patients should be placed on contact precautions (restricted to a single-patient room, use of personal protective equipment), with clear signage to indicate the precautions required. Environmental cleaning should be carried out using registered hospital-grade disinfectants proved to be effective against *C. auris*. Thorough daily and terminal cleaning and disinfection are required in patient-care areas. Shared medical equipment should also be cleaned and disinfected.

**CONCLUSIONS:** *C. auris* is a serious threat with potentially rapid transmission in healthcare settings. Accurate detection and effective infection control are essential to control outbreaks. Many of the recommended infection control procedures are standard practices.

# CLINICAL PERFORMANCE OF (1,3) BETA-D GLUCAN FOR THE DIAGNOSIS OF *PNEUMOCYSTIS* PNEUMONIA (PCP) IN CANCER PATIENTS TESTED WITH PCP POLYMERASE CHAIN REACTION

*Clinical Infectious Diseases, 2019 September 27; 69(8):1303–9*

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**BACKGROUND & AIM:** *Pneumocystis* pneumonia (PCP), caused by *Pneumocystis jirovecii*, is common in immunocompromised patients and is associated with a high rate of mortality. Direct visualization of cysts in tissue samples remains the standard method for detecting PCP, but it is not always adequate for establishing a diagnosis. Polymerase chain reaction (PCR) can be used to detect *P. jirovecii* DNA, but although it is more sensitive than conventional detection methods, it has limited ability to differentiate between *P. jirovecii* colonization and infection. Serum (1,3)-beta-D glucan (BDG) is an antigenic component of the cell wall of *P. jirovecii* and is a valuable non-invasive test to support a diagnosis of PCP. The lack of specificity of BDG for PCP, however, precludes its use as a stand-alone diagnostic test. The aim of this study was to evaluate the diagnostic performance of serum BDG in conjunction with PCP PCR to diagnose PCP in patients with cancer at high risk of PCP infection.

**STUDY DESIGN:** Retrospective study.

**ENDPOINTS:** Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

**METHOD:** The study included 438 hospitalized adults who were evaluated for PCP between 2012 and 2015 using serum BDG and PCP PCR on bronchoscopy samples. Diagnostic accuracy was assessed at different BDG thresholds using receiver-operating characteristic methodology.

**RESULTS:** Among the 438 participants, 53 had a positive PCP PCR test, including 40 who had definite or probable PCP and 13 who had possible PCP. Based on all participants, and using PCP PCR as the reference, BDG at a threshold of ≥80 pg/mL had a sensitivity of 69.8%, specificity of 81.2%, PPV of 34.6% and NPV of 95.2% for PCP. At a BDG threshold of ≥200 pg/mL, specificity improved to 90.4%, but sensitivity fell to 52.8%. Among the 53 patients who were PCP PCR-positive, a BDG threshold of ≥200 pg/mL resulted in a sensitivity of 70%, specificity of 100%, PPV of 100% and NPV of 52.0% for PCP.

**CONCLUSIONS:** In patients with cancer, a BDG threshold of ≥200 pg/mL in conjunction with a positive PCR, was strongly supportive of a diagnosis of PCP infection. Patients who were PCP-negative by both BDG and PCR were unlikely to have PCP.

# EFFECT OF CASPOFUNGIN VS FLUCONAZOLE PROPHYLAXIS ON INVASIVE FUNGAL DISEASE AMONG CHILDREN AND YOUNG ADULTS WITH ACUTE MYELOID LEUKEMIA:

## A RANDOMIZED CLINICAL TRIAL

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**BACKGROUND & AIM:** During periods of neutropenia whilst undergoing chemotherapy, patients with acute myeloid leukaemia (AML) have a high risk of developing life-threatening invasive fungal disease (IFD) with yeasts (e.g. *Candida*) and moulds (e.g. *Aspergillus*). Antifungal prophylaxis is required to prevent such infections. Fluconazole is widely used for prophylaxis in children with AML; however, it is only active against yeasts. Caspofungin, which is active against both yeasts and moulds, could be a better alternative. The aim of this study was to compare the efficacy of caspofungin and fluconazole for preventing IFD during periods of chemotherapy-associated neutropenia in children, adolescents and young adults with AML.

**STUDY DESIGN:** Multicentre, randomized, open-label clinical trial.

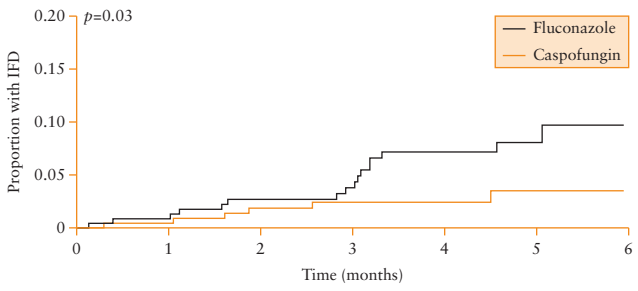
**ENDPOINTS:** Primary endpoint: proven or probable IFD. Key secondary endpoint: proven or probable invasive aspergillosis (IA).

**METHOD:** The study included patients aged between 3 months and 30 years with newly diagnosed *de novo*, relapsed or secondary AML who attended one of 115 US and Canadian hospitals between 2011 and 2016. During their first chemotherapy cycle, patients were randomly assigned to receive prophylaxis with caspofungin (*n*=257) or fluconazole (*n*=260), which was administered during the neutropenic period following each cycle. The main endpoints were assessed at 5 months.

**RESULTS:** In total, 508 (98%) patients completed the trial. Overall, 23 patients had proven or probable IFD (6 recipients of caspofungin versus 17 with fluconazole), representing a 5-month cumulative incidence of proven or probable IFD of 3.1% (95% confidence interval 1.3–7.0%) with caspofungin versus 7.2% (95% CI 4.4–11.8%) with fluconazole (*p*=0.03; figure). Moreover, 14 patients had proven or probable IA (4 with caspofungin versus 10 with fluconazole), representing a 5-month cumulative incidence of 0.5% (95% CI 0.1–3.5%) with caspofungin versus 3.1% (95% CI 1.4–6.9%) with fluconazole (*p*=0.046).

**CONCLUSIONS:** In children, adolescents and young adults with neutropenia following chemotherapy for AML, antifungal prophylaxis with caspofungin resulted in significantly lower incidences of IFD and IA compared with fluconazole.

Time to proven or probable invasive fungal disease (IFD)



# RAPID CLINICAL RESPONSE TO ADJUVANT CORTICOSTEROIDS IN CHRONIC DISSEMINATED CANDIDIASIS COMPLICATED BY GRANULOMAS AND PERSISTENT FEVER IN ACUTE LEUKEMIA PATIENTS

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**BACKGROUND & AIM:** Invasive fungal infections (IFIs) are a serious complication of acute leukaemia and are associated with significant morbidity and mortality. A severe, two-phase, disseminated clinical variant of IFI has been reported in some patients. The second phase is characterized by recurrent fevers and hepatalgia during neutrophil recovery, in the absence of ongoing infection, and is thought to be an immune reconstitution inflammatory syndrome (IRIS). There is some evidence that corticosteroids can be beneficial in IFI patients who develop IRIS. This case review reported the outcomes of adjuvant corticosteroid therapy in several patients undergoing treatment for acute leukaemia who developed chronic disseminated candidiasis (CDC) complicated by granuloma formation and IRIS.

**ARTICLE TYPE:** Retrospective case review.

**FINDINGS:** The review included three patients undergoing treatment for acute leukaemia at a tertiary haemato-oncology unit. This treatment was complicated by IFI, granuloma formation and IRIS. The patients presented with febrile episodes during aplasia, which was initially treated with empirical antibiotic and antifungal therapy. The causative organism was *Candida albicans* in two cases, and was not identified in the third.

In the first patient, prednisolone 10 mg twice daily was started, with the dose tapered until the patient stopped treatment prematurely at 12 weeks. Fevers settled 14 days after commencing steroids, and had ceased by 12 weeks, at which time maintenance chemotherapy was started and continued for 2.5 years. The patient was still in remission 8 months later.

The second patient started dexamethasone 10 mg/day and experienced a dramatic response, with resolution of fevers and improvement in inflammatory markers. The fevers returned after the steroids were stopped, so dexamethasone was resumed at 3 mg/day. After switching to prednisolone and reducing the dose further, symptoms recurred and treatment was consolidated with allogeneic stem-cell transplantation, following which the steroids were stopped. The patient was still in remission 20 months after the transplant.

In the third patient, prednisolone 30 mg/day was started, and fevers resolved rapidly while inflammatory markers also improved. The steroids were tapered successfully over a 4-week period, and the patient underwent allogeneic stem-cell transplantation 4 months later. The patient was still in remission 18 months later.

**CONCLUSIONS:** Anti-inflammatory corticosteroid therapy resolved symptoms and improved the clinical status of patients with CDC complicated by granulomas and IRIS, and allowed consolidation of their anti-leukaemia treatment.

# LACK OF TOXICITY WITH LONG-TERM ISAVUCONAZOLE USE IN PATIENTS WITH HEMATOLOGIC MALIGNANCY

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**BACKGROUND & AIM:** Isavuconazole is a new triazole antifungal agent that is increasingly being used in immunocompromised patients because of its broad range of activity. The long-term use of other triazoles is associated with toxicity, and although isavuconazole was well tolerated in clinical trials, data on its safety during chronic use in a real-world setting are lacking. The aim of this study was, therefore, to investigate the tolerability of long-term isavuconazole in patients with a haematological malignancy treated in routine clinical practice.

**STUDY DESIGN:** Single-centre, retrospective, cohort study.

**ENDPOINTS:** Toxicities.

**METHOD:** The study included 50 consecutive patients with haematological malignancies who were treated with continuous isavuconazole at a dose of 372 mg/day (orally or intravenously) for 6 months or longer. Participants' medical records were reviewed for the occurrence of any toxicities known to be associated with the acute or chronic use of other triazoles, including hepatotoxicity, skin rashes, peripheral neuropathy, skin cancers, heart failure and bone changes. The likelihood of isavuconazole being the cause of the toxicity was assessed using the World Health Organization Collaborating Centre for International Drug Monitoring–Uppsala Monitoring Centre probability scale. Relevant laboratory values during and after treatment were also noted.

**RESULTS:** Participants received isavuconazole for a median of 356 (range 180–832) days. Liver enzyme values generally remained stable throughout chronic isavuconazole treatment, although eight patients (16%) had documented transaminitis or hyperbilirubinaemia, of which four cases (8%) were considered possibly related to treatment. Although there were some reports of cardiac abnormalities during treatment, none were attributed to isavuconazole. Among 23 patients who received bone scans, there were 14 reports (61%) of new or worsening osteopenia or osteoporosis during treatment, including three patients with increased bone turnover markers, and one with evidence of stage II avascular necrosis in bilateral femoral heads. New skin rashes possibly related to isavuconazole were reported in six patients (12%). Fourteen patients (28%) had symptoms of neurological toxicity, although only one case (2%) was considered possibly related to treatment. Blood pressure remained stable in most patients, with just two cases of grade 3 systolic hypertension and three cases of grade 3 diastolic hypertension.

**CONCLUSION:** Long-term isavuconazole was well tolerated in patients with haematological malignancy treated in a routine clinical practice setting.