# FramingHam

## *on systemic fungal infections*

Liposomal amphotericin B – the present

*Journal of Antimicrobial Chemotherapy, 2022 November 25; 77(Supplement 2):ii11–20*

Comparing invasive pulmonary aspergillosis mortality between liposomal amphotericin B and voriconazole in patients with hematological malignancy or hematopoietic stem cell transplantation

*Cureus, 2022 November 21; 14(11):e31762*

Incidence of invasive fungal infections in liver transplant recipients under targeted echinocandin prophylaxis

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ISSUE 2, 2023

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*Acta Pathologica, Microbiologica, et Immunologica Scandinavica, 2023 April 6; Epub ahead of print*

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# LIPOSOMAL AMPHOTERICIN B – THE PRESENT

*Journal of Antimicrobial Chemotherapy, 2022 November 25; 77(Supplement 2):ii11–20*

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**BACKGROUND & AIM:** New therapies, including immunosuppressants, are rapidly being introduced to treat adults and children for various conditions, leading to new groups of patients at risk of invasive fungal infections. While echinocandins and mould-active azoles are the first-line therapies for invasive *Candida* infections and invasive aspergillosis, respectively, resistance is becoming a major issue with both of these drug classes. One potential alternative is liposomal amphotericin B, a broad-spectrum antifungal agent with a low risk of resistance. The aim of this review was to discuss the current role of liposomal amphotericin B.

**ARTICLE TYPE:** Expert review.

**FINDINGS:** Liposomal amphotericin B has the advantages of predictable pharmacokinetics, rapid accumulation at the infection site, few drug–drug interactions and a low risk of both acute and chronic toxicities. Its disadvantages include its parenteral-only route of delivery and a risk (albeit low) of moderate to severe renal impairment.

Liposomal amphotericin B can be used both empirically in patients with a suspected fungal infection based on a prolonged neutropenic fever that is unresponsive to antibacterial therapy, and preemptively based on mycological markers or radiological features of invasive fungal infection. It is also an excellent second-line therapy for patients in the haematology setting or in the intensive care unit who have a documented fungal disease but can no longer tolerate first-line azole or echinocandin therapy, or where resistance to that therapy has developed. In addition, liposomal amphotericin B is the first-line drug for the primary treatment of invasive mucormycosis in patients with haematological malignancies.

Liposomal amphotericin B is one of the few antifungals that is approved for use in children (age 1 month–18 years), and it is strongly recommended (along with caspofungin) for empirical antifungal therapy in high-risk children. It has a favourable safety profile in the paediatric population, although there is an increased incidence of hypokalaemia and infusion-related vomiting with doses over 5 mg/kg/day. Liposomal amphotericin B is also recommended for the first-line treatment of invasive candidiasis and mucormycosis in children with cancer and those undergoing haematopoietic stem-cell transplantation, and as a second-line treatment for those with invasive aspergillosis.

**CONCLUSIONS:** Despite being developed several decades ago, liposomal amphotericin B retains a vital role in treating fungal infections in many patient populations.

https://doi.org/10.1093/jac/dkac352

# COMPARING INVASIVE PULMONARY ASPERGILLOSIS MORTALITY BETWEEN LIPOSOMAL AMPHOTERICIN B AND VORICONAZOLE IN PATIENTS WITH HEMATOLOGICAL MALIGNANCY OR HEMATOPOIETIC STEM CELL TRANSPLANTATION

*Cureus, 2022 November 21; 14(11):e31762*

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**BACKGROUND & AIM:** Invasive pulmonary aspergillosis (IPA) is an opportunistic fungal infection that affects primarily immunocompromised patients, including those with haematological malignancies and recipients of haematopoietic stem-cell transplantation (HSCT). Current recommended first-line therapy for IPA is voriconazole, with liposomal amphotericin B being a therapeutic alternative. Real-life data regarding IPA treatment outside the clinical trial setting, including comparisons between treatments, are lacking. The aim of this study was to compare liposomal amphotericin B with voriconazole for the treatment of IPA in patients with haematological malignancies or HSCT in a real-life setting.

**STUDY DESIGN:** Retrospective, single-centre cohort study.

**ENDPOINTS:** The primary endpoint was the 12-week mortality rate. Secondary endpoints included the 6-week mortality rate and the rate of successful response (i.e. complete or partial response).

**METHOD:** The study included adults with haematological malignancy or HSCT recipients who were diagnosed with IPA on the basis of chest computed tomography (CT) findings and were treated with either liposomal amphotericin B ($n$=15) or voriconazole ($n$=24) between 2016 and 2021.

**RESULTS:** The patients had a median age of 48.5 years. Overall, 45.7% were HSCT recipients and 47.8% had acute myeloid leukaemia. CT findings included dense, well-circumscribed lesion(s) with or without a halo sign (80.4%), and the presence of a cavity (15.2%) or air-crescent sign (4.1%). The 12-week mortality rate was 13.3% (2/15) with liposomal amphotericin B and 25.0% (6/24) with voriconazole ($p$=0.178). Six-week mortality rates were 6.7% (1/15) versus 16.7% (4/24), respectively ($p$=0.341). A successful response was observed in 80% (12/15) of the patients treated with liposomal amphotericin B and 83.3% (20/24) of those treated with voriconazole. On multivariate analysis, no associations were found between 12-week mortality and disease severity, neutropenia, HSCT, successful response or CT findings of dense well-circumscribed lesions with or without a halo sign. Side effects leading to drug discontinuation were more frequent with voriconazole (12.5%; 3/24) compared with liposomal amphotericin B (6.67%; 1/15). No mortality related to IPA was observed.

**CONCLUSIONS:** In this small study involving patients with haematological malignancy or HSCT recipients diagnosed with IPA, treatment with liposomal amphotericin B or voriconazole provided similar clinical outcomes and mortality rates.

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# INCIDENCE OF INVASIVE FUNGAL INFECTIONS IN LIVER TRANSPLANT RECIPIENTS UNDER TARGETED ECHINOCANDIN PROPHYLAXIS

*Journal of Clinical Medicine, 2023 February 14; 12(4):1520*

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**BACKGROUND & AIM:** Targeted prophylaxis against invasive fungal infections (IFIs) is recommended for high-risk liver-transplant recipients, but there is a lack of consensus on the definition of a high-risk patient and on the agent and duration of antimycotic prophylaxis that should be used. This study investigated the incidence of IFIs in high-risk liver-transplant recipients receiving targeted echinocandin prophylaxis.

**STUDY DESIGN:** Retrospective, single-centre study.

**ENDPOINTS:** Primary: 90-day incidence of IFI. Secondary; risk factors for IFI, 90-day mortality for a diagnosed IFI, adverse events related to antifungal prophylaxis.

**METHOD:** Medical records for all 224 adults who underwent an orthotopic, first-time liver transplant, with or without kidney transplant, between 2017 and 2020 at a single centre were reviewed. Targeted antimycotic prophylaxis was given to high-risk liver recipients, as defined by the presence of at least two of 15 perioperative risk factors. These patients received echinocandins (micafungin or anidulafungin) for 7–14 days, with the option to prolong for up to 28 days.

**RESULTS:** Overall, 109 patients (49%) were classified as high risk for IFI, of whom 90 (83%) received antifungal prophylaxis. A total of 26 patients (12%) developed an IFI, with 23 IFIs occurring in the high-risk group (23/109; 21%) and three in the low-risk group (3/115; 2.6%). The algorithm used to identify high- versus low-risk patients had sensitivity of 89% and specificity of 57%. Factors associated with an increased risk of IFI within 90 days are shown in the table. IFI-related mortality in the 90 days after transplantation was 53%, and none of the five patients with invasive aspergillosis survived to discharge. There were seven drug-related adverse events, all associated with micafungin; none were serious or dose-limiting.

**CONCLUSIONS:** In this single-centre study, the 90-day incidence of IFI among first-time orthotopic liver-transplant recipients was 12%. Patients who received targeted echinocandin prophylaxis based on the presence of prespecified risk factors for IFI remained at risk of IFI and death.

**Variables associated with an increased risk of invasive fungal infection within 90 days after liver transplantation (multivariable analysis)**

| Variable | Hazard ratio | *p* |
|---|---|---|
| Recipient age | 0.97 | 0.027 |
| Split liver transplantation | 5.18 | 0.014 |
| Massive intraoperative blood transfusion | 24.08 | 0.004 |
| Donor-derived infection | 9.70 | <0.001 |
| Re-laparotomy | 4.62 | 0.003 |

https://doi.org/10.3390/jcm12041520

# CRYPTOCOCCAL MENINGITIS AND CLINICAL OUTCOMES IN PERSONS WITH HIV: A GLOBAL VIEW

*Clinical Infectious Diseases, 2023 February 23; Epub ahead of print*

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**BACKGROUND & AIM:** Cryptococcal meningitis (CM) remains a major cause of morbidity and mortality among people with HIV (PWH), despite the availability of combination antiretroviral therapy (ART). However, there is incomplete knowledge about the full impact of CM on PWH globally, particularly since ART became widely available. The aim of this study was therefore to examine CM incidence and mortality, both before and after ART initiation, in a large global cohort of PWH.

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

**ENDPOINTS:** CM incidence; all-cause mortality after CM diagnosis.

**METHOD:** Data were retrieved on PWH aged ≥16 years who were enrolled in the International Epidemiology Databases to Evaluate AIDS (IeDEA) cohort between 1996 and 2017 (*n*=518,852). Data from PWH in the North America, Latin America, Asia-Pacific, East Africa and Southern Africa regions were included. Participants were followed from enrolment until death, loss to follow-up or the database closure date. CM diagnosis was obtained from clinical records. The incidence of CM diagnosis and incidence rate ratios were estimated using univariate and multivariable models, and mortality after CM diagnosis was estimated using Kaplan–Meier curves.

**RESULTS:** Participants were followed for a median of 3.4 years (interquartile range 0.9–7.7 years) from enrolment, and 78% of the total follow-up time was after ART initiation. A total of 3857 participants (0.7%) were diagnosed with CM during follow-up, giving an incidence of 1.54 per 1000 person-years. The unadjusted incidence of CM (per 1000 person-years) was highest in Latin America (2.17), followed by East Africa (2.08), South Africa (1.69), North America (0.89) and Asia-Pacific (0.58). The incidence of CM decreased over time, from 2.56 per 1000 person-years in 2005 to 0.97 per 1000 person-years in 2015. Overall mortality for participants diagnosed with CM was 31.6% over a median follow-up of 2.6 years from CM diagnosis (IQR 0.3–7.0 years), although 1121 participants (29%) were lost to follow-up. A total of 2478 participants (64%) were diagnosed with CM after starting ART (median 253 days from ART start to CM diagnosis). In adjusted analyses, older age, lower CD4 count and earlier year of CM diagnosis were associated with a higher risk of death.

**CONCLUSIONS:** PWH were found to have a high rate of mortality after CM diagnosis. CM commonly developed after the start of ART.

https://doi.org/10.1093/cid/ciad076

# DIAGNOSTIC PERFORMANCE OF THE IMMY CRYPTOCOCCAL ANTIGEN LATERAL FLOW ASSAY ON SERUM AND CEREBROSPINAL FLUID FOR DIAGNOSIS OF CRYPTOCOCCOSIS IN HIV-NEGATIVE PATIENTS:

## A SYSTEMATIC REVIEW

*BMC Infectious Diseases, 2023 April 6; 23(1):209*

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**BACKGROUND & AIM:** Cryptococcal infection mostly affects people living with HIV, but cases in HIV-negative patients are increasing in high-income countries. This is partly due to greater use of immunosuppressive therapies for cancer and organ transplantation, although cases of cryptococcal disease have also been reported in apparently immunocompetent individuals. Cryptococcal antigen (CrAg) detected using a lateral flow assay (LFA) is a cornerstone of the diagnosis of cryptococcal infection, but its performance in serum or cerebrospinal fluid (CSF) from HIV-negative cohorts has not been systematically evaluated. The aim of this review was to characterize the diagnostic performance of IMMY CrAg® LFA (the most sensitive commercially available cryptococcal diagnostic test) compared with other cryptococcal diagnostic tests in HIV-negative populations.

**STUDY DESIGN:** Systematic review.

**ENDPOINTS:** Sensitivity and specificity.

**METHOD:** Studies reporting on the diagnostic performance of the IMMY CrAg® LFA for the diagnosis of cryptococcosis using serum or CSF in HIV-negative populations (adults and children), written in English and published from 2009 onwards, were identified using a systematic search of Medline, Embase, Global Health, CENTRAL, WoS Science Citation Index, SCOPUS, Africa-Wide Information, LILACS and WHO Global Health Library. Fixed-effect meta-analysis was used to estimate the diagnostic sensitivity and specificity of IMMY CrAg® LFA versus alternative cryptococcal diagnostic tests, including clinical composite endpoints.

**RESULTS:** Nine studies met the inclusion criteria and a total of 528 HIV-negative participants were analysed. The mean number of patients per study was 59, participants were aged 8–88 years, and 50–73% were male. Seven studies included some immunosuppressed patients (12–55% per study). Eight studies compared the diagnostic performance of IMMY CrAg® LFA versus eight other tests/composites using serum, yielding a pooled median sensitivity of 96% (95% credible interval 68–100%) and a pooled median specificity estimate of 96% (95% CrI 84–100%). Six studies compared the diagnostic performance of IMMY CrAg® LFA versus 10 other tests/composites using CSF, yielding a pooled median sensitivity of 99% (95% CrI 95–100%) and a pooled median specificity of 99% (95% CrI 95–100%).

**CONCLUSION:** Based on a small number of studies, this systematic review found high sensitivity and specificity for IMMY CrAg® LFA in identifying cryptococcosis in HIV-negative adults and children using serum or CSF.

https://doi.org/10.1186/s12879-023-08135-w

# REAL-LIFE COMPARISON OF POSACONAZOLE VERSUS FLUCONAZOLE FOR PRIMARY ANTIFUNGAL PROPHYLAXIS DURING REMISSION-INDUCTION CHEMOTHERAPY FOR ACUTE LEUKEMIA

*Journal of the Association of Medical Microbiology and Infectious Disease Canada, 2023 March 1; 8(1):18–28*

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**BACKGROUND & AIM:** Individuals with acute leukaemia who undergo remission-induction intensive chemotherapy are at high risk of life-threatening invasive fungal infections (IFIs), which can be challenging to diagnose in a timely manner. Therefore, primary antifungal prophylaxis with a mould-active agent such as posaconazole may be a suitable strategy. In clinical trials, posaconazole was superior to fluconazole for reducing the incidence of IFIs in patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndrome (MDS). However, real-world efficacy data for posaconazole in the broader acute leukaemia population are limited. Therefore, the current study compared, in a real-life setting, the efficacy of posaconazole prophylaxis with that of fluconazole in patients undergoing remission-induction chemotherapy for acute leukaemia or MDS.

**STUDY DESIGN:** Retrospective cohort study.

**ENDPOINTS:** Primary endpoint: incidence of probable/proven IFI. Key secondary endpoint: IFI-related mortality.

**METHOD:** The study included all adults who received primary antifungal prophylaxis with posaconazole or fluconazole while undergoing remission-induction chemotherapy for acute leukaemia at a single Canadian centre between 2008 and 2017. An episode was defined as the time between first dose of antifungal prophylaxis agent and day 100, new chemotherapy treatment (reinduction or consolidation), haematopoietic stem-cell transplantation, death or last day of contact, whichever occurred first.

**RESULTS:** Overall, 233 patients experienced 299 episodes (201 involving posaconazole and 98 involving fluconazole), 67.9% of which were first inductions. AML/MDS were the most common underlying haematological malignancies (88% of episodes), with acute lymphoblastic leukaemia (9%) and other types of acute leukaemia (3%) making up the remainder. There were 20 probable/proven IFIs overall, comprising 17 cases of invasive aspergillosis and three of invasive candidiasis; 14 cases were breakthrough IFIs. The incidence of IFI was significantly lower in the posaconazole group compared with the fluconazole group (3.5% versus 13.2%, $p$=0.001), whereas the incidence of IFI-related mortality did not differ significantly (0.5% versus 3.1%, $p$=0.1047). Use of empirical or targeted antifungal therapy was reduced in the posaconazole group (24.4% versus 48.0%, $p$<0.001).

**CONCLUSION:** Among patients undergoing remission-induction chemotherapy for acute leukaemia or MDS in a real-life setting, primary antifungal prophylaxis with posaconazole significantly reduced the incidence of IFI compared with fluconazole.

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# PREVALENCE OF OCULAR CANDIDIASIS AND *CANDIDA* ENDOPHTHALMITIS IN PATIENTS WITH CANDIDEMIA:

## A SYSTEMATIC REVIEW AND META-ANALYSIS

*Clinical Infectious Diseases, 2023 May 24; 76(10):1738–49*

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**BACKGROUND & AIM:** The 2016 Infectious Diseases Society of America guidelines recommend routine ophthalmological examination for all patients with candidaemia, in order to detect *Candida* endophthalmitis. However, the American Academy of Ophthalmology recommends against such routine screening because of the low quality of supporting evidence and the poor cost-effectiveness of this strategy. The prevalence of concordant *Candida* endophthalmitis (i.e. the most stringent definition) has previously been estimated at <0.9%. The aim of the current study was to evaluate current evidence on the prevalence of ocular candidiasis and *Candida* endophthalmitis in patients with candidaemia, and to explore associated factors.

**STUDY DESIGN:** Systematic review and meta-analysis.

**ENDPOINTS:** Prevalence of ocular candidiasis and *Candida* endophthalmitis.

**METHOD:** PubMed, Embase and SCOPUS were searched for observational studies providing data on the prevalence of ocular candidiasis or *Candida* endophthalmitis in patients with candidaemia. The meta-analyses included 70 studies of ocular candidiasis and 66 studies of *Candida* endophthalmitis (35 using the concordant definition and 31 the discordant definition), representing a total of 8599 patients with candidaemia who underwent ophthalmological screening.

**RESULTS:** Amongst candidaemia patients who were screened, the pooled prevalence of ocular candidiasis was 10.7% (95% confidence interval 8.4–13.5%) and the overall pooled prevalence of *Candida* endophthalmitis was 3.1% (95% CI 2.1–4.5%). The pooled prevalence of concordant endophthalmitis was 1.8% (95% CI 1.3–2.6%) while that of discordant *Candida* endophthalmitis was 7.4% (95% CI 4.5–12%). The prevalence of concordant *Candida* endophthalmitis was significantly higher ($p$<0.01) in Asian countries than in European or American countries (table). Factors associated with *Candida* endophthalmitis included total parenteral nutrition (pooled odds ratio 6.92, 95% CI 3.58–13.36) and the presence of *Candida albicans* (OR 3.02, 95% CI 1.67–5.46).

**CONCLUSIONS:** This analysis found a higher prevalence of concordant *Candida* endophthalmitis in patients with candidaemia than reported previously, and a higher prevalence in Asian countries than elsewhere. Optimized screening protocols are needed to detect ocular involvement in patients with candidaemia.

**Pooled prevalence of concordant *Candida* endophthalmitis by region**

| Region | Pooled prevalence among screened patients (95% confidence interval) |
|---|---|
| Asian countries | 3.6% (2.9–4.6%) |
| European countries | 1.4% (0.4–5.0%) |
| American countries | 1.4% (1.0–2.2%) |

https://doi.org/10.1093/cid/ciad064

# HOW TO USE BIOMARKERS OF INFECTION OR SEPSIS AT THE BEDSIDE:

## GUIDE TO CLINICIANS

*Intensive Care Medicine, 2023 February; 49(2):142–53*

AUTHORS: Póvoa P, Coelho L, Dal-Pizzol F, Ferrer R, Huttner A, Conway Morris A, Nobre V, Ramirez P, Rouze A, Salluh J, Singer M, Sweeney DA, Torres A, Waterer G, Kalil AC
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**BACKGROUND & AIM:** It has been suggested that biomarkers might be able to provide clinicians with additional information to help with predicting and diagnosing sepsis, deciding which antibiotics to use and assessing response to therapy. More than 250 potential biomarkers have been studied to date. The aim of this review was to provide clinicians with guidance on the use of pathogen-specific and host-response biomarkers of infection or sepsis.

**ARTICLE TYPE:** Narrative review.

**FINDINGS:** Pathogen-specific biomarkers are already used in routine practice in critically ill patients. One example is (1,3)-β-D-glucan (BDG), which detects invasive *Candida* infection with a high sensitivity of 0.81 (although this varies by fungal species) but a poor specificity of 0.60. The sensitivity and specificity of this test is increased by using two consecutive positive samples, increasing the cut-off value or combining the test with another specific *Candida* biomarker (e.g. mannan).

Pathogen-specific, biomarker-guided algorithms have been developed and tested, including a BDG-guided strategy for discontinuing empirical antifungal therapy in critically ill patients with suspected invasive candidiasis. Two randomized controlled trials investigating this algorithm found that it was safe and reduced the duration of antifungal therapy.

The main host-response markers used in critically ill patients in routine clinical practice are procalcitonin (PCT) and C-reactive protein (CRP). Studies in critically ill patients have shown that PCT is a poor predictor of sepsis in the intensive care unit. There is no agreed PCT cut-off value for diagnosing sepsis, and several non-infectious inflammatory states are also associated with elevated PCT levels. However, PCT may have use in guiding antibiotic therapy, and this strategy has been associated with a shorter duration of therapy and improved survival.

Changing CRP levels have been reported to predict sepsis. CRP has been well studied as a biomarker of response to therapy for several severe infections, and CRP trajectory after the start of antibiotics has been shown to correlate with clinical course and prognosis. Of note, the ratio of each day's CRP concentration relative to the day 0 level (i.e. the CRP-ratio) is more informative than absolute change.

**CONCLUSIONS:** Pathogen-specific and host-response biomarkers of infection or sepsis can be useful tools that provide additional information on a patient's health status. Serial measurements provide more information than single values.

https://doi.org/10.1007/s00134-022-06956-y

# FOOD AND DRUG ADMINISTRATION PUBLIC WORKSHOP SUMMARY – DEVELOPMENT CONSIDERATIONS OF ANTIFUNGAL DRUGS TO ADDRESS UNMET MEDICAL NEED

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**BACKGROUND & AIM:** In 2020, the US Food and Drug Administration (FDA) invited experts from academia, industry, patient groups and government agencies to participate in a public workshop on the unmet needs in treating invasive fungal infections (IFIs) and strategies for developing antifungal therapies. The aim of this paper was to summarize key discussions from the workshop.

**ARTICLE TYPE:** FDA workshop review.

**FINDINGS:** The first session of the workshop was on preclinical and clinical considerations with respect to antifungal products. It was highlighted that regulatory authorities such as the FDA and European Medicines Agency are aware of the scientific and economic challenges in developing antifungal agents, and offer incentives and accelerated regulatory pathways to encourage their development. It was noted that both oral and intravenous formulations should be considered so as to allow therapeutic flexibility, and that drug–drug interactions should be fully assessed for any new products because of the frequent coadministration of antifungals with other therapeutic agents.

The second session concerned current therapies and antifungal drug development considerations. Limitations of current agents include unpredictable absorption and metabolism of agents, extensive drug–drug interactions among azoles, and substantial systemic toxicities. It was noted that no single agent acts against all pathogenic fungi, underscoring the need for novel or combination therapies. Barriers to conducting large randomized controlled trials in IFIs were examined, including the relative rarity of IFIs and the exclusion of many patients because of other infections or antifungal pretreatment. Trial enrichment strategies and statistical considerations (e.g. using surrogate endpoints and external/historical controls) were discussed.

The final session was on the current state of *Candida auris* and emerging resistant *Candida* species. The increasing number of *Candida* species with high minimum inhibitory concentrations and resistance to azoles, polyenes and echinocandins was noted. The industry perspective in this area was represented by speakers who presented on the lessons learned from the development of fosmanogepix, ibrexafungerp and rezafungin.

**CONCLUSIONS:** IFIs are a major threat to public health, and there are few new products in development to combat them. Challenges for development programmes include a lack of diagnostics, identifying acceptable patient populations, and difficulties in creating feasible trial designs with relevant endpoints and durations.

https://doi.org/10.1093/cid/ciad195

# POPULATION PHARMACOKINETICS AND CSF PENETRATION OF FLUCYTOSINE IN ADULTS WITH HIV-ASSOCIATED CRYPTOCOCCAL MENINGOENCEPHALITIS

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**BACKGROUND & AIM:** Flucytosine has long been used to treat cryptococcal meningoencephalitis, in part because of its good penetration into the cerebrospinal fluid (CSF). However, the best dosing strategy to balance toxicity with drug exposure is not well understood. This study aimed to obtain population-level estimates of key flucytosine pharmacokinetic (PK) variables, including CSF penetration, and the extent of variability around these estimates.

**STUDY DESIGN:** Single-centre, PK modelling study.

**ENDPOINTS:** Population PK parameter estimates.

**METHOD:** The study recruited 64 patients with HIV-associated cryptococcal meningoencephalitis who were given flucytosine 100 mg/kg/day (split into 25 mg/kg every 6 hours) for 7–14 days. On days 1 and 7, peripheral blood samples were taken at 0, 2, 4, 7, 12 and 23 hours after flucytosine administration and CSF was collected by lumbar puncture on days 1, 7 and 14. Flucytosine concentrations were determined using liquid chromatography-mass spectrometry. PK estimates were calculated using a four-compartment model assuming first-order distribution and elimination. Monte Carlo modelling was used to simulate drug exposure with different regimens for the same overall flucytosine dose.

**RESULTS:** The PK dataset comprised 595 plasma and 209 CSF flucytosine measurements, equivalent to 9.2 plasma and 3.5 CSF samples per patient. In the optimized PK model, apparent volumes of the central and CSF compartments were estimated at 17.50 L and 41.73 L, respectively, with mean apparent clearance of 5.88 L/h and a plasma elimination half-life of approximately 14.5 hours. Individual patients' plasma and CSF drug exposure at steady state (days 6–7) were found to vary considerably; median values with interquartile range are shown in the table. Monte Carlo simulations showed that for a total dose of 100 mg/kg/day, different regimens (split doses every 6 or 12 hours or one dose every 24 hours) resulted in almost the same steady-state flucytosine exposure.

**CONCLUSIONS:** While marked interindividual variation in flucytosine plasma and CSF PK parameters was found, the estimates obtained may help to design more rational flucytosine dosing regimens for patients with HIV-associated cryptococcal meningoencephalitis.

**Estimates of flucytosine exposure and penetration into CSF in patients with HIV-associated cryptococcal meningoencephalitis (flucytosine 100 mg/kg/day in four split doses)**

| Parameter | Median value (interquartile range) |
|---|---|
| Plasma $AUC_{24}$ at steady state (days 6–7), mg.h/L | 890.38 (603.81–1213.70) |
| CSF $AUC_{24}$ at steady state (days 6–7), mg.h/L | 595.66 (425.69–776.64) |
| CSF $AUC_{24}$/plasma $AUC_{24}$ ratio (days 6–7) | 0.69 (0.58–0.82) |

$AUC_{24}$=area under the concentration–time curve over 24 hours; CSF=cerebrospinal fluid.

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# COVID-19-ASSOCIATED MUCORMYCOSIS:
## A SYSTEMATIC REVIEW AND META-ANALYSIS OF 958 CASES

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**BACKGROUND & AIMS:** Mucormycosis is an infection caused by fungi that are ubiquitous in the environment, with known risk factors including a variety of conditions that result in impaired immune function. Mucormycosis requires immediate treatment with systemic antifungals and adjunctive surgery. Although usually rare, the number of reported mucormycosis cases increased with the onset of the COVID-19 pandemic. The aim of this study was to provide a comprehensive overview of the characteristics of COVID-19–associated mucormycosis (CAM).

**STUDY DESIGN:** Systematic review and meta-analysis.

**ENDPOINTS:** Clinical characteristics; predictors of mortality.

**METHOD:** A systematic literature search of MEDLINE, PubMed, Scopus, Web of Science, Cochrane Library and CINAHL for the period January 2020 to December 2022 identified 298 studies involving adults with CAM for whom individual patient data were available. Fifty-six cases provided by the collaborators were added to 902 eligible cases identified by the literature search (total $n$=958). The chi-squared test and $t$-test were used in univariate analyses, and multivariate logistic regression was used to determine independent determinants of mortality.

**RESULTS:** Forty-five countries were represented, with most CAM cases (88.1%) occurring in low- and middle-income countries (LMICs). Median patient age was 53 years, the most common comorbidity was diabetes mellitus (77.9%), and most patients had received corticosteroids (78.5%). CAM developed a mean of 22 days after COVID-19 onset. Overall CAM mortality was 38.9%. The mortality rate was higher in CAM patients aged >65 years ($p$=0.001), and in those with diabetic ketoacidosis ($p$<0.001), malignancy ($p$<0.001), renal disease ($p$<0.001), underlying pulmonary disease ($p$=0.017), hypertension ($p$=0.040) or body mass index >30 kg/m$^2$ ($p$<0.001). Mortality was also higher in CAM patients who had severe COVID-19 ($p$<0.001), received tocilizumab ($p$=0.018), had hospital-onset mucormycosis ($p$<0.001) or had *Aspergillus* co-infection ($p$=0.037). The mean time until mucormycosis diagnosis was longer for patients with *Aspergillus* co-infection versus those without (15.4 versus 5.1 days). Independent predictors of mortality included diabetic ketoacidosis ($p$<0.001), mechanical ventilation for COVID-19 ($p$=0.002) and pulmonary mucormycosis ($p$=0.002).

**CONCLUSIONS:** CAM-associated mortality was high. Most reports of CAM came from LMICs and novel risk factors identified for CAM included older age, various comorbidities and *Aspergillus* co-infection.

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# ASSOCIATIONS BETWEEN INVASIVE ASPERGILLOSIS AND CYTOMEGALOVIRUS IN LUNG TRANSPLANT RECIPIENTS:

## A NATIONWIDE COHORT STUDY

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**BACKGROUND & AIM:** Lung transplant recipients need to receive lifelong immunosuppressive therapies to prevent graft rejection. However, this puts them at increased risk of opportunistic infections, particularly cytomegalovirus (CMV) and invasive aspergillosis (IA), both of which are associated with an increased risk of graft rejection and mortality. Timely diagnosis and treatment of these infections could help to improve outcomes for lung transplant recipients. The aim of this study was to evaluate the incidence of CMV after IA and vice versa, to determine whether screening for one infection would be warranted after detection of the other.

**STUDY DESIGN:** Retrospective nationwide cohort study.

**ENDPOINTS:** Incidence rate of CMV after IA and vice versa; incidence rate ratios (IRRs).

**METHOD:** The study included all patients who received a lung transplant in Denmark between 2010 and 2019. Participants were followed for 2 years after transplantation for CMV infection and IA (with the latter defined according to International Society for Heart and Lung Transplantation criteria). Poisson regression analysis, adjusted for time after transplantation, was conducted to provide adjusted IRRs (aIRRs) for the two infections.

**RESULTS:** Among 295 lung transplant recipients included in the study, 128 (43%) were diagnosed with CMV infection and 48 (16%) were diagnosed with IA. The incidence rate for CMV during the first 3 months after diagnosis of IA was 98 per 100 patient-years of follow-up (95% confidence interval 47–206), and the incidence rate for IA during the first 3 months after diagnosis of CMV infection was 30 per 100 patient-years of follow-up (95% CI 15–60). The risk of CMV was not increased significantly during the first 3 months after diagnosis of IA compared with the period without IA (aIRR 1.42, 95% CI 0.65–3.10). However, the risk of IA was significantly greater in the first 3 months after diagnosis of CMV infection compared to the period without CMV (aIRR 2.91, 95% CI 1.32–6.44). Overall, seven patients needed to be screened to diagnose one case of CMV infection in the first 3 months after IA, and eight patients needed to be screened to diagnose one case of IA after CMV infection.

**CONCLUSIONS:** Among lung transplant recipients, there was an increased risk of IA following CMV infection, and a non-significant tendency towards an increased risk of CMV infection after IA. Therefore, after diagnosis of one of these infections, systematic screening for the other infection may be warranted.

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