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on systemic fungal infections

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Clinical Microbiology and Infection, 2023 December; 29(12):1604.e1–6

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Journal of Clinical Microbiology, 2023 November 21; 61(11):e0087323

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Mycoses, 2023 October 4; Epub ahead of print

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Transplant Infectious Disease, 2023 November; 25 Suppl 1: e14162

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Antimicrobial Agents and Chemotherapy, 2023 November 15; 67(11):e0072523

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Mycopathologia, 2023 December; 188(6):983–94

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CLINICAL IMPACT OF POLYMERASE CHAIN REACTION-BASED *ASPERGILLUS* AND AZOLE RESISTANCE DETECTION IN INVASIVE ASPERGILLOSIS.

A PROSPECTIVE MULTICENTER STUDY

Clinical Infectious Diseases, July 5; 77(1):38–45

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BACKGROUND & AIM: Invasive aspergillosis (IA) caused by a triazole-resistant *Aspergillus fumigatus* infection has a high mortality rate, which is increased if there is a delay in receiving appropriate antifungal therapy. Earlier initiation of appropriate treatment could be facilitated by faster detection of azole-resistant infections. The aim of this study was to assess the clinical value of a multiplex real-time polymerase chain reaction (PCR) test that allows early detection of azole-resistant *Aspergillus* species in patients suspected of having IA.

STUDY DESIGN: Prospective, multicentre study.

ENDPOINT: The primary endpoint was the antifungal treatment failure rate in patients with azole-resistant IA.

METHOD: The study included 323 adults with a haematological malignancy who were suspected of having IA based on a new pulmonary infiltrate on computed tomography, for which bronchoalveolar lavage fluid sampling was planned or performed within 48 hours. The novel azole resistance real-time PCR test was carried out on bronchoalveolar lavage fluid samples. Patients with mixed azole-susceptible/resistant infections were excluded from the main analysis.

RESULTS: Among the study participants, 276 patients (94%) had complete mycological (PCR, galactomannan, culture) and radiological information available, and a diagnosis of probable IA was made in 99 patients (36%). Among 293 patients (91%) with enough bronchoalveolar fluid to allow PCR testing, *Aspergillus* species DNA was detected in 116 patients (40%) and *A. fumigatus* DNA was detected in 89 (30%). A conclusive resistance PCR testing result was obtained in 58 of the 89 patients with *A. fumigatus* (65%), with azole resistance detected in eight patients (14%). A mixed azole-susceptible/resistant infection was detected in two of these patients who were therefore excluded from the primary analysis. Among the remaining six patients with probable azole-resistant IA, one patient (16.7%) had treatment failure. Increased mortality was seen in patients who were galactomannan positive versus negative (p=0.004), whereas mortality was not significantly increased in patients with duplicate positive PCR tests (versus negative PCR, p=0.457). In patients with an isolated positive *Aspergillus* species PCR result, mortality was similar to that in patients lacking any positive mycological evidence (p=0.829).

CONCLUSIONS: In patients suspected of having IA, real-time PCR-based testing to identify azole resistance can facilitate timely use of appropriate antifungal therapy in this high-risk patient population.

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QUESTIONING THE 14-DAY DOGMA IN CANDIDEMIA TREATMENT DURATION

Mycoses, 2023 October 27; Epub ahead of print

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BACKGROUND & AIM: Antimicrobial resistance, including resistance to antifungals, is a major concern worldwide. Prolonged use of antifungal agents might lead to the spread of yeasts and moulds that have resistance mutations, and could allow aggressive opportunistic fungi to cause infection. Candidaemia is primarily found in severely ill and immunocompromised patients and is associated with a crude death rate of 45%. Current guidelines for candidaemia recommend treatment for 14 days after clearance of blood cultures, initially with an echinocandin, followed by azole treatment (if isolates are susceptible). Evidence for this approach is lacking, however. The aim of this review was to summarize the current evidence for shortening antifungal treatment duration, specifically for candidaemia, following a negative blood culture.

ARTICLE TYPE: Systematic literature search and narrative review.

FINDINGS: PubMed, cochranelibrary.com and clinicaltrials.gov were searched to identify literature published between 1993 and 2023 describing the use of antifungal treatment durations of less than the recommended 14 days after bloodstream clearance in cases of uncomplicated candidemia. Nine manuscripts (two case series and seven studies) were identified; no prospective observational or interventional trials were found.

In patients experiencing candidemia, several reports suggested that treatment duration had no significant effect on the risk of relapse or survival. Nevertheless, comprehensive assessment is needed to determine the optimal treatment duration for individual patients because candidemia is a serious condition influenced by many factors. Such considerations include neutropenia, previous intravenous drug use, nosocomial causes, concomitant gastrointestinal disease, and the presence of cardiovascular medical devices, as well as assessment of the extent of spread of *Candida* infection using interventions such as transoesophageal echocardiography.

The toxicity profile of echinocandins includes gastrointestinal adverse events, infusion-related reactions, liver toxicity and skin reactions; however, these are usually mild and controllable, and could be further reduced by decreasing treatment duration. Azole antifungals can result in liver toxicity, neurotoxicity and phototoxicity even with short treatment durations, and drug–drug interactions are possible. In cases of azole-refractory infection, once-weekly echinocandin administration is a promising option, as it allows earlier hospital discharge, thus improving patients' quality of life.

CONCLUSIONS: The authors advocate adherence to the current 14-day minimum treatment recommendation for candidaemia, in the absence of evidence-based clinical trials evaluating shorter treatment durations.

https://doi.org/10.1111/myc.13672

INFLUENZA-ASSOCIATED INVASIVE ASPERGILLOSIS IN PATIENTS ADMITTED TO THE INTENSIVE CARE UNIT IN SWEDEN:

A PROSPECTIVE MULTICENTRE COHORT STUDY

Infectious Diseases, 2024 February; 56(2):110–5

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BACKGROUND & AIM: Among critically ill patients in intensive care units (ICUs), the reported incidence of influenza-associated pulmonary aspergillosis (IAPA) is 5–29%. Most ICU cases of IAPA occur in the absence of classical risk factors, such as neutropenia or immunosuppression, and IAPA is associated with a high mortality rate. The aim of the present study was to evaluate the incidence of IAPA among patients admitted to ICUs in Sweden.

STUDY DESIGN: Prospective, multicentre, cohort study.

ENDPOINTS: The primary endpoint was IAPA diagnosis. Secondary endpoints included classical IAPA risk factors, and ICU and 30-day mortality rates.

METHOD: The study enrolled adults with PCR-verified influenza A or B, who were admitted to 12 ICUs across Sweden between 2019 and 2023. At inclusion, and weekly during ICU stay, all participants underwent screening with serum galactomannan tests, β-D-glucan tests and respiratory fungal cultures. If feasible, bronchoalveolar lavage was also conducted. IAPA diagnosis was based on criteria proposed by Verweij et al. in 2020 (table). The presence of classical risk factors for IAPA was assessed, and mortality rates were evaluated.

RESULTS: The analysis included 55 patients (58% male) with a median age of 59 years. All participants underwent at least one galactomannan test, β-D-glucan test and respiratory culture; 24 (44%) patients also underwent bronchoalveolar lavage. None of the patients had proven IAPA. Five (9%) patients were diagnosed with probable IAPA, four of whom had no classical risk factors for the condition. Seven (13%) patients died in the ICU, comprising 3/5 (60%) with versus 4/50 (8%) without IAPA (p=0.01). Ten (18%) patients died within 30 days of ICU admission, comprising 3/5 (60%) with versus 7/50 (14%) without IAPA (p=0.04).

CONCLUSIONS: Among patients admitted to the ICU with PCR-verified influenza A or B, the incidence of IAPA was 9%. Only one-fifth of those with IAPA had classical risk factors. Patients with IAPA had a significantly higher rate of mortality than patients without IAPA.

Case definition for influenza-associated pulmonary aspergillosis (IAPA) in intensive care unit patients (Verweij et al. 2020)

Proven IAPA	Lung biopsy showing invasive fungal elements and *Aspergillus* growth on culture or *Aspergillus* PCR-positive tissue sample
Probable IAPA	Pulmonary infiltrate plus ≥1 of: serum galactomannan index >0.5, bronchoalveolar lavage galactomannan index ≥1.0, positive bronchoalveolar lavage culture, cavitating infiltrate and positive sputum/tracheal aspirate culture

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META-PHARMACOKINETIC ANALYSIS OF POSACONAZOLE FOLLOWING DOSING OF ORAL SUSPENSION, DELAYED-RELEASE TABLET, AND INTRAVENOUS INFUSION IN PATIENTS VS. HEALTHY VOLUNTEERS:

IMPACT OF CLINICAL CHARACTERISTICS AND RACE

International Journal of Antimicrobial Agents, 2023 December; 62(6):106995

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BACKGROUND & AIM: Posaconazole is an antifungal agent that is available as an oral suspension, delayed-release tablet and intravenous infusion. While the pharmacokinetics of these formulations have been reported in healthy volunteers, posaconazole exposure can be affected by the presence of pathology and concomitant treatment, and there is also evidence that the Chinese population has reduced clearance compared with the global population. These factors can put patients at risk of breakthrough infections or treatment failure. The aim of this study was to analyse the pharmacokinetics of these three posaconazole formulations in patients and healthy volunteers, and to assess the effects of clinical characteristics and Chinese race.

STUDY DESIGN: Integrated pharmacokinetic analysis.

ENDPOINTS: Pharmacokinetic parameters, including bioavailability.

METHOD: The analysis included pharmacokinetic data pooled from 105 Caucasian patients (92% of whom had a haematological malignancy) who were receiving posaconazole as an oral suspension, delayed-release tablet or intravenous infusion (total of 1046 posaconazole plasma concentrations), as well as 182 healthy volunteers who had been analysed previously (3898 concentrations). In addition, 292 samples were collected from 80 Chinese patients who had been receiving posaconazole oral suspension. An integrated population pharmacokinetic model was developed, and the impact of clinical characteristics and Chinese race was assessed.

RESULTS: In patients, the bioavailability of posaconazole was 38.2% in those who received the oral suspension at a dose of 100 mg, decreasing to 24.6% when the dose was increased to 600 mg. When administered by delayed-release tablet, the bioavailability of posaconazole in patients was 59% regardless of dose. The bioavailability of oral posaconazole in patients decreased by 61%, 36%, 44%, 48% and 29% in patients with mucositis, diarrhoea, nasogastric tube administration, concomitant proton pump inhibitors, and concomitant metoclopramide, respectively. Compared with healthy volunteers, patients had an 84.4% larger peripheral volume of distribution, and a 67.5% lower intercompartmental clearance. People with hypoalbuminaemia (<30 g/L) had reduced clearance compared with those without hypoalbuminaemia (5.1 versus 7.0 L/h). Chinese race did not appear to affect the pharmacokinetics of posaconazole.

CONCLUSIONS: The pharmacokinetics of posaconazole are considerably different in patients compared with healthy volunteers, and the bioavailability of an oral dose is affected by clinical characteristics, but pharmacokinetics did not differ between Chinese and Caucasian subjects.

https://doi.org/10.1016/j.ijantimicag.2023.106995

ANTIFUNGAL RESISTANCE IN *CANDIDA* SPP WITHIN THE INTRA-ABDOMINAL CAVITY:

STUDY OF RESISTANCE ACQUISITION IN PATIENTS WITH SERIAL ISOLATES

Clinical Microbiology and Infection, 2023 December; 29(12):1604.e1–6

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BACKGROUND & AIM: The intra-abdominal cavity is recognized as a hidden reservoir of echinocandin-resistant *Candida glabrata*, and susceptibility testing on intra-abdominal isolates is therefore recommended. However, testing only a single isolate per patient may result in underestimation of antifungal resistance. The aim of this study was to assess whether testing sequential isolates from individual patients increases the likelihood of detecting antifungal resistance in the intra-abdominal cavity, particularly to echinocandins.

STUDY DESIGN: Retrospective study.

ENDPOINTS: Antifungal resistance rates.

METHOD: The study analysed intrabdominal *C. albicans*, *C. parapsilosis*, *C. glabrata* and *C. tropicalis* isolates from patients participating in the CANDIdaemia in MADrid study between January 2019 and June 2022 who had multiple intra-abdominal isolates from the same species. Antifungal susceptibility testing for amphotericin B, azoles, anidulafungin, micafungin and ibrexafungerp was carried out using EUCAST methodology. Resistant isolates, as well as susceptible isolates from patients harbouring resistant isolates, were characterized molecularly.

RESULTS: The study included 308 intra-abdominal isolates from 112 patients treated at seven of the 16 hospitals participating in the CANDIMAD study. Of these, 125 were incident (initial) and 183 were sequential isolates. Overall (incident plus sequential isolates), fluconazole and echinocandin resistance was identified in 15/112 patients (13.4%) and 10/112 patients (8.9%), respectively. When only incident isolates were considered, resistance rates were 9/112 (8%) for fluconazole and 2/112 (1.8%) for echinocandins. Therefore, per patient resistance rates were numerically higher when all isolates (incident plus sequential) were analysed compared with analysis of incident isolates only; the difference was not statistically significant for fluconazole (proportions difference 5.4%, 95% confidence interval –2.7% to 13.5%, p=0.09) but was significant for echinocandins (proportions difference 7.1%, 95% CI 1.2–12.9%, p=0.01). Considering both incident and sequential isolates, antifungal resistance was detected in 18 patients; resistance would have been missed in 11/18 patients (61.1%) if only incident isolates had been tested. Among the patients with fluconazole- or echinocandin-resistant isolates, 14/15 and 8/10 patients, respectively, had received or were receiving fluconazole or echinocandins.

CONCLUSIONS: These findings confirm that the intra-abdominal cavity is a reservoir of antifungal resistance, primarily for echinocandin-resistant *C. glabrata*, and highlight the importance of testing multiple intra-abdominal *Candida* species isolates per patient to detect antifungal resistance.

https://doi.org/10.1016/j.cmi.2023.08.021

POINT-OF-CARE TESTING FOR VIRAL-ASSOCIATED PULMONARY ASPERGILLOSIS

Expert Review of Molecular Diagnostics, 2023 September 9; Epub ahead of print

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BACKGROUND & AIM: Severe respiratory viral infections such as those caused by the influenza virus and SARS-CoV-2 increase the risk of critically ill patients developing viral-associated pulmonary aspergillosis (VAPA). Diagnosis of VAPA can be delayed, in part due to the length of time required for fungal culture and galactomannan testing of respiratory specimens. More rapid identification could improve patient outcomes. This paper reviews the performance of point-of-care diagnostic tests (POCTs) for invasive aspergillosis in identifying VAPA using respiratory and blood specimens.

ARTICLE TYPE: Review.

FINDINGS: An *Aspergillus* galactomannan lateral flow assay (LFA) developed by IMMY has been shown to perform at least as well as the galactomannan enzyme immunoassay in detecting invasive aspergillosis. The performance of the IMMY LFA in VAPA patients is summarized in the table. Data for other POCTs are limited.

Performance of IMMY lateral flow assay for IPA diagnosis in patients with viral-associated pulmonary aspergillosis (pooled data)

Specimen	Sensitivity/Specificity (%)	PPV/NPV for 10% IPA prevalence (%)	PPV/NPV for 20% IPA prevalence (%)
BALF	76/80	30.2/96.8	49.4/93.1
Tracheal aspirate	90/51	17.0/97.9	31.6/95.5
Serum	55/96	53.4/95.3	72.1/90.1

BALF, bronchoalveolar lavage fluid; IPA, invasive pulmonary aspergillosis; NPV, negative predictive value; PPV, positive predictive value.

Most studies that have evaluated the ability of POCTs to detect VAPA have involved patients infected with SARS-CoV-2.

With respect to respiratory samples, LFAs have been shown to be useful in detecting COVID-19–associated pulmonary aspergillosis (CAPA) in respiratory specimens, particularly bronchoalveolar lavage fluid (BALF). In particular, the IMMY LFA provided good sensitivity and specificity. It has been suggested that a positive IMMY LFA result for a patient with COVID-19 with acute respiratory failure should prompt the initiation of treatment for invasive aspergillosis. There are few data regarding the effectiveness of other POCTs in detecting CAPA using respiratory samples. There is also limited information regarding the effectiveness of POCTs in detecting influenza-associated pulmonary aspergillosis (IAPA).

Data on the effectiveness of LFAs in detecting VAPA using blood specimens are scarce and relate only to patients with CAPA. Available data suggest that LFAs have limited sensitivity using serum samples and that a negative test result is not sufficient to rule out VAPA.

CONCLUSIONS: POCTs for invasive aspergillosis can help in the diagnosis of VAPA. Notably, IMMY LFA testing of BALF shows promise for the diagnosis of CAPA. However, data on other LFA tests, on the testing of serum samples and on the diagnosis of IAPA are scarce.

https://doi.org/10.1080/14737159.2023.2257597

A CONCEPTUAL FRAMEWORK FOR NOMENCLATURAL STABILITY AND VALIDITY OF MEDICALLY IMPORTANT FUNGI:

A PROPOSED GLOBAL CONSENSUS GUIDELINE FOR FUNGAL NAME CHANGES SUPPORTED BY ABP, ASM, CLSI, ECMM, ESCMID-EFISG, EUCAST-AFST, FDLC, IDSA, ISHAM, MMSA, AND MSGERC

Journal of Clinical Microbiology, 2023 November 21; 61(11):e0087323

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BACKGROUND & AIM: Advances in understanding of medically important fungi have led to considerable changes in microbial taxonomy over the years. Traditionally, the naming system includes separate categories for the sexual and asexual forms of particular species. However, DNA sequencing and other methods can now establish species with more certainty, and the dual naming system is becoming obsolete. The rapid shifts in microbial taxonomy present challenges for clinical microbiology practice. Some authors have presented lists of recommended names based on the species level, while others recommend adopting generic name changes. The current article makes practical suggestions on ways to reduce the number of name changes without disrupting the advancement of science.

ARTICLE TYPE: Global consensus guideline.

FINDINGS: Changes in the names of medically important fungi should be meaningful, and should be applied with care in order to reduce confusion among those involved in patient care. Name changes should be based on fundamental evolutionary differences and clinical relevance. There are two sources of diversity, at the species and genus level, and these have different drivers.

For species, official categories of nomenclature (e.g. subspecies, variety, form) should be used, and individual clones and genotypes should be numbered instead of named. To describe closely related species, phenotypic, ecological, clinical or evolutionarily relevant parameters should be included in addition to phylogenetic distance. For species in complexes or series, the overarching species complex name should be used, followed by that of the molecular sibling or cryptic species. (Epi)type material should be available for future investigation, and deposition of a living culture in a reference collection is recommended.

Genera should be based on phenotypic characteristics (in addition to molecular distance) that reflect their ecological and medical significance. Genera should be maintained at the largest possible size if there is no convincing reason to split them up.

Species or genera name changes should occur only after the underlying taxonomy has been confirmed by multiple groups, and they have been reviewed for medical relevance, validity and stability, preferably by a standing committee. To allow for the unavoidable use of different names for the same species for some time to come, an open-access online database of the names of all medically important fungi should be established.

CONCLUSION: A framework for reducing the number of name changes for medically important fungi has been developed.

https://doi.org/10.1128/jcm.00873-23

TOOLS AND TECHNIQUES TO IDENTIFY, STUDY, AND CONTROL *CANDIDA AURIS*

PLoS Pathogens, 2023 October 19; 19(10):e1011698

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BACKGROUND & AIM: *Candida auris* is a multidrug-resistant fungal pathogen that mainly colonizes the skin, and has been classified as an urgent threat by the US Centers for Disease Control and Prevention (CDC). It is found in acute and long-term care facilities, spreads easily and can cause life-threatening systemic infections, with mortality rates of 40% to 60%. Risk factors for *C. auris* infection include extensive exposure to healthcare, older age, chronic medical conditions and exposure to broad-spectrum antibiotics. This article reviews current knowledge about the transmission of *C. auris*, and current tools to identify, understand and control infections.

ARTICLE TYPE: Review.

FINDINGS: *C. auris* efficiently colonizes the skin, including the nares, palms, fingertips, axilla, inguinal crease and toe webs. This can also result in the contamination of surfaces such as floors, beds, trolleys and mobile phones, where it can persist for up to 2 weeks, as well as medical equipment that has been in contact with the patient. Contamination of the environment therefore plays a significant role in the cross-transmission of *C. auris* in healthcare settings.

The effective control and treatment of *C. auris* in healthcare environments requires efficient environmental and patient surveillance. A number of PCR-based assays are available to identify *C. auris* in the healthcare environment, while real-time PCR and loop-mediated isothermal amplification-based assays can be used to screen for the infection on skin. Antifungal susceptibility is currently assessed using traditional growth assays.

Mice appear to offer the best animal model when investigating the pathogenesis of *C. auris* infection, and a number of genetically modified animals and well-characterized immunological tools are available. These tools have identified differences in the virulence potential between *C. auris* and other *Candida* species, findings that can help provide a better understanding of the differences in virulence mechanisms between these pathogens. Other animal-based model systems are also in use, which have specific advantages over mammalian models in some situations.

There is not currently any effective skin decolonization strategy for *C. auris*. Chlorhexidine gluconate skin wash can help reduce the skin burden, but high concentrations are required to achieve this. The use of environmental disinfectants is also crucial to control infection, and the CDC provides a list of recommended products and practices.

CONCLUSIONS: *C. auris* can cause life-threatening infections and is challenging to control and treat. More research is needed to develop new strategies.

https://doi.org/10.1371/journal.ppat.1011698

NEW AND EMERGING OPTIONS FOR MANAGEMENT OF INVASIVE FUNGAL DISEASES IN PAEDIATRIC PATIENTS

Mycoses, 2023 October 4; Epub ahead of print

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BACKGROUND & AIMS: Immunocompromised children with invasive fungal diseases (IFDs) differ from adults with respect to host biology, IFD presentation and epidemiology, and the pharmacology of antifungal agents. The incidence of IFDs in this patient population is associated with decreased overall survival. The aim of this review was to summarize progress in the development and use of antifungal agents for the treatment of IFDs in children and adolescents with acute leukaemia or undergoing allogeneic haematopoietic stem-cell transplantation (HSCT).

ARTICLE TYPE: Narrative review.

FINDINGS: Anidulafungin is an echinocandin that was approved for use in children aged ≥1 year with invasive *Candida* infections in the USA and the European Union (EU) in 2020. It has been shown to be well tolerated in children and, with the exception of the intravenous carrier polysorbate 80 in newborns, there have been no safety concerns. It has since been approved for the treatment of invasive candidiasis in children aged ≥1 month in the USA and the EU.

Posaconazole is a triazole with broad-spectrum activity against medically relevant yeasts and moulds, including many rare fungal pathogens. It has been approved in both the USA and the EU for IFD prophylaxis in high-risk children aged ≥2 years, including those with acute myeloid leukaemia or who are undergoing allogeneic HSCT. However, approval for the treatment of invasive aspergillosis in both regions has been postponed until the results of a phase 2 clinical trial are published.

Another triazole, isavuconazole, is at an advanced stage of paediatric development and may soon be approved for the treatment of invasive aspergillosis or mucormycosis in children aged ≥1 year. However, it does not provide a therapeutic advantage over existing treatment options in children aged <1 year. Caspofungin, an echinocandin, was recently shown to have efficacy in preventing invasive aspergillosis in children with acute myeloid leukaemia.

Novel antifungal agents in development that have improved pharmacological features or novel targets include rexafungin (a modified form of anidulafungin), ibrexafungerp (a first-in-class triterpenoid with some cross-resistance to echinocandins), fosmanogepix (a novel Gwt1 enzyme/GPI Achor Protein inhibitor) and olorofim (an inhibitor of dihydro-orotate dehydrogenase).

CONCLUSION: The development and approval of antifungal agents for IFDs in children who have acute leukaemia or who are undergoing allogeneic HSCT has the potential to improve treatment in the coming years.

https://doi.org/10.1111/myc.13654

BREAKTHROUGH INVASIVE FUNGAL INFECTIONS ON ISAVUCONAZOLE PROPHYLAXIS IN HEMATOLOGIC MALIGNANCY & HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS

Transplant Infectious Disease, 2023 November; 25 Suppl 1: e14162

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BACKGROUND & AIM: Patients with haematological malignancy (HM) and recipients of haematopoietic stem-cell transplants and cellular therapies (TCT) have an increased risk of invasive fungal infections due to their immunocompromised status. Isavuconazole is used as fungal prophylaxis in patients with a history of HM/TCT. Although isavuconazole has a favourable side-effect profile, breakthrough invasive fungal infections (bIFIs) have been reported. The aim of this study was to evaluate the incidence of bIFIs in patients with HM/TCT receiving isavuconazole prophylaxis and identify associated risk factors.

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

ENDPOINTS: Cumulative incidence of bIFIs during isavuconazole treatment; risk factors for bIFI.

METHOD: The study included 106 adults with a history of HM or TCT who received isavuconazole as either primary or secondary antifungal prophylaxis for a period of at least 7 consecutive days. Data on demographics, treatment, bIFIs, patient outcomes and laboratory findings were extracted from electronic medical records. Patients were followed up from isavuconazole initiation until 90 days after discontinuation of treatment.

RESULTS: Most patients were male (60.4%), and the median age was 65 (range 21–91) years. The most common HM was acute myeloid leukaemia, occurring in 48 patients (45.3%). At the time of initiation of isavuconazole prophylaxis, most patients were either receiving ongoing chemotherapy with unknown clinical status (38 patients, 35.8%) or had relapsed/refractory disease (43 patients, 40.6%). Most patients received isavuconazole as primary prophylaxis; two patients received it as secondary prophylaxis. The cumulative incidence of all bIFIs was 17.9% (19 patients). There were nine proven, four probable and six possible bIFIs. The nine proven bIFIs included three *Fusarium*, two *Candida*, two *Mucorales* plus *Aspergillus*, one *Mucorales*, and one *Colletotrichum* infections. Prior to bIFI diagnosis, 12 patients were neutropenic, for a median of 28 (range 8–253) days. Among the 19 patients with bIFIs, all-cause mortality was 47.4%. Clinically significant cytomegalovirus co-infection was observed in 1/19 patients (5.3%). No significant differences in baseline comorbidities and potential risk factors were identified between patients with versus those without bIFIs.

CONCLUSION: In patients with HM/TCT, isavuconazole prophylaxis was associated with a high cumulative incidence of bIFIs, highlighting the need for clinical vigilance.

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β-(1→3)-D-GLUCAN- AND MANNAN-GUIDED EARLY TERMINATION OF ANTIFUNGAL THERAPY IN ICU PATIENTS:

A RANDOMIZED CONTROLLED STUDY

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BACKGROUND & AIM: *Candida* species are commonly found in patients hospitalized in intensive care units (ICUs), and these fungi most often represent colonization rather than infection, meaning that antifungal therapy is strongly discouraged. Despite this, many of these individuals will ultimately receive an antifungal agent, and such overtreatment is associated with side effects, the emergence of resistant strains of *Candida* and significant costs. Fungal biomarkers such as β-(1→3)-D-glucan (BDG) and mannan have the potential to guide discontinuation of empirical antifungal therapy. The aim of this study was therefore to investigate if this strategy is able to reduce antifungal use in patients in the ICU.

STUDY DESIGN: Prospective, non-blinded, randomized, intervention study.

ENDPOINTS: The primary endpoint was antifungal use; secondary endpoints included 28-day mortality, length of ICU stay, invasive candidiasis and costs.

METHOD: The study included all adult ICU patients at a university hospital who had newly started systemic antifungal therapy, and who had not had a fungal infection in the previous 7 days. Participants were randomized into intervention and control groups, and serum BDG and mannan were assessed on days 1 and 2 of treatment. If these biomarkers were negative on both days (<80 pg/mL for BDG and <62.5 pg/mL for mannan), antifungal therapy was discontinued in the intervention group, but not in the control group. The decision to discontinue antifungal therapy in the control group was at the discretion of the treating physician, who did not know the biomarker results.

RESULTS: The study was stopped after 12 months because an interim analysis showed that it would not be possible to demonstrate significant between-group differences in the primary and secondary endpoints. At this point, 41 patients had been enrolled, including 19 in the intervention group and 22 in the control group. Among those in the intervention group, 17 had positive BDG or mannan results on days 1 and/or 2 of treatment, while only two had negative results on both days and subsequently stopped antifungal therapy. One of these patients had to restart therapy after developing candidaemia. There were no significant differences between the intervention and control groups in any of the study endpoints.

CONCLUSIONS: The use of BDG and mannan biomarkers to guide discontinuation of empirical antifungal therapy did not reduce antifungal consumption in this study of ICU patients, mainly because these tests were positive in most participants.

https://doi.org/10.1128/aac.00725-23

PREDICTORS FOR PROLONGED HOSPITAL STAY SOLELY TO COMPLETE INTRAVENOUS ANTIFUNGAL TREATMENT IN PATIENTS WITH CANDIDEMIA:

RESULTS FROM THE ECMM CANDIDA III MULTINATIONAL EUROPEAN OBSERVATIONAL COHORT STUDY

Mycopathologia, 2023 December; 188(6):983–94

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BACKGROUND & AIM: Early first-line therapy with intravenous echinocandin antifungal agents is recommended for patients with candidaemia, before stepdown to an oral azole, ideally within 5 days. However, because of increasing azole resistance among non-albicans *Candida* species, it is not always feasible to stepdown to oral azole therapy. This results in prolongation of intravenous antifungal therapy and the duration of hospital stay. The aim of this study was to evaluate the characteristics of adults with candidaemia requiring prolonged hospitalization solely to complete intravenous antifungal therapy, and to identify predictors.

STUDY DESIGN: Sub-analysis of a multicentre, observational, cohort study.

ENDPOINT: Prolongation of hospital stay solely to complete intravenous antifungal therapy.

METHOD: In the pan-European Candida III study, each centre provided data for the first 10 adults with blood culture-proven candidaemia after 1st July 2018. Investigators stated whether patients' hospital stays were prolonged solely to complete intravenous antifungal therapy. Multivariable binary logistic regression was used to identify factors predictive of prolonged hospital stay for this reason.

RESULTS: Overall, 100/621 (16.1%) participants had their hospital stay prolonged solely to complete intravenous antifungal therapy, by a median of 16 (interquartile range 8–28) days. In multivariate analysis, the only positive predictor of this outcome was initial echinocandin therapy (table). Negative predictors included neutropenia, intensive care unit admission, catheter-related candidaemia, total parenteral nutrition and *C. parapsilosis* as the causative pathogen (table). Patient age, haematological malignancy and major surgery had no significant effect. *C. glabrata* as the causative pathogen was a significant positive predictor in univariate analysis but not in multivariate analysis (odds ratio 1.74, 95% confidence interval 0.95–3.20; p=0.075).

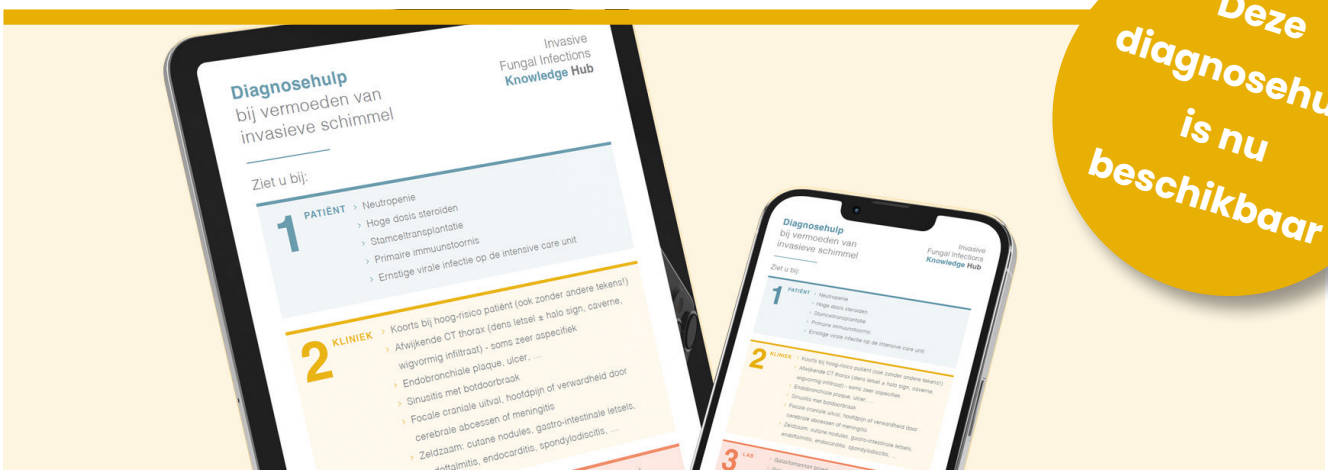
CONCLUSIONS: Approximately 1 in 7 patients across Europe with blood culture-proven candidaemia experienced prolongation of their hospital stay solely to complete intravenous antifungal therapy. These patients were less likely to be severely ill or to have *C. parapsilosis* as the causative fungal pathogen, and were more likely to have received initial therapy with an echinocandin.

Factors associated with prolonged hospitalization solely to complete intravenous antifungal therapy

Predictor	Odds ratio (95% confidence interval)	p
Initial echinocandin therapy	2.87 (1.55–5.32)	<0.001
Neutropenia	0.25 (0.09–0.67)	0.006
Intensive care unit admission	0.45 (0.24–0.85)	0.014
Catheter-related candidaemia	0.22 (0.09–0.56)	0.002
Total parenteral nutrition	0.31 (0.13–0.70)	0.005
C. parapsilosis as causative pathogen	0.28 (0.09–0.85)	0.025

https://doi.org/10.1007/s11046-023-00776-4

Diagnosehulp
bij vermoeden van invasieve schimmelinfecties



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Vroege diagnose en tijdig starten van antifungale therapie zijn cruciale stappen in het klinisch management van patiënten met een invasieve schimmelinfectie[1]. De interactieve diagnosehulp kan hierbij helpen!

Dr. Jochem Buil; arts-microbioloog in het Radboud umc, en dr. Toine Mercier, hematoloog in het AZ Sint-Maarten en consulent in het UZ Leuven, hebben een handig overzicht ontwikkeld met de volgende thema's uit de diagnostiek: Klinische beelden, risicogroepen, diagnostiek en de toepassingen op klinische situaties aan de hand van 3 patiëntencasussen.

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Diagnosticeren vraagt een multidisciplinaire aanpak met de patiënt centraal.
De diagnosehulp ondersteunt hierbij.

1. Cornely OA et al. Efficacy outcomes in a randomised trial of liposomal amphotericin B based on revised EORTC/MSG 2008 definitions of invasive mould disease Mycoses 2011; 54(5): e449-455

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