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on systemic fungal infections

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Redox Biology, 2022 September; 55:102391

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Clinical Infectious Diseases, 2022 July 21; Epub ahead of print

Molecular mechanisms of acquired antifungal drug resistance in principal fungal pathogens and EUCAST guidance for their laboratory detection and clinical implications

Journal of Antimicrobial Chemotherapy, 2022 July 28; 77(8):2053–73

Antifungal resistance and the role of new therapeutic agents

Current Infectious Disease Reports, 2022; 24(9):105–16

Statin use may be associated with a lower risk of invasive aspergillosis in lung transplant recipients

Clinical Infectious Diseases, 2022 July 28; Epub ahead of print

Comparison of four diagnostic criteria for invasive pulmonary aspergillosis—a diagnostic accuracy study in critically ill patients

Mycoses, 2022 August; 65(8):824–33

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Nature Microbiology, 2022 August; 7(8):1127–40

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ISSUE 3, 2022

ND-UNB-0091 Date of preparation: Feb 2024

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Framingham bv
Postbus 1593
1200 BN Hilversum
The Netherlands
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Framingham *on systemic fungal infections* is supported by **Gilead Sciences Denmark ApS,**
Gammel Kongevej 60,
1850 Frederiksberg C,
DENMARK

GENETIC DETERMINANTS OF FUNGI-INDUCED ROS PRODUCTION ARE ASSOCIATED WITH THE RISK OF INVASIVE PULMONARY ASPERGILLOSIS

Redox Biology, 2022 September; 55:102391

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BACKGROUND & AIM: The production of reactive oxygen species (ROS) is an essential part of the innate host defence against fungal infections. A deficient response is associated with increased susceptibility to invasive fungal infections, so a better understanding of the genetic factors that regulate ROS-mediated defence would be of value in designing new therapies. The aim of this study was to use quantitative trait locus (QTL) mapping to identify genetic variants that affect ROS production in response to *Candida albicans* and *Aspergillus fumigatus* in immune cells, and to assess their association with the risk of invasive pulmonary aspergillosis (IPA).

STUDY DESIGN: Population-based cohort study and genetic association study.

ENDPOINTS: Identification of ROS-QTLs, and their association with IPA.

METHOD: The population-based cohort comprised 197 healthy adults, from whom peripheral blood mononuclear cells were isolated and stimulated with fungal cultures of *C. albicans* and *A. fumigatus*, and ROS production was measured. The participants were genotyped, and QTL mapping was used to identify genetic loci involved in regulating ROS levels in response to either or both of these pathogens. ROS-QTLs were then analysed for their impact on the risk of IPA in 386 haematological patients undergoing allogeneic haematopoietic stem-cell transplantation (HSCT), who were stratified according to the donor's single nucleotide polymorphism genotype.

RESULTS: QTL mapping identified ten QTLs potentially associated with ROS production following stimulation with *C. albicans*, and nine potentially related to *A. fumigatus* ($p<9.99\times10^{-6}$). Two QTLs were associated with ROS production in response to both pathogens. The top five most significant ROS-QTLs were analysed for their association with IPA in HSCT recipients, and two QTLs were found to be significantly associated with the risk of IPA. In a multivariate model controlling for patient age and sex, haematological malignancy, type of transplantation, conditioning regimen, acute graft-versus-host-disease grades III–IV and antifungal prophylaxis, the donor GA + AA genotype combination at rs4685368 remained associated with the risk of IPA (hazard ratio 1.81, 95% confidence interval 1.22–2.71, p=0.0036).

CONCLUSIONS: A common genetic variation can affect ROS production in response to fungal infection, and so have an impact on the risk of developing IPA in HSCT recipients.

https://doi.org/10.1016/j.redox.2022.102391

OUTPATIENT CRYPTOCOCCAL ANTIGEN SCREENING IS ASSOCIATED WITH FAVORABLE BASELINE CHARACTERISTICS AND IMPROVED SURVIVAL IN PERSONS WITH CRYPTOCOCCAL MENINGITIS IN UGANDA

Clinical Infectious Diseases, 2022 July 21; Epub ahead of print

AUTHORS: Levin AE, Bangdiwala AS, Nalintya E, Kagimu E, Kasibante J, Rutakingirwa MK, Mpoza E, Jjunju S, Nuwagira E, Naluyima R, Kirumira P, Hou C, Ssebambulidde K, Musubire AK, Williams DA, Abassi M, Muzoora C, Hullsiek KH, Rajasingham R, Meya DB, Boulware DR, Skipper CP
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BACKGROUND & AIM: Cryptococcal meningitis is a common complication of HIV infection, and so the WHO recommends cryptococcal antigen (CrAg) screening for all patients presenting with advanced HIV (CD4 <100 cells/μL), and fluconazole treatment for those who are CrAg positive. However, many of these individuals will still develop fulminant cryptococcal meningitis, and it is not known whether their survival is better than those who present directly to hospital with overt meningitis. This study compared the outcomes of patients with cryptococcal meningitis who were CrAg screened and referred to hospital versus those who presented directly to hospital with symptomatic meningitis.

STUDY DESIGN: Observational cohort study.

ENDPOINTS: Primary endpoint: all-cause mortality at 14 days. Secondary endpoints: mortality at 10 weeks, and baseline mental status, cerebrospinal fluid (CSF) culture burden and opening pressure.

METHOD: The study prospectively enrolled 489 Ugandans with HIV-associated cryptococcal meningitis between 2018 and 2021, of whom 194 (40%) underwent blood CrAg screening and were then referred to hospital, while 295 (60%) presented directly to hospital with overt meningitis. The diagnosis was confirmed with a CrAg lateral flow assay. Patients received standard-of-care treatment with intravenous amphotericin B and fluconazole for 14 days, followed by consolidation and maintenance therapy with fluconazole.

RESULTS: The 14-day mortality rate was significantly lower in CrAg-screened individuals than in those who were not screened (12% versus 21%; hazard ratio 0.51, 95% confidence interval 0.32–0.83, p=0.006), as was the 10-week mortality rate (HR 0.70, 95% CI 0.49–0.99, p=0.04). However, the effect on mortality was attenuated in multivariate analysis. CrAg screening was associated with a lower incidence of altered mental state (Glasgow Coma Scale <15), lower CSF culture burden and lower CSF opening pressure at baseline (table). In multivariate analysis, altered mental state was the strongest predictor of 14-day mortality (HR 5.22, p<0.001).

CONCLUSIONS: Among patients with HIV-associated cryptococcal meningitis, survival was better among those who underwent CrAg screening versus those who did not. Screened patients had more favourable baseline characteristics, suggesting that screening detected the disease at an earlier stage, allowing timely therapy.

Differences in baseline characteristics between patients with HIV-associated cryptococcal meningitis who underwent CrAg screening and those who did not

Parameter	CrAg screened	Not screened	p
Glasgow Coma Scale score <15 (% of patients)	29	41	0.02
CSF culture burden (CFU/mL), median	4570	26,900	0.01
CSF opening pressure (mmH_2O), median	190	225	0.004

https://doi.org/10.1093/cid/ciac599

MOLECULAR MECHANISMS OF ACQUIRED ANTIFUNGAL DRUG RESISTANCE IN PRINCIPAL FUNGAL PATHOGENS AND EUCAST GUIDANCE FOR THEIR LABORATORY DETECTION AND CLINICAL IMPLICATIONS

Journal of Antimicrobial Chemotherapy, 2022 July 28; 77(8):2053–73

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BACKGROUND & AIM: The management of invasive fungal infections is challenging, and the detection of pathogens in clinical samples and *in vitro* antifungal susceptibility testing are crucial to guide treatment. Molecular methods are increasingly being used to detect fungi as well as gene mutations and other mechanisms associated with antifungal drug resistance. This article reviews mechanisms of acquired antifungal drug resistance in the principal human fungal pathogens, and the tools available for their detection.

ARTICLE TYPE: Review.

FINDINGS: Most research on antifungal drug resistance in *Aspergillus* species has focused on triazole resistance in *A. fumigatus*, and these mechanisms are mainly related to alterations in the *cyp51A* gene which is involved in the synthesis of ergosterol, a component of fungal membranes. Polymerase chain reaction (PCR) tests are available to analyse triazole resistance in *A. fumigatus* due to this mechanism, but they are less sensitive than PCR tests that detect presence of the fungus. A positive resistance test indicates the need to avoid triazole therapy, but a negative test does not confirm susceptibility.

Drug resistance rates in *Candida* species vary according to the specific pathogen and the area of the world. Acquired azole resistance in *Candida* species is not common, and can be caused by several mechanisms, including mutations in the *erg11* gene (equivalent to *cyp51A* for *Aspergillus*) and upregulation of efflux systems. Molecular tests to detect antifungal drug resistance therefore have little clinical value, and ruling out one mechanism does not confirm susceptibility. Echinocandin resistance in most *Candida* species is caused by mutations in the *fks1* gene, and acquired resistance is most common in *C. glabrata*. While PCR can target the hotspot regions of the *fks* genes, this is technically challenging and is species specific.

The article also discusses molecular tests for the detection of antifungal drug resistance in *Cryptococcus* and *Pneumocystis jirovecii*.

In general, molecular testing for antifungal drug resistance may be considered in patients who fail antifungal therapy, have a relapse of infection after therapy, or develop a new fungal infection after therapy. It may also be an option in areas with high rates of resistance for particular fungal species, where there is limited access to phenotypic susceptibility testing, or where phenotypic testing gives a borderline result and a definitive answer would aid clinical decision making.

CONCLUSIONS: Molecular detection of antifungal drug resistance has a role in certain circumstances but should be applied in conjunction with culture-based susceptibility testing.

https://doi.org/10.1093/jac/dkac161

ANTIFUNGAL RESISTANCE AND THE ROLE OF NEW THERAPEUTIC AGENTS

Current Infectious Disease Reports, 2022; 24(9):105–16

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BACKGROUND & AIM: The epidemiology of invasive fungal infections is continually evolving due to changes in healthcare such as the prescription of broad-spectrum antibiotics, developments in the use of surgical procedures, new chemotherapies that contribute to immune compromise, and the emergence of fungi with multidrug resistance. This all contributes to greater complexity in how fungal infections are managed. This article reviews mechanisms of antifungal resistance and the role of new antifungal agents

ARTICLE TYPE: Review.

FINDINGS: The three main classes of antifungal agents are azoles, echinocandins and polyenes. Both acquired and intrinsic resistance to azole antifungals have been identified, and a number of mechanisms can be involved, including expression of drug efflux pumps and upregulation or mutations in *erg11* in *Candida* species, and mutations or overexpression of *cyp51A* and upregulation of ABC transport proteins in *Aspergillus* species. The most common form of resistance to echinocandins involves mutations of *fks1*, but upregulated chitin production is also possible. Acquired resistance to polyene antifungals can occur via the selection of inherently less susceptible fungal strains, while mutations in *erg* genes may be responsible for resistance in some *Candida* species.

The two newest antifungal agents are isavuconazole and ibrexafungerp. Isavuconazole is a broad-spectrum triazole antifungal which has been recommended as an alternative regimen for aspergillosis and as a first-line agent for mucormycosis. It may also have a role as oral step-down therapy, especially for infections involving resistant *Candida* species. There is evidence that isavuconazole maintains its *in vitro* activity against select fluconazole-resistant *Candida* species. In the treatment of *Aspergillus* species, increasing the dose of isavuconazole may help overcome the higher minimum inhibitory concentrations of resistant strains. Ibrexafungerp is an oral glucan synthase inhibitor, and studies have shown its efficacy against fluconazole-resistant strains of *Candida* species. It has been shown to have activity against *C. auris*, including isolates that are resistant to both azoles and echinocandins.

Other new antifungals currently in development include rezafungin, oteseconazole, olorofim, fosmanogepix and opelconazole.

CONCLUSIONS: An increasing range of antifungal agents is needed in order to combat the growth in antifungal resistance. However, one consequence will be greater complexity in the management of resistant fungal infections.

https://doi.org/10.1007/s11908-022-00782-5

EARLY EMPIRICAL ANIDULAFUNGIN REDUCES THE PREVALENCE OF INVASIVE CANDIDIASIS IN CRITICALLY ILL PATIENTS:

A CASE-CONTROL STUDY

The Journal of Critical Care Medicine, 2022 May 12; 8(2):89–99

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BACKGROUND & AIM: Invasive candidiasis, including candidaemia, *Candida* pneumonia and *Candida* urinary tract infections, causes high morbidity and mortality in intensive care unit (ICU) patients. Because of increasing resistance to fluconazole, echinocandins have become preferred for empirical antifungal therapy, but there are few data on outcomes in ICU patients. The aim of this study was to evaluate the impact of early empirical echinocandin use on the risk of invasive candidiasis in ICU patients.

STUDY DESIGN: Retrospective, single-centre, case–control study.

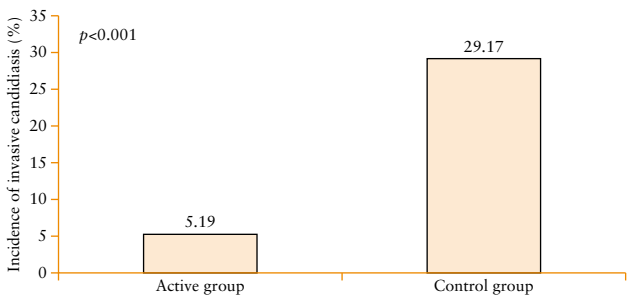
ENDPOINTS: Incidence of invasive candidiasis, length of ICU stay and 30-day all-cause mortality.

METHOD: Data on patients admitted to the ICU of a tertiary-level hospital with bacterial pneumonia and sepsis (± septic shock) between 2019 and 2020 were analysed. All received high-dose corticosteroids and broad-spectrum antibiotics for their sepsis and pneumonia. Some were also given a 14-day course of empirical prophylactic treatment with anidulafungin, starting within 6 hours of ICU admission (active group, *n*=77). The remaining patients (control group, *n*=72) were only given anidulafungin in response to culture-confirmed *Candida* infection.

RESULTS: The two groups had similar characteristics at ICU admission, apart from a slightly higher prevalence of hypertension and diabetes (both $p=0.001$) and a slightly higher mean Apache II score (18.7 versus 17.2, $p=0.005$) in the active group. During their ICU stay, significantly fewer patients in the active group were diagnosed with invasive candidiasis compared with the control group (figure), with a relative risk of 0.175 (95% confidence interval 0.064–0.493). Thirty-day mortality was also lower in the active group (10.39% versus 19.44%, $p=0.04$). Moreover, 48/77 (62.34%) of active-group patients were discharged from the ICU within 10 days, compared with 39/72 (54.17%) in the control group (p-value not stated).

CONCLUSIONS: Prompt empirical prophylactic treatment with anidulafungin led to a lower incidence of invasive candidiasis, fewer deaths and quicker ICU discharge among critically ill patients with bacterial pneumonia and sepsis.

Incidence of invasive candidiasis among critically ill patients in the intensive care unit



https://doi.org/10.2478/jccm-2022-0006

EMPIRIC VERSUS PRE-EMPTIVE ANTIFUNGAL STRATEGY IN HIGH-RISK NEUTROPENIC PATIENTS ON FLUCONAZOLE PROPHYLAXIS:

A RANDOMIZED TRIAL OF THE EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC 65091)

Clinical Infectious Diseases, 2022 July 30; Epub ahead of print

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BACKGROUND & AIM: High-risk patients with neutropenia and persistent fever are at risk of developing life-threatening invasive fungal diseases, and so the standard of care for this group is empirical therapy with an antifungal agent such as liposomal amphotericin B or caspofungin. However, this can lead to overtreatment, associated toxicity and increased costs. An alternative, pre-emptive, approach is to start antifungal therapy based on the detection of abnormalities on chest computed tomography (CT) scan or mycological testing. The aim of this study was to compare the survival of high-risk neutropenic patients managed using a pre-emptive versus empirical approach to antifungal therapy.

STUDY DESIGN: Phase 3, multicentre, randomized, open-label trial.

ENDPOINTS: Primary endpoint: overall survival at day 42. Secondary endpoints included overall survival and invasive fungal disease at day 84, and adverse events.

METHOD: The study included 549 patients with acute myeloid leukaemia or myelodysplastic syndrome, or who were allogeneic haematopoietic cell transplant recipients, none of whom had had a previous invasive fungal infection. All participants received daily fluconazole as prophylaxis. They were randomized 1:1 to receive caspofungin either empirically (given for unexplained fever or a new febrile episode) or pre-emptively (on the basis of a positive galactomannan assay or new pulmonary infiltrate on chest X-ray or CT scan, or positive *Aspergillus* sputum culture).

RESULTS: After 42 days, overall survival was 96.7% (95% confidence interval 93.8–98.3%) in those who received pre-emptive caspofungin compared with 93.1% (95% CI 89.3–95.5%) in those who received empirical caspofungin. Using a non-inferiority margin of 1.62, pre-emptive therapy was non-inferior to empirical therapy. Overall survival at day 84 was also similar in the pre-emptive and empirical groups (92.6% versus 90.5%), as was the rate of invasive fungal disease (7.7% versus 6.6%). Fewer patients in the pre-emptive group received caspofungin compared with the empirical group (27% versus 63%, $p<0.001$). Rates of adverse events did not differ between groups.

CONCLUSIONS: A pre-emptive antifungal strategy was safe and non-inferior to empirical therapy in high-risk neutropenic patients receiving fluconazole prophylaxis.

https://doi.org/10.1093/cid/ciac623

INCREASED DEATHS FROM FUNGAL INFECTIONS DURING THE COVID-19 PANDEMIC— NATIONAL VITAL STATISTICS SYSTEM, UNITED STATES, JANUARY 2020–DECEMBER 2021

Clinical Infectious Diseases, 2022 June 19; Epub ahead of print

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BACKGROUND & AIM: The risk of severe fungal infections appears to be increased among patients with COVID-19. This is likely to be due to COVID-19–related immune system dysfunction, structural lung damage and treatment-associated impairment of host defences. Severe fungal infections occurring in patients with COVID-19 can lead to adverse outcomes, including death. The aim of this study was to investigate the disease burden, temporal trends and demographic characteristics of patients who died of fungal infections at the height of the COVID-19 pandemic.

STUDY DESIGN: Retrospective database analysis.

ENDPOINTS: Number and age-adjusted rate per 100,000 head of population of death from fungal infection.

METHOD: The study used data from the US National Vital Statistics System (NVSS) Provisional Multiple Cause of Death database, which included final mortality data for 2018–2020 and provisional data for 2021. The numbers and age-adjusted rates per 100,000 head of population of deaths from fungal infection were calculated, stratified by fungal pathogen, COVID-19 association, patient characteristics and year.

RESULTS: In 2019, there were 4833 deaths from fungal infection, representing an age-adjusted rate of 1.2 per 100,000 head of population. The age-adjusted rate in 2018 was also 1.2 per 100,000. By comparison, in 2021 there were 7199 deaths from fungal infection, giving an age-adjusted rate of 1.8 per 100,000. Across 2020–2021, a total of 13,121 deaths were attributed to fungal infection, of which 2868 (21.9%) were COVID-19–associated. Relative to non–COVID-19–associated deaths due to fungal infection, those that were COVID-19–associated were more frequently due to infection by *Candida* species (23.7% versus 27.1%) and *Aspergillus* species (14.5% versus 23.3%). For the period 2020–2021, age-adjusted rates of COVID-19–associated deaths due to fungal infection per 100,000 head of population were greater among individuals who were American Indian or Alaskan Native (1.3), Hispanic (0.7) or Black (0.6) versus those who were White (0.2) or Asian (0.3).

CONCLUSIONS: Compared with previous years, there was a marked increase in deaths from fungal infection during 2020–2021 in the USA. This was driven mainly by COVID-19–associated fungal deaths, especially those due to *Aspergillus* and *Candida*. Rates of COVID-19–associated death due to fungal infection were highest among non-White and non-Asian individuals.

https://doi.org/10.1093/cid/ciac489

STATIN USE MAY BE ASSOCIATED WITH A LOWER RISK OF INVASIVE ASPERGILLOSIS IN LUNG TRANSPLANT RECIPIENTS

Clinical Infectious Diseases, 2022 July 28; Epub ahead of print

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BACKGROUND & AIM: Invasive aspergillosis (IA) is a significant risk after lung transplantation and has a mortality rate of up to 29%. Prophylactic antifungal therapy is standard in patients judged to be at higher risk of IA. Statins have various biological effects, including antifungal activity, but have not been formally evaluated as antifungal agents. The aim of this study was to determine whether lung transplant recipients (LTRs) given statins were less likely to develop IA.

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

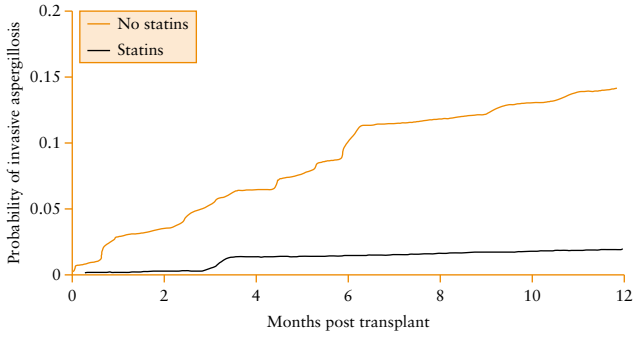
ENDPOINTS: Occurrence of IA during 1 year post-transplant.

METHOD: Data on 785 consecutive adult LTRs operated on at Toronto General Hospital between 2010 and 2017 were analysed. Cases of proven or probable IA and *Aspergillus* colonization were identified according to ISHLT criteria. Fine and Gray's competing risk regression model was used to identify factors associated with an increased risk of IA, with mortality as the competing risk.

RESULTS: Among the 785 LTRs, 451 (57%) were given a statin (atorvastatin in 68% of cases and rosuvastatin in 20%) for at least 2 weeks post-transplant (median duration 347 days), of whom 89% had been on statin therapy pre-transplant. Fewer patients in the statin group received antifungal medications compared with the non-statin group (30% versus 39%, p=0.027). After transplantation, 237 (30%) patients developed *Aspergillus* colonization (34% of those not taking a statin and 27% of those given a statin, p=0.038) and 55 (7%) developed IA, at a median of 149 days post-transplant. IA developed in 46/334 (13.7%) patients not taking a statin versus 9/451 (2%) of those who received a statin (p<0.001); figure. Multivariable regression analysis showed that only statin use was independently associated with a reduced risk of IA (hazard ratio 0.3, 95% confidence interval 0.14–0.64, p=0.002), while post-transplant *Aspergillus* colonization substantially increased the risk (HR 9.05, 95% CI 4.77–17.28, p<0.001).

CONCLUSIONS: Post-transplant statin use significantly reduced the risk of IA in lung transplant recipients.

Cumulative risk of invasive aspergillosis after lung transplantation according to statin use



https://doi.org/10.1093/cid/ciac551

ISAVUCONAZOLE PLASMA CONCENTRATIONS IN CRITICALLY ILL PATIENTS DURING EXTRACORPOREAL MEMBRANE OXYGENATION

Journal of Antimicrobial Chemotherapy, 2022 August; 77(9):2500–5

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BACKGROUND & AIM: Critically ill patients with severe acute respiratory distress syndrome (ARDS) can require extracorporeal membrane oxygenation (ECMO) to provide prolonged cardiopulmonary support. Such critically ill patients are at risk of developing invasive pulmonary aspergillosis and may require antifungal therapy. Isavuconazole is a triazole antifungal used in the treatment of invasive fungal infections. However, little is known about its plasma concentrations in patients undergoing ECMO. Therefore, this study evaluated isavuconazole plasma concentrations in critically ill patients during ECMO.

STUDY DESIGN: Exploratory clinical study.

ENDPOINTS: Isavuconazole plasma concentration; influence of the ECMO circuit immediately after the first isavuconazole loading dose.

METHOD: The study included seven critically ill patients treated with standard doses of isavuconazole whilst undergoing ECMO. Isavuconazole was administered intravenously as a loading dose of 200 mg every 8 hours for six doses, followed by a maintenance dose of 200 mg every 24 hours, with a 60-minute infusion duration, as per the prescribing information. To measure isavuconazole concentrations, a total of 64 blood samples were collected at intervals between 2 and 168 hours after the first dose of isavuconazole. To assess any potential isavuconazole clearance effect of the ECMO oxygenation device, another 27 blood samples (from three patients) were collected directly from the device's inflow and outflow lines.

RESULTS: Median (interquartile range) age of the patients was 58 (50–62) years and three were women. Six patients underwent veno-venous ECMO for COVID-2019–related severe ARDS, and one received veno-atrial ECMO following cardiac arrest during heart surgery. At 24 and 96 hours after the first isavuconazole loading dose, median (min–max) plasma isavuconazole concentrations were 1.09 (0.83–1.73) µg/mL and 2.31 (0.84–2.97) µg/mL, respectively. Immediately after the first loading dose, there was a direct correlation between isavuconazole plasma concentrations before (inflow line) and after (outflow line) the membrane oxygenator (ρ=0.987, R^2=0.994, p<0.001). Moreover, there was also a direct correlation between post-membrane oxygenator plasma isavuconazole concentrations and those measured at the same time in samples from the arterial lines of patients (ρ=0.942, R^2=0.945, p<0.001).

CONCLUSIONS: Isavuconazole plasma concentrations may be influenced by the higher volume of distribution in patients undergoing ECMO, but levels were unaffected by the ECMO oxygenation device itself. Median concentrations in excess of 1 µg/mL were measured at 24 hours after the first loading dose.

https://doi.org/10.1093/jac/dkac196

COMPARISON OF FOUR DIAGNOSTIC CRITERIA FOR INVASIVE PULMONARY ASPERGILLOSIS—

A DIAGNOSTIC ACCURACY STUDY IN CRITICALLY ILL PATIENTS

Mycoses, 2022 August; 65(8):824–33

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BACKGROUND & AIM: The diagnosis of invasive pulmonary aspergillosis (IPA) in critically ill patients is challenging and the reported incidence varies from 0.3% to 19%. Histopathological assessment of lung tissue is mandatory for the diagnosis of proven IPA, but this is difficult in critically ill patients because of the need for invasive sampling. Consequently, various diagnostic algorithms for IPA have been developed, based on the presence of clinical symptoms, imaging characteristics, microbiological features and underlying conditions. The key challenge is to differentiate between IPA as an infectious disease and *Aspergillus* colonization. The aim of this study was to compare the ability of four diagnostic algorithms to differentiate between probable IPA requiring antifungal treatment and colonization that did not require such treatment.

STUDY DESIGN: Diagnostic accuracy study.

ENDPOINTS: Diagnosis of probable IPA; agreement between, and specificity and sensitivity of, four diagnostic algorithms.

METHOD: Data on all critically ill patients with a positive *Aspergillus* culture admitted to an intensive care unit between 2005 and 2020 (*n*=684; 69% medical, 31% surgical) were reviewed retrospectively. Agreement between the following four diagnostic algorithms for a diagnosis of probable IPA was assessed: the 2012, 2018 and 2020 AspICU algorithms and the 2021 European Organisation for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) algorithm. Sensitivity and specificity for proven IPA were evaluated in a subgroup of patients with lung tissue histopathology available.

RESULTS: Overall, 62%, 62%, 17% and 17% of patients had probable IPA according to the 2012, 2018 and 2020 AspICU algorithms and the 2021 EORTC/MSGERC algorithm, respectively. A total of 543 (79%) patients fulfilled the criteria for probable IPA according to at least one algorithm, but only 29 (4%) fulfilled the criteria for all four. Agreement between the four algorithms was low (Cohen's kappa 0.07–0.29). Lung tissue was available for 85 patients, 34 (40%) of whom had confirmed IPA. When the four algorithms were applied to these patients, the 2021 EORTC/MSGERC algorithm performed best, with a specificity of 0.73 and a sensitivity of 0.59. The specificity and sensitivity of the 2012, 2018 and 2020 AspICU algorithms were 0.27 and 0.82, 0.29 and 0.65, and 0.78 and 0.29, respectively.

CONCLUSIONS: In a mixed group of critically ill patients, agreement between four algorithms for diagnosing probable IPA was poor. In patients with histopathologically confirmed IPA, the 2021 EORTC/MSGERC algorithm showed the highest diagnostic accuracy for proven IPA.

https://doi.org/10.1111/myc.13478

OCCURRENCE OF CANDIDEMIA IN PATIENTS WITH COVID-19 ADMITTED TO FIVE ICUS IN FRANCE

Journal of Fungi, 2022 June 28; 8(7):678

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BACKGROUND & AIM: The incidence of candidaemia has been estimated to be two- to ten-fold higher among patients with severe coronavirus disease 2019 (COVID-19) compared with non–COVID-19 patients. However, it remains unclear whether severe COVID-19 itself is a risk factor for developing candidaemia, as such patients generally require admittance to an intensive care unit (ICU), which itself carries an increased risk of invasive candidiasis. The aim of the present study was to evaluate the incidence of candidaemia among patients admitted to the ICU with severe SARS-CoV-2–related pneumonia.

STUDY DESIGN: Retrospective case series.

ENDPOINTS: Yeast colonization; fungal pathogens; candidaemia diagnosis; ICU mortality; positive beta-glucan test.

METHOD: The study included patients with severe SARS-CoV-2–related pneumonia who had been admitted to five ICUs across France between March 2020 and January 2021, all of whom underwent screening for fungal complications. The above endpoints were evaluated and the effect of candidaemia upon ICU mortality was estimated.

RESULTS: Among 264 patients (median age 56 years; 78 females and 186 males), 87.5% were immunocompetent. All required mechanical ventilation and 62.7% received extracorporeal membrane oxygenation support. A total of 4883 blood cultures from 261 patients underwent microbiological analysis, and 975 serum samples from 209 patients underwent beta-glucan testing. Overall, 164 patients had a history of yeast colonization of the respiratory tract and/or skin and/or digestive tract and/or urinary tract, most frequently by *Candida albicans* (*n*=123; 75%), followed by *C. glabrata* and *C. parapsilosis* (each *n*=14; 8.5%). A total of 13 (4.9%) patients were diagnosed with candidaemia, most commonly due to *C. albicans* (*n*=6) and *C. parapsilosis* (*n*=5). Twelve (92.3%) of the 13 patients with candidaemia were among those patients observed to have yeast colonization. There was no significant difference in the rate of ICU mortality between patients with candidaemia (5/12; 41.7%; one patient lost to follow-up) versus non-candidaemic patients (100/232; 43.1%; *p*=1.00). A positive beta-glucan test was observed in six (50%) of 12 patients with candidaemia and 49 (25%) of 197 patients without candidaemia (six with aspergillosis and 43 false positives with no documented fungal complications).

CONCLUSIONS: In this retrospective case series, the incidence of candidaemia was low among individuals admitted to the ICU with severe SARS-CoV-2–related pneumonia. Almost all patients who developed candidaemia had a history of yeast colonization. Beta-glucan testing was ineffective in the diagnosis of candidaemia in this patient population.

https://doi.org/10.3390/jof8070678

COVID-19-ASSOCIATED FUNGAL INFECTIONS

Nature Microbiology, 2022 August; 7(8):1127–40

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BACKGROUND & AIM: COVID-19–associated invasive fungal infections affect a significant number of critically ill, hospitalized patients with COVID-19, and are caused by three groups of fungal pathogens: *Aspergillus*, *Mucorales* and *Candida* species. This article reviews the incidence of these COVID-19–associated invasive fungal infections, as well as the epidemiology, risk factors and antifungal treatment options.

ARTICLE TYPE: Review.

FINDINGS: COVID-19–associated pulmonary aspergillosis (CAPA) has a prevalence of approximately 10% among invasively ventilated patients with COVID-19, and is primarily caused by *A. fumigatus*. The incidence varies between centres because of different approaches to treatment and diagnosis, as well as different genetic risk factors. Other risk factors include environmental exposure in the intensive care unit (ICU), and a range of host factors such as other treatments, underlying lung or other diseases, lung damage from COVID-19, and mechanical ventilation. First-line treatment for CAPA is voriconazole or isavuconazole, with liposomal amphotericin B, posaconazole and echinocandins as second-line treatments.

The prevalence of COVID-19–associated mucormycosis varies between countries, with reported rates of 0.27% among hospitalized COVID-19 patients in India, and 1–2% among invasively ventilated COVID-19 patients in Europe. *Rhizopus* species are of particular concern, and patients can suffer from rhino-orbital, rhino-orbital cerebral, pulmonary, gastrointestinal or disseminated infection. Risk factors include environmental air exposure (including in the ICU) and farming, as well as host factors such as repeated nasopharyngeal swab testing, mechanical ventilation and comorbid conditions. Treatments include surgical debridement, liposomal amphotericin B, and isavuconazole or posaconazole if there is renal compromise.

The combination of ICU treatment, parenteral nutrition, mechanical ventilation and systemic corticosteroid therapy predisposes COVID-19 patients to *Candida* infections, the most common being *C. albicans*, although *C. auris* is predominant in some regions. Infections affect the bloodstream or abdomen. Other risk factors include central venous catheters, previous antifungal exposure (*C. auris*) and use of broad-spectrum antibiotics. Outbreaks of COVID-19–associated candidiasis have occurred in several countries, but its prevalence is not known. First-line treatments include caspofungin and micafungin, with liposomal amphotericin B as a second-line option.

CONCLUSIONS: To reduce the impact of fungal infections in patients with COVID-19, increased awareness and routine diagnostic strategies are needed, as well as increased resources for low- and middle-income countries that are disproportionately affected.

https://doi.org/10.1038/s41564-022-01172-2