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on systemic fungal infections

The added value of (1,3)-β-D-glucan for the diagnosis of invasive candidiasis in ICU patients: a prospective cohort study

Infection, 2024 February; 52(1):73–81

Age difference of patients with and without invasive aspergillosis: a systematic review and meta-analysis

BMC Infectious Diseases, 2024 February 19; 24(1):220

A systematic review of the therapeutic outcome of mucormycosis

Open Forum Infectious Diseases, 2023 December 30; 11(1):ofad704

Lower blood levels of isavuconazole in critically ill patients compared with other populations: possible need for therapeutic drug monitoring

Journal of Antimicrobial Chemotherapy, 2024 April 2; 79(4):835–45

Beyond the first year: epidemiology and management of late-onset opportunistic infections after kidney transplantation

Transplant International, 2024 February 26; 37:12065

Impact of climate change and natural disasters on fungal infections

The Lancet Microbe, 2024 March 19; Epub ahead of print

Modeling invasive aspergillosis risk for the application of prophylaxis strategies

Open Forum Infectious Diseases, 2024 February 6; 11(3):ofae082

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Clinical Infectious Diseases, 2024 February 17; 78(2):361–70

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THE ADDED VALUE OF (1,3)-B-D-GLUCAN FOR THE DIAGNOSIS OF INVASIVE CANDIDIASIS IN ICU PATIENTS:

A PROSPECTIVE COHORT STUDY

Infection, 2024 February; 52(1):73–81

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BACKGROUND & AIM: The diagnosis of invasive candidiasis is usually based on the presence of clinical risk factors and microbiological criteria, but this has low specificity and may result in excessive or unnecessary antifungal treatment. Clinical decision-making can be supported by the use of biomarkers, and the (1,3)-β-D-glucan (BDG) assay has been suggested as a tool to aid the diagnosis of candidaemia and invasive candidiasis in high-risk patients in the intensive care unit (ICU). However, its value in this setting is uncertain, with variable results reported to date. The aim of this study was to assess the performance of the Fujifilm Wako BDG-test in diagnosing invasive candidiasis in high-risk ICU patients.

STUDY DESIGN: Prospective, observational cohort study.

ENDPOINTS: Diagnostic sensitivity and specificity.

METHOD: The study included 174 ICU patients (median age 63 years, 75.7% males) who were receiving empirical antifungal therapy with echinocandins for suspected invasive candidiasis. BDG testing was performed using the Fujifilm Wako BDG-test every 24–48 hours for the full duration of antifungal therapy, starting on the first day of echinocandin administration. Invasive candidiasis was identified based on at least two positive blood cultures growing *Candida* species, or the detection of *Candida* by direct microscopy or culture from a site with evidence of an infectious disease. The diagnostic accuracy of the BDG test was assessed for single and serial testing strategies, using a range of thresholds.

RESULTS: A total of 46 of the 174 patients (26.4%) were classified as having invasive candidiasis, including 35 (20.1%) who had repeatedly positive blood cultures. On initial testing, participants with invasive candidiasis had higher levels of serum BDG and higher test positivity rates than those without. Using the manufacturer's threshold value, BDG testing had moderate sensitivity of 74% (95% confidence interval 59–86%) and poor specificity of 45% (95% CI 36–54%) for the diagnosis of invasive candidiasis. Repeated testing did not lead to any improvement in diagnostic accuracy, and the specificity and positive predictive value remained low. Adding BDG test results to a pre-specified multivariable regression model improved the model's performance, but the likelihood of a correct diagnosis was increased in only a small number of cases.

CONCLUSION: BDG testing had insufficient accuracy for the diagnosis of invasive candidiasis in high-risk ICU patients.

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AGE DIFFERENCE OF PATIENTS WITH AND WITHOUT INVASIVE ASPERGILLOSIS:

A SYSTEMATIC REVIEW AND META-ANALYSIS

BMC Infectious Diseases, 2024 February 19; 24(1):220

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BACKGROUND & AIM: Prompt diagnosis and treatment of patients with invasive aspergillosis (IA) is known to improve patient outcomes, but can be challenging due to the limited sensitivities of fungal diagnostic tests. Improved knowledge of risk factors that predispose individuals to IA is essential to facilitate its early recognition and the design of new, more specific management strategies. Studies to date have reported differing findings regarding whether patient age is an independent risk factor for the development of IA. The aim of this study was to explore the relationship between patient age and the development of IA.

STUDY DESIGN: Systematic review and meta-analysis.

ENDPOINT: Patient age.

METHOD: A systematic search of National Center for Biotechnology Information databases was performed, following PRISMA guidelines, to identify papers published up until October 2023 on IA or aspergillosis in general and associated risk factors. Age was not included as a keyword, to ensure that studies that reported age but did not identify it as a major risk factor were not missed. Risk of bias and quality were assessed using the Newcastle–Ottawa Scale. Pooled estimates were derived by random-effects meta-analysis with inverse-variance weighting. Sources of heterogeneity were assessed by meta-regression and subgroup analyses.

RESULTS: The 55 retrospective observational studies included in the final meta-analysis presented data on 13,983 patients. The mean age difference between patients who developed IA compared with patients who did not develop IA was +2.58 years (95% confidence interval 1.84–3.31, $p<0.0001$, $I^2=26.1\%$). Variability in observed effect sizes could not be explained by moderator variables. Subgroup analyses involving patients with severe pulmonary infections, haematological patients, and all other patients showed the mean age differences between those with and without IA to be 3.37 years (95% CI 2.46–4.27), 1.95 years (95% CI 0.41–3.49) and 1.58 years (95% CI 0.09–3.06), respectively. The difference between the subgroups was significant, suggesting that the difference in age between IA and non-IA patients was likely to be more substantial among patients with severe pulmonary infections than for other subgroups.

CONCLUSIONS: Patients with IA were on average 2.5 years older than those without IA. Further research is needed to determine whether age is an independent risk factor for IA.

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A SYSTEMATIC REVIEW OF THE THERAPEUTIC OUTCOME OF MUCORMYCOSIS

Open Forum Infectious Diseases, 2023 December 30; 11(1):ofad704

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BACKGROUND & AIM: Mucormycosis is an aggressive fungal infection that can lead to tissue necrosis, vascular thrombosis and dissemination. It is potentially lethal and is difficult to manage. The infection particularly affects transplant recipients and patients with malignancies. A rise in the global number of cases may be due to an increasing prevalence of diabetes, the use of new immune-modulating therapies, and/or increased awareness and diagnosis. The authors of this paper reviewed the case distribution, diagnosis, management and therapeutic outcomes of mucormycosis worldwide.

STUDY DESIGN: Systematic review.

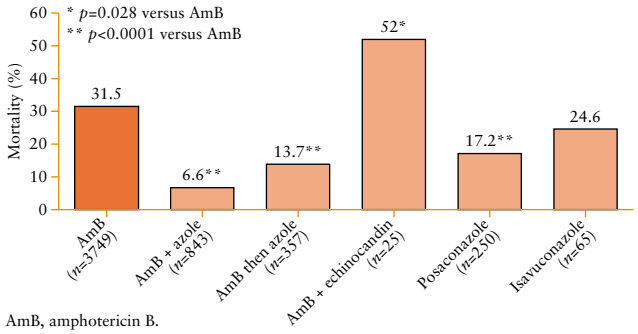
ENDPOINTS: Clinical characteristics, treatments and therapeutic outcomes.

METHOD: A search of Medline and Embase identified 126 articles (published between 2000 and 2022) describing a total of 10,335 patients with proven or probably mucormycosis (diagnosed according to EORTC/MSG criteria) and their therapeutic outcomes. Outcomes with different therapies were compared with amphotericin B alone, which was considered standard therapy.

RESULTS: The mean age range of patients was 12.6–62 years, 66% were males, and most (66%) were Asian. The most common underlying condition was diabetes (60%), followed by COVID-19 (17%) and haematological disease (16.4%); 2.1% of patients had no underlying disease. The most common clinical form of mucormycosis was rhino-orbitocerebral (69.3%), followed by pulmonary (10.3%), disseminated (5.8%), cutaneous (4.1%) and gastrointestinal (1.4%). Outcome data were available for 5364 patients. The most common treatment was amphotericin B monotherapy in 3749 patients (70%), with an associated mortality rate of 31.5%. Compared with amphotericin B monotherapy, lower mortality was seen with amphotericin B plus azole combination/sequential therapy and posaconazole monotherapy (figure). The mortality rate was significantly lower in patients who underwent surgical resection than in those who did not (37.6% versus 66.7%, p=0.008).

CONCLUSIONS: Mucormycosis is most frequent in Asia, and comorbid diabetes is common. Antifungal therapy is often effective, but survival may be further improved by surgical resection.

Mortality in patients with mucormycosis according to antifungal therapy



AmB, amphotericin B.

https://doi.org/10.1093/ofid/ofad704

ENDOGENOUS FUNGAL ENDOPHTHALMITIS:

A SINGLE-CENTER RETROSPECTIVE STUDY AND REVIEW OF THE LITERATURE

American Journal of Ophthalmology, 2024 January 26; 262:97–106

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BACKGROUND & AIM: The management of endogenous fungal endophthalmitis (EFE) can be challenging due to the small proportion of positive cultures among intraocular fluid samples (25%) and the lack of systemic manifestations of infection in some patients. Initial management is therefore often empirical, with infectious disease specialists working with an ophthalmologist to determine the best course of treatment. The authors evaluated practice patterns in the treatment of EFE, particularly regarding factors that inform systemic antifungal choices.

STUDY DESIGN: Single-centre, retrospective case series.

ENDPOINTS: Factors influencing systemic treatment, systemic therapy modification, surgical intervention, and presence of or improvement in vitritis or chorioretinitis.

METHOD: The medical charts of 16 patients (total of 20 eyes) diagnosed with EFE based on clinical examination by an ophthalmologist between 2010 and 2023 were reviewed. Data collected included clinical characteristics, culture/susceptibility results (including the serum Fungitell test), medical and surgical management, treatment modifications, and status of any vitritis or chorioretinitis.

RESULTS: Overall, seven (43.8%) patients tested positive for *Candida* species, six (37.5%) were culture-negative (two Fungitell positive) and three (18.8%) were positive for *Aspergillus* species. Vitritis and/or macula-involving chorioretinitis was present in 90% of eyes, but only 37.5% of patients had systemic symptoms at the time of evaluation. Seven patients (43.8%) were initially managed with intravenous (IV) antifungals (five with voriconazole and two with amphotericin B) and these patients were more likely to have a history of immune compromise, positive fungal culture, positive Fungitell assay or systemic symptoms. Initial oral antifungal treatment was used in the majority of *Candida* infections (63%) and culture-negative EFE (73%). More eyes initially treated with oral versus IV antifungals underwent surgical intervention (45.5% versus 11.1%), and vitritis improved more rapidly in eyes treated versus not treated with intravitreal antifungals (mean 8.7 versus 29 days). Systemic antifungal therapy modification was required in two patients due to worsening chorioretinitis: one case due to *Candida dubliniensis* infection which improved on switching from oral to IV fluconazole; the other due to voriconazole-resistant aspergillosis which improved on treatment with IV amphotericin B.

CONCLUSIONS: In EFE patients, the choice of initial systemic treatment was driven by immune compromise, positive cultures and systemic symptoms. Some patients required switching to, or modification of, systemic therapy due to worsening chorioretinitis.

https://doi.org/10.1016/j.ajo.2024.01.018

DIAGNOSTIC PERFORMANCE OF SERUM GALACTOMANNAN AND B-D-GLUCAN FOR INVASIVE ASPERGILLOSIS IN SUSPECTED PATIENTS: A META-ANALYSIS

Medicine, 2024 February 2; 103(5):e37067

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BACKGROUND & AIM: The early diagnosis and antifungal treatment of invasive aspergillosis (IA) is important to optimize patient survival, but a confirmed diagnosis relies on culture and histopathological examinations, which can be challenging in immunocompromised individuals. Non–culture-based diagnostic tools such as the detection of galactomannan (GM) and β-D-glucan (BG) have improved the diagnosis of IA, but reported sensitivity and specificity values vary between 30% and 90%. The aim of this meta-analysis was to evaluate the diagnostic performance of GM, BG and their combination as markers of symptomatic IA.

STUDY DESIGN: Meta-analysis.

ENDPOINTS: Diagnostic sensitivity and specificity.

METHOD: A search of PubMed, the Web of Science and Embase identified 16 studies evaluating the accuracy of GM and BG assessments for the diagnosis of IA. Using the data provided, patients were classified into four groups: proven IA, probable IA, possible IA and no IA. The combined performance of the GM and BG assays was evaluated based on positivity in both or either of the assays. Diagnostic parameters were pooled using a bivariate model, and the diagnostic performance of the tests used alone or in combination was compared.

RESULTS: Pooled sensitivity and pooled specificity values for serum GM and serum BG for the diagnosis of proven or probable IA are presented in the table. The sensitivity of BG assays was significantly greater than for the GM assays, while the specificity was higher for GM than for BG (both $p<0.05$). The area under the receiver operating characteristic curve (AUROC) values for serum GM and serum BG are also presented in the table; there was no significant difference between these values. Combining the GM and BG assays resulted in a pooled sensitivity that was significantly greater than for either test alone, while the specificity was lower (both $p<0.05$); see table. The AUROC value for the combination was not significantly different compared with the individual tests.

CONCLUSIONS: Serum GM and BG assays are similarly accurate in the diagnosis of IA in suspected patients. The diagnostic sensitivity can be improved by combining these markers.

Diagnostic performance of galactomannan (GM), β-D-glucan (BG) and their combination for the diagnosis of proven/probable invasive aspergillosis

Test	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	AUROC (95% CI)
GM	0.53 (0.40–0.66)	0.94 (0.91–0.97)[a]	0.90 (0.87–0.92)
BG	0.72 (0.61–0.81)[a]	0.82 (0.73–0.88)	0.83 (0.80–0.86)
GM/BG	0.84 (0.69–0.86)[b]	0.76 (0.69–0.81)[c]	0.83 (0.80–0.86)

[a] Significantly higher versus other individual test ($p<0.05$). [b] Significantly higher versus each individual test ($p<0.05$). [c] Significantly lower versus each individual test ($p<0.05$). AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

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MANAGEMENT OF POLYPHARMACY AND POTENTIAL DRUG–DRUG INTERACTIONS IN PATIENTS WITH PULMONARY ASPERGILLOSIS:

A 2-YEAR STUDY OF A MULTIDISCIPLINARY OUTPATIENT CLINIC

Journal of Fungi, 2024 January 26; 10(2):107

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BACKGROUND & AIM: Treatment of pulmonary aspergillosis with azole antifungals is often complicated by their potential for drug–drug interactions (DDIs), given the frequency with which such patients take concomitant medications. The aim of this study was to establish how common such interactions are in routine practice and whether therapeutic drug monitoring (TDM) of azoles or concomitant medications might be warranted.

STUDY DESIGN: Retrospective analysis.

ENDPOINTS: Incidence and type of clinically significant DDIs; incidence of sub-/super-therapeutic trough drug concentrations.

METHOD: Data on medication use for patients with pulmonary aspergillosis seen at a single hospital outpatient clinic between 2021 and 2023 were analysed by two experts. Potential DDIs were classified as red-/orange-/yellow-flag concerns according to their severity and clinical relevance. Where TDM of azoles (voriconazole, itraconazole or isavuconazole) was undertaken, levels outside the recommended therapeutic zone were identified. The experts subsequently provided recommendations to the attending physicians about whether changes to therapy were needed.

RESULTS: Among 34 patients with pulmonary aspergillosis (56% male, mean age 67 years), 18 (53%) received voriconazole, 14 (41%) isavuconazole and 2 (6%) itraconazole. In 24 patients the infection was chronic, in eight it was associated with COPD and in two it was invasive. Only one patient was not taking any concomitant medication; in the other 33, the mean number of medications was 7.2 (range 1–16). A total of 172 potential DDIs were identified (8% red-flag, 74% orange-flag, 18% yellow-flag), 49% involving antifungal drugs and 51% involving other drugs. Of 14 red-flag DDIs found, 10 (71%) involved voriconazole ($p<0.05$). The most common potential DDIs were a risk of QT prolongation (36%), impaired respiratory function (29%) and statin-related muscle toxicity (14%). The most common recommendations made were to implement TDM ($n=20$), perform electrocardiography ($n=17$) or change the dose of concomitant medication, most often to reduce or stop proton pump inhibitors ($n=15$) or inhaled corticosteroids ($n=8$). TDM findings were available for 16/18 patients taking voriconazole, 13/14 patients taking isavuconazole and 2/2 patients taking itraconazole. For voriconazole, 3 (19%) patients had trough levels below the therapeutic range and 2 (13%) above it, while for isavuconazole 2 (15%) were below and 2 (15%) above.

CONCLUSIONS: Undetected potential DDIs were common in patients being treated for pulmonary aspergillosis. Trough azole levels outside the recommended therapeutic range were also common.

https://doi.org/10.3390/jof10020107

LOWER BLOOD LEVELS OF ISAVUCONAZOLE IN CRITICALLY ILL PATIENTS COMPARED WITH OTHER POPULATIONS:

POSSIBLE NEED FOR THERAPEUTIC DRUG MONITORING

Journal of Antimicrobial Chemotherapy, 2024 April 2; 79(4):835–45

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BACKGROUND & AIM: Therapeutic drug monitoring is not routinely undertaken during therapy with isavuconazole, as clinical trial data suggested that blood levels are almost always above the minimum therapeutic level. However, critically ill patients in the intensive care unit (ICU) have been reported to have subtherapeutic levels, and factors responsible for this are not completely understood. The aim of this study was to compare isavuconazole blood levels between ICU and non-ICU patients and to identify factors predisposing to low levels.

STUDY DESIGN: Single-centre, retrospective analysis.

ENDPOINT: Isavuconazole trough blood level.

METHOD: The study analysed data for patients given standard isavuconazole therapy between January 2019 and October 2022 whose steady-state trough blood level of the drug was determined. Only data from the first month of therapy were included and patients were grouped according to whether they were in the ICU or not when isavuconazole was started.

RESULTS: Among 72 patients (68% male, median age 65 years) who had their isavuconazole trough levels measured at least once, 33 were treated in the ICU and 39 on a medical ward. ICU patients were more likely to have a body mass index >25 kg/m^2, to be given continuous renal replacement therapy, and to have a SARS-CoV-2 infection, but were much less likely to have an underlying haematological condition than non-ICU patients (9.1% versus 79.5%). During the first month, 188 determinations of trough isavuconazole level were made (mean 2.6 per patient), and ICU patients were found to have a median level of 1.98 mg/L compared with 4.10 mg/L in non-ICU patients (p<0.001). Among the ICU patients, 11/33 (33.3%) had trough levels that never reached 2 mg/L, compared with 3/39 (7.7%) of the non-ICU patients. Multivariable regression showed that location in the ICU was the most significant determinant of low isavuconazole level (p<0.001), followed by BMI >25 kg/m^2 (p=0.041) and a bilirubin level >1.2 mg/dL (p=0.045). Location remained significant if only the first 2 weeks of treatment, or only the first measurement, were considered.

CONCLUSIONS: Isavuconazole trough levels were lower in ICU patients versus non-ICU patients during the first month of treatment. Therapeutic drug monitoring of isavuconazole is warranted in ICU patients, and perhaps in patients with elevated BMI.

https://doi.org/10.1093/jac/dkae037

BEYOND THE FIRST YEAR: EPIDEMIOLOGY AND MANAGEMENT OF LATE-ONSET OPPORTUNISTIC INFECTIONS AFTER KIDNEY TRANSPLANTATION

Transplant International, 2024 February 26; 37:12065

AUTHORS: Esnault V, Hoisnard L, Peiffer B, Fihman V, Fourati S, Angebault C, Champy C, Gallien S, Attias P, Morel A, Grimbert P, Melica G, Matignon M
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BACKGROUND & AIM: Opportunistic infections (OI) affect up to a quarter of kidney transplant recipients, with the first 12 months post-transplant seen as a high-risk period. Standardized antimicrobial prophylaxis has reduced infections during this period, but late-onset OI remain a concern. The aim of this study was to characterize late infections after kidney transplant.

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

ENDPOINTS: Incidence of a first OI >12 months post-transplant (late-OI; primary endpoint); overall survival and graft survival; risk factors for late-OI.

METHOD: The study examined hospital records of all adult kidney transplant recipients between 2008 and 2018, excluding multi-organ transplants and those with graft failure within 30 days. Infection prophylaxis followed international guidelines throughout the study period. Post-transplant occurrence of any one of an agreed list of bacterial, viral, fungal and parasitic infections was taken as evidence of OI. Patients were grouped for analysis as having no OI, early-OI (<12 months) or late-OI.

RESULTS: During a mean of 68.7 months of follow-up of 954 kidney transplant recipients, 185 (19.4%) experienced an OI, of whom 65 (35.1%) had an early-OI (at a median of 4.4 months post-transplant) and 120 (64.9%) had a late-OI (at a median of 37.5 months). Late-OI were predominantly viral (69.2%) and fungal (20.8%), as were early-OI (58.5% and 27.7%, respectively). Late viral infections were mainly due to herpes zoster (43.4%), BK virus (18.1%) and cytomegalovirus (13.3%). Late fungal infections were more likely than early infections to be due to *Pneumocystis jirovecii* (48.0% versus 0%, p=0.002), but less likely to be invasive aspergillosis (12.0% versus 55.6%, p=0.01). Bacterial and parasitic infections were uncommon in both groups. Multivariate regression showed that late-OI was associated with a younger age at transplant (p=0.006) and a lower incidence of acute graft rejection (p=0.003). Comparing late-OI patients with 724 patients alive 12 months after transplant without an OI found similar overall survival at 36 months (94.5% versus 92.7%) and allograft survival (96.3% versus 93.8%).

CONCLUSIONS: Late-onset OI after kidney transplantation were more common in younger patients and were typically herpes zoster and *Pneumocystis jirovecii* infections, but did not significantly affect patient or graft survival.

https://doi.org/10.3389/ti.2024.12065

IMPACT OF CLIMATE CHANGE AND NATURAL DISASTERS ON FUNGAL INFECTIONS

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BACKGROUND & AIM: Climate change is having a significant effect on invasive fungal diseases. Fungi are adapting to increases in the Earth's temperature, and have become more virulent and potent, leading to changes in epidemiology and the emergence of new pathogens. Climate change has also affected the spread of endemic fungal diseases, while the evolution of fungal plant pathogens threatens global food security. Furthermore, the increased risk of natural disasters has led to global fungal outbreaks. This article reviews the impact of climate change and natural disasters on the risk of fungal diseases, as well as potential strategies for intervention.

ARTICLE TYPE: Review.

FINDINGS: While most fungi are not adapted to withstand mammalian body temperatures, rising environmental temperatures may result in them adapting to heat stress and therefore becoming more pathogenic in humans. Climate change can also affect host susceptibility to pathogenic fungi as average body temperatures are decreasing, further narrowing the thermal exclusion gradient between fungi and humans. A combination of factors has led to climate change influencing the epidemiology of fungal infections, including new emerging species, the spread of existing species to wider geographical endemic areas, and increased propagation. One example of an emerging species is *Candida auris*, which is hypothesized to have become pathogenic to humans by adapting to higher temperatures.

Historically, infections such as coccidioidomycosis and histoplasmosis have been endemic to specific geographical areas, but recent evidence shows a spread to previously non-endemic regions, and modelling data suggests they will continue to spread further. This may be due to fungi adapting to previously inhospitable environments such as polluted habitats and urban areas. Climate change can also affect the airborne dispersal of fungal spores (such as warmer temperatures resulting in increased atmospheric turbulence), which also affects the geographical distribution of pathogens. Temperature changes can also alter synchronization patterns of spore ejection.

Climate change has been associated with an increasing frequency of natural disasters, which often trigger fungal disease outbreaks via the creation of conditions conducive to fungal growth and fungal exposure, as well as the risk of traumatic injuries. These outbreaks have the greatest effects on populations who are socially vulnerable, and the diagnosis of invasive fungal disease may be compromised in disaster-affected regions.

CONCLUSIONS: Climate change has had a significant impact on the spread of fungal diseases. More awareness, research and funding are needed to improve prevention, detection and treatment.

https://doi.org/10.1016/S2666-5247(24)00039-9

MODELING INVASIVE ASPERGILLOSIS RISK FOR THE APPLICATION OF PROPHYLAXIS STRATEGIES

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BACKGROUND & AIM: It is important to be able to identify patients at high risk of invasive aspergillosis (IA) in order to administer prophylactic antifungal agents during their periods of high susceptibility. However, the optimal use of prophylaxis in this context is uncertain because published studies are limited by small sample sizes, retrospective designs and/or heterogeneous populations. In addition, IA risk in specific populations can change over time. This article describes a model using the Sankey approach that provides a visual model to help identify patient populations at risk of IA, the periods when their risk is highest, and therefore who may benefit from prophylaxis and when.

ARTICLE TYPE: Review.

FINDINGS: A Sankey diagram is a type of flow diagram in which nodes are used to represent specific variables, and the height of each node is proportional to the number of patients at risk. The change in risk between each node is shown as flow within the diagram, and this flow can be colour coded to represent other variables.

The diagram presented in this article displays IA risk, with nodes on the left-hand side representing patient populations with medical conditions such as malignancy, blood neoplasm or topical colonization that place them at risk for IA, and who may therefore be candidates for prophylaxis. Nodes on the right-hand side of the diagram represent the concluding level of immunocompromise and therefore the ultimate degree of risk. Nodes in the middle represent risk events such as therapies administered, with splits in the medical path depending on treatment responses. Each node height is related to the size of the risk group, and the colour of the nodes and flow between them represents the level of IA risk at that stage and whether prophylaxis may be required.

An internet-based version of such a diagram can be interactive, allowing users to expand the details within each node, and click through to links presenting the evidence supporting each change in flow and risk level. Populations at a high risk of IA during specific periods can then be targeted for antifungal prophylaxis of an appropriate intensity during those periods. The diagram is designed for use by a range of clinicians including infection disease physicians, haematologists, clinical caregivers and transplant surgeons, as well as outpatient services.

CONCLUSIONS: A Sankey diagram modelling IA risk has been designed to guide clinical decision-making regarding the use of prophylaxis, particularly in patients whose conditions and risk levels change over time.

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HIGH BURDEN OF COVID-19-ASSOCIATED PULMONARY ASPERGILLOSIS IN SEVERELY IMMUNOCOMPROMISED PATIENTS REQUIRING MECHANICAL VENTILATION

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BACKGROUND & AIM: Mechanically ventilated patients with severe COVID-19 frequently develop COVID-19–associated pulmonary aspergillosis (CAPA), leading to increased mortality. Since the introduction of COVID-19 vaccination, the proportion of patients with severe COVID-19 who are severely immunocompromised has increased. It is not known if this has affected the incidence of CAPA. This study investigated the impact of widespread COVID-19 vaccination and of EORTC/MSGERC host factors on the incidence and outcomes of CAPA among patients with severe COVID-19.

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

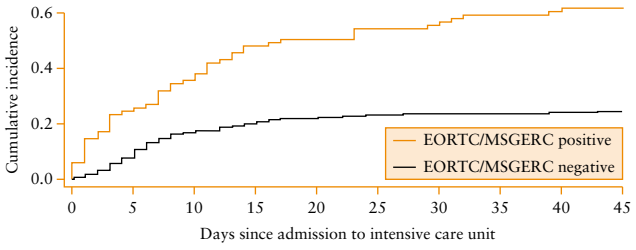
ENDPOINT: Diagnosis of probable or proven CAPA.

METHOD: The study used data for adults with severe COVID-19 admitted to the ICU for mechanical ventilation at a Belgian tertiary referral centre between March 2020 and November 2022. Probable or proven CAPA was diagnosed according to 2020 ECMM/ISHAM criteria, and the incidence was compared between the pre-vaccination and vaccination eras (cut-off 4 October 2021 for high vaccination prevalence) and between patients with versus without EORTC/MSGERC host factors for invasive mould disease.

RESULTS: Among 335 patients with severe COVID-19 disease, the overall incidence of CAPA was 33% (n=112). The incidence was higher among individuals with EORTC/MSGERC host factors (62%; 50/81) than in patients without such host factors (24%; 62/254) (p<0.001; figure). Moreover, the incidence of CAPA was significantly higher in the COVID-19 vaccination era (59%; 55/94) compared with the pre-vaccination era (24%; 57/541) (p=0.001). Binary logistic regression found that ICU admission in the vaccination era and the presence of EORTC/MSGERC host factors were both independently associated with the development of CAPA. Cox proportional hazards analysis showed that CAPA was independently associated with mortality during the vaccination era.

CONCLUSIONS: Among mechanically ventilated ICU patients with severe COVID-19, the incidence of CAPA increased in the COVID-19 vaccination era. This was mainly driven by an increase in the proportion of patients with EORTC/MSGERC host factors for invasive mould disease.

Incidence of CAPA in patients with versus without EORTC/MSGERC host factors for invasive mould disease



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IN VIVO PHARMACODYNAMIC CHARACTERIZATION OF A NEXT-GENERATION POLYENE, SF001, IN THE INVASIVE PULMONARY ASPERGILLOSIS MOUSE MODEL

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BACKGROUND & AIM: While the prevention and treatment of invasive pulmonary aspergillosis (IPA) has been improved by the development of mould-active triazoles, there are still therapeutic difficulties. Resistance to triazoles has been reported in some regions, and complicating factors such as drug–drug interactions and pharmacokinetic variability can limit the use of triazoles in some individuals. SF001 is a next-generation polyene with increased specificity to the ergosterol found in fungal membranes, and studies have shown that it has long-acting, broad-spectrum activity. The aim of the current study was to characterize the pharmacokinetic/pharmacodynamic relationships of SF001 against *Aspergillus fumigatus* using a neutropenic mouse model of IPA.

STUDY DESIGN: Animal experiments.

ENDPOINTS: Pharmacokinetic and pharmacodynamic characteristics.

METHOD: The experiments were performed using six isolates of *A. fumigatus*, including three with *CYP51* mutations and one with an *FKS1* mutation. The minimum inhibitory concentrations (MICs) of SF001 for each of these isolates were determined using a broth microdilution method. The mouse IPA model comprised neutropenic and immunosuppressed animals that were infected with *A. fumigatus* isolates using an aspiration pneumonia model. Drug treatment was administered 2 hours after infection, at SF001 doses of 0.25–64 mg/kg/day over 96 hours. Pulmonary fungal burden was assessed using real-time quantitative polymerase chain reaction. Plasma and epithelial lining fluid (ELF) pharmacokinetics were assessed following single intraperitoneal doses of SF001 at 1, 4, 16 and 64 mg/kg.

RESULTS: A dose-dependent reduction in pulmonary fungal burden was seen. The MICs of SF001 against the six isolates of *A. fumigatus* varied from 0.5 to 2.0 mg/L. Non-linear regression analysis showed strong 24-hour exposure–response relationships for the area under the concentration time curve:MIC ratio and for the free-drug maximum concentration (C_{max}):MIC ratio, for both plasma and ELF pharmacokinetic indices. The strength of these pharmacokinetic/pharmacodynamic relationships was indicated by coefficient of determination values of 0.75 for plasma and 0.74 for ELF. The median plasma C_{max}/MIC ratio needed to achieve a net static effect was 0.51 and to achieve a 1-log kill (1-$\log_{10}$ reduction in organism burden) was 0.66.

CONCLUSIONS: SF001 showed efficacy against wild-type, azole-resistant and echinocandin-resistant isolates of *A. fumigatus*. The pharmacodynamic/pharmacokinetic target exposures that were identified may help optimize future drug dosing regimens.

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