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on systemic fungal infections

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Clinical Infectious Diseases, 2020 August 29; Epub ahead of print

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Antimicrobial Agents and Chemotherapy, 2020 December 16; 65(1):e01511-20

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A NATIONAL STRATEGY TO DIAGNOSE CORONAVIRUS DISEASE 2019-ASSOCIATED INVASIVE FUNGAL DISEASE IN THE INTENSIVE CARE UNIT

Clinical Infectious Diseases, 2020 August 29; Epub ahead of print

AUTHORS: White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, Pandey M, Whitaker H, May A, Morgan M, Wise MP, Healy B, Blyth I, Price JS, Vale L, Posso R, Kronda J, Blackwood A, Rafferty H, Moffitt A, Tsitsopoulou A, Gaur S, Holmes T, Backx M
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BACKGROUND & AIMS: Secondary fungal infections are a known complication of respiratory virus infections. Fungal co-infection increases morbidity and mortality but can be treated effectively if it is diagnosed promptly. Invasive pulmonary aspergillosis has been reported in patients with severe respiratory distress due to coronavirus disease 2019 (COVID-19), but data are currently limited to small studies and case reports. The aims of this study were to evaluate the incidence, risk factors and impact of invasive fungal disease in adult patients with COVID-19 infection and severe respiratory distress.

STUDY DESIGN: Multicentre, prospective, cohort study.

ENDPOINTS: Incidence of, and risk factors for, invasive fungal infection in critically ill COVID-19 patients.

METHOD: A cohort of 135 adult patients in intensive care units who had refractory severe respiratory illness or deterioration of respiratory function 1 week after diagnosis of COVID-19 were screened for the presence of invasive fungal infections using an algorithm-guided testing strategy. Blood and deep respiratory samples were obtained for mycological evaluation to determine the presence of yeast and mould infections. Antifungal therapy was prescribed at the discretion of the treating physicians.

RESULTS: The median age of the cohort was 57 years, and the ratio of male to female patients was 2.2 to 1. The incidence of invasive fungal infection was 26.7%, with 14.1% of patients diagnosed with invasive pulmonary aspergillosis and 12.6% with invasive yeast infections. The overall mortality rate in the COVID-19 cohort was 38%. Mortality was significantly higher among patients with fungal co-infection compared to those without fungal disease (53% versus 31%, p=0.0387). Among patients with invasive fungal infection, treatment with appropriate antifungal agents significantly reduced mortality compared with those who did not receive such therapy (38.5% versus 90%, p=0.008); corresponding rates were 46.7% versus 100% among those with aspergillosis, and 27.3% versus 83.3% among those with invasive yeast infections. A history of chronic respiratory disease (p=0.05) and use of high-dose systemic corticosteroids (p=0.007) increased the risk of aspergillosis. No significant risk factors for yeast infections were identified.

CONCLUSIONS: Invasive fungal disease was common among COVID-19 patients with severe respiratory distress. Antifungal therapy improved survival. These results suggest that critically ill COVID-19 patients should be screened for invasive fungal disease, and those with risk factors should receive antifungal prophylaxis.

HOW LONG DO WE NEED TO TREAT AN INVASIVE MOLD DISEASE IN HEMATOLOGY PATIENTS?

FACTORS INFLUENCING DURATION OF THERAPY AND FUTURE QUESTIONS

Clinical Infectious Diseases, 2020 July 27; 71(3):685–92

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BACKGROUND & AIM: Long-term antifungal therapy is often used to treat invasive mould disease (IMD) in patients with haematological cancer, but prolonged antifungal use can increase the risk of toxicity, drug interactions and the development of resistant fungi, as well as having cost implications. The optimal duration of antifungal therapy in this population is not standardized, and involves several complex and inter-related factors. Concerns about IMD relapse during chemotherapy or treatment for graft-versus-host disease (GvHD) sometimes means that antifungal therapy is prolonged indefinitely. This article reviews key issues influencing the decision on when to stop antifungal therapy for IMD in patients who have undergone chemotherapy or transplantation for the treatment of a haematological malignancy.

ARTICLE TYPE: Review.

FINDINGS: An important risk factor for the relapse of previously controlled IMD is a compromised immune system, which may result from the underlying disease or the treatment administered. Immunosuppression can be due to prolonged neutropenia, relapsed or refractory leukaemia, haematopoietic stem-cell transplantation (HSCT), GvHD, or treatment with small-molecule kinase inhibitors that target immune-signalling pathways. In addition, the type of mould infection might influence how long it persists in tissues, and therefore how likely it is to relapse after discontinuation of antifungal therapy. The extent of lung infection can also affect the risk of relapse; involvement of more than one pulmonary lobe or dissemination outside the lung increases the risk of relapse. Other potential risk factors for IMD relapse include viral or bacterial coinfections, and comorbidities such as diabetes mellitus, malnutrition or iron overload.

Computed tomographic (CT) imaging is the most commonly used technique for guiding treatment decisions in pulmonary IMD, but there is not yet a prognostic cut-off for changes in lung lesion size that predict no IMD relapse after stopping antifungal therapy. However, there is now evidence that the addition of ^{18}fluoro-2-deoxy-D-glucose positron emission tomography to multidetector CT (FDG-PET/CT) can help discriminate between active and residual fungal lesions, and therefore aid decisions about stopping therapy.

The authors propose an algorithm to determine when to stop antifungals in patients with invasive aspergillosis (the most common IMD). This includes assessments of polymorphonuclear cells, fungal biomarkers and signs/symptoms of active IMD, as well as CT results and HSCT status, with the use of FDG-PET/CT in equivocal cases.

CONCLUSION: An individualized approach is necessary to determine the duration of antifungal therapy for IMD in patients with a haematological malignancy.

RISK FACTORS FOR RESPIRATORY *ASPERGILLUS FUMIGATUS* IN GERMAN CYSTIC FIBROSIS PATIENTS AND IMPACT ON LUNG FUNCTION

Scientific Reports, 2020 November 4; 10(1):18999

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BACKGROUND & AIM: Infection of the lungs by *Pseudomonas aeruginosa* is common in patients with cystic fibrosis (CF) and may be chronic, requiring prolonged antibiotic treatment. Infection by fungi such as *Aspergillus fumigatus* can also occur, and may accompany *P. aeruginosa* infection. However, the consequences of such fungal infections are not well delineated. The aim of this study was to gain a better understanding of the frequency and impact of *A. fumigatus* colonization in patients with CF.

STUDY DESIGN: Retrospective registry analysis.

ENDPOINTS: Prevalence of, and risk factors for, persistent lung colonization by *A. fumigatus*.

METHOD: Data were examined from all patients included in the German Cystic Fibrosis Registry during 2016 and 2017 who had not had a lung transplant. Subgroup analyses were conducted on those with at least two clinic visits involving antifungal diagnostic evaluation showing zero, one, or a minimum of two positive results for *A. fumigatus* (indicating no, transient or persistent colonization, respectively). Data from 2016 and 2017 were analysed separately; results for 2017 are summarized here.

RESULTS: *A. fumigatus* colonization increased with increasing age in the overall cohort in 2017 (n=5665), averaging 25.5% and plateauing at approximately 30% from the age of 18. Among those with two or more clinic visits in that year (n=4153), 13.9% had two or more positive *A. fumigatus* cultures, indicating persistent colonization, and 7.4% had allergic bronchopulmonary aspergillosis. Patients with persistent colonization had a higher prevalence of CF-related diabetes and liver disease (both p<0.0001) and arthritis/arthrosis (p<0.05) compared with uncolonized patients. They were also more likely to experience pulmonary exacerbations requiring antibiotic treatment and were more likely to be diagnosed with *P. aeruginosa* co-infection (both p<0.0001). Among patients without chronic *P. aeruginosa* infection, those with persistent *A. fumigatus* colonization had worse lung function than uncolonized patients (p<0.0001). In multivariate regression analysis, greater age was the most significant risk factor for persistent colonization (e.g. odds ratio 10.75, 95% confidence interval 6.23–18.57, for those aged 21–30 versus age ≤10 years, p<0.0001), followed by continuous antibiotic treatment (OR 2.29, 95% CI 1.71–3.06, p<0.0001). Other clinical factors such as pancreatic insufficiency, genotype and use of CFTR modulators were not consistent risk factors across both study years.

CONCLUSIONS: Age and continuous antibiotic use were significant risk factors for persistent *A. fumigatus* colonization, which was common among patients with CF.

POINT OF CARE ASPERGILLUS TESTING IN INTENSIVE CARE PATIENTS

Critical Care, 2020 November 10; 24(1):642

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BACKGROUND & AIM: Invasive pulmonary aspergillosis (IPA) can be difficult to diagnose owing to the non-specific nature of the clinical symptoms and imaging characteristics. *Aspergillus* lateral flow tests, developed to expedite IPA diagnosis, have yielded encouraging results using bronchoalveolar lavage fluid (BALf) samples from haematology patients. The aim of this study was to evaluate the effectiveness of the IMMY lateral flow assay (LFA) for the diagnosis of IPA among intensive care unit (ICU) patients.

STUDY DESIGN: Retrospective clinical study.

ENDPOINTS: Assay performance characteristics.

METHOD: Performance of the IMMY *Aspergillus* galactomannan LFA was evaluated using leftover BALf samples from 178 adult patients from two university hospital ICUs. IPA was defined according to the 2008 European Organization for Research and Treatment of Cancer Mycoses study group (EORTC-MSG), AspICU and modified AspICU criteria, all of which encompass microbiological and radiological findings as well as patient characteristics. Researchers blinded to the final clinical diagnosis and IPA classification read the LFA visually and using a digital reader.

RESULTS: Among the 178 patients, 55 were classified as having IPA, as follows: six proven and 26 probable cases according to the EORTC-MSG criteria plus another 23 cases according to the modified AspICU criteria. The original AspICU criteria, which include *A. fumigatus* culture positivity as a criterion for probable or putative IPA, identified six cases of proven and 12 cases of putative IPA. The LFA had good sensitivity and specificity whichever IPA diagnostic criteria were used (table). Values for the area under the receiver operating characteristic curve for the LFA indicated good overall performance. Digital readout of the LPA increased the sensitivity and negative predictive value compared to visual readout.

CONCLUSION: The IMMY LFA test performed well as a rapid diagnostic test for IPA in ICU patients.

Diagnostic performance characteristics of the IMMY lateral flow assay (digital readout), according to the criteria used to define invasive pulmonary aspergillosis

Disease definition criteria	Sensitivity (95% CI)	Specificity (95% CI)	Negative predictive value (95% CI)	Positive predictive value (95% CI)	AUC-ROC
EORTC-MSG	0.88 (0.71–0.96)	0.81 (0.73–0.88)	0.94 (0.86–0.97)	0.67 (0.58–0.75)	0.920
AspICU	0.94 (0.73–1.00)	0.81 (0.73–0.88)	0.97 (0.84–1.00)	0.68 (0.60–0.76)	0.939
Modified AspICU	0.87 (0.76–0.95)	0.81 (0.73–0.88)	0.94 (0.88–0.97)	0.67 (0.58–0.75)	0.904

AUC-ROC = area under the receiver operating characteristic curve; CI = confidence interval.

MULTIDRUG-RESISTANT *CANDIDA AURIS* INFECTIONS IN CRITICALLY ILL CORONAVIRUS DISEASE PATIENTS, INDIA, APRIL–JULY 2020

Emerging Infectious Diseases, 2020 November; 26(11):2694–6

AUTHORS: Chowdhary A, Tarai B, Singh A, Sharma A
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BACKGROUND & AIM: Concerns regarding hospital-acquired infections in critically ill patients with coronavirus disease 2019 (COVID-19) have been highlighted in reports from China and New York. *Candida auris* can cause nosocomial outbreaks, and although bloodstream infections with *Candida* species have not been documented in COVID-19 patients undergoing prolonged intensive care unit (ICU) stays, there is the potential for nosocomial spread of *C. auris* due to the rapid expansion of critical care facilities during the pandemic. The aim of this study was to report bloodstream infections caused by multidrug-resistant *C. auris* in an ICU treating COVID-19 patients in New Delhi, India.

STUDY DESIGN: Observational study.

ENDPOINTS: *C. auris* infection and multidrug resistance.

METHOD: The study included all patients with confirmed COVID-19 admitted to one ICU in New Delhi between April and July 2020. In patients with detected candidaemia, data on baseline demographics, medical history, laboratory parameters, microbiological findings, treatments and concomitant antimicrobial drug use were collected. The specific *Candida* species were identified and antifungal susceptibility testing was performed.

RESULTS: Among 596 patients with COVID-19 admitted to the ICU, 15 (2.5%) had candidaemia, of whom 10 (67%) had *C. auris* as the predominant organism. These 10 patients were mostly male and elderly with underlying chronic conditions such as hypertension, diabetes mellitus and chronic kidney or liver disease. All 10 had been in the ICU for prolonged periods (20–60 days), with indwelling central lines and urinary catheters, and five of them received medical ventilation due to severe COVID-19 pneumonia. The candidaemia caused by *C. auris* developed 10–42 days after admission and the fatality rate was 60%. Overall, 70% of the *C. auris* isolates were multidrug resistant (including 30% that were resistant to three drug classes), and 30% were multiazole (fluconazole plus voriconazole) resistant. However, all of the isolates were susceptible to echinocandins.

CONCLUSIONS: Candidaemia was identified in 2.5% of COVID-19 patients admitted to an ICU in New Delhi. Two-thirds of affected patients had *C. auris*, and 60% of those infected with *C. auris* died. Multidrug resistance was common among *C. auris* isolates. Extra caution is warranted during the COVID-19 pandemic in areas where *C. auris* is prevalent.

DRUG-RESISTANT *ASPERGILLUS FLAVUS* IS HIGHLY PREVALENT IN THE ENVIRONMENT OF VIETNAM:

A NEW CHALLENGE FOR THE MANAGEMENT OF ASPERGILLOSIS?

Journal of Fungi, 2020 November 18; 6(4):296

AUTHORS: Duong TM, Nguyen PT, Le TV, Nguyen HL, Nguyen BN, Nguyen BP, Nguyen TA, Chen SC, Barrs VR, Halliday CL, Sorrell TC, Day JN, Beardsley J
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BACKGROUND & AIM: Infection with *Aspergillus* causes many diseases, most commonly chronic pulmonary aspergillosis. Such infections are generally treated using antifungals, but the emergence of azole-resistant strains is threatening the efficacy of therapy. Azole resistance to *A. fumigatus*, the most common causative agent of *Aspergillus* infections, is well described, but little is known about the resistance of other species, such as *A. flavus*, to antifungal agents. The *A. flavus* complex appears to be well-adapted to hot and humid conditions and is the predominant *Aspergillus* species among clinical isolates from Asia, the Middle East and Africa. The aim of this study was to determine the prevalence of azole resistance in environmental *A. flavus* isolates from a rural province of southern Vietnam.

STUDY DESIGN: Environmental study.

ENDPOINTS: Prevalence of azole resistance; minimal inhibitory concentration (MIC) ranges and geometric means.

METHOD: Environmental samples (*n*=450) were taken from 150 locations in Ca Mau, Vietnam between January and March 2019. *A. flavus* isolates were identified morphologically, confirmed by sequencing of the beta-tubulin gene, and tested for susceptibility to azoles and amphotericin B according to EUCAST methodologies.

RESULTS: *A. niger* (99 isolates, recovery rate 22%), *A. flavus* (64 isolates, 14%) and *Aspergillus fumigatus* (54 isolates, 12%) were the three most commonly isolated *Aspergillus* species. Among 35 confirmed *A. flavus* isolates, 77.1% were resistant to posaconazole, 48.6% to itraconazole, 17.1% to voriconazole and 25.7% to amphotericin B. Overall, more than 85% of *A. flavus* isolates were resistant to one or more azole. MIC geometric means for posaconazole, itraconazole, voriconazole and amphotericin B were 0.91, 1.52, 2.16 and 4 mg/L respectively; corresponding MIC ranges were 0.5–2, 1–8, 1–4 and 2 to >16 mg/L. These MIC values are higher than those reported for other countries in recent surveys (table).

CONCLUSIONS: The prevalence of azole resistance among *A. flavus* in Vietnam was unexpectedly high. Further work is needed to elucidate the drivers of resistance in this particular *Aspergillus* species.

Minimum inhibitory concentration (MIC) values for *Aspergillus flavus* environmental isolates from Ca Mau, Vietnam and from recent surveys in other countries

	Geometric mean (range) MIC, mg/L			
	Itraconazole	Posaconazole	Voriconazole	Amphotericin B
Vietnam	1.52 (1–8)	0.91 (0.5–2)	2.16 (1–4)	4 (2 to >16)
Brazil	1.41 (0.5–8)	0.188 (0.03–0.25)	1.017 (0.5–2)	– (–)
Iran	0.25 (0.031–2)	0.13 (0.03–0.5)	0.55 (0.063–2)	3.4 (1–16)
India	0.06 (0.03–0.125)	0.022 (0.015–0.06)	0.5 (0.15–1)	– (–)
Europe	– (0.03–0.25)	– (0.06–0.125)	– (0.125–0.25)	– (–)

MICs were obtained using EUCAST methodology except for Europe where the Sensititre YeastOne panel was used.

INVASIVE DERMATOPHYTE INFECTION:
A SYSTEMATIC REVIEW

Mycoses, 2020 November 20; Epub ahead of print

AUTHORS: Wang R, Huang C, Zhang Y, Li R
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BACKGROUND & AIM: Dermatophyte infections generally present as superficial fungal infections of the outer layer of the skin, nails and hair (e.g. tinea pedis, tinea corporis, onychomycosis, tinea capitis). Rarely, some dermatophytes penetrate the stratum corneum, giving rise to invasive infections of the hair follicles, dermis, subcutaneous tissue and, sometimes, lymph nodes, bone and brain. Invasive infections usually occur in patients who are immunosuppressed or who have lymphoproliferative disorders, genetic predispositions, chronic superficial fungal infections, diabetes or atopic dermatitis. The authors undertook a systematic review of all cases of invasive dermatophytosis reported during the last 20 years.

STUDY DESIGN: Systematic review.

ENDPOINTS: Characteristics, risk factors, diagnosis and treatment.

METHOD: A search of PubMed/Medline, EMBASE and Web of Science (2000–2020) for articles reporting individual patients with a confirmed diagnosis of an invasive dermatophytosis identified 123 papers reporting on 160 cases (103 male). Diagnoses were reconfirmed, based on clinical features and histopathological findings.

RESULTS: Overall, 52 patients (32.5%) had Majocchi's granuloma, 89 (55.6%) had deeper dermal dermatophytosis, 11 (6.9%) had pseudomycetoma and 8 (5.0%) had disseminated dermatophytosis. Risk factors included superficial dermatophytosis (56.9%), solid-organ transplantation (26.9%), topical immunosuppressant use (15.6%), genetic mutations (14.4%) and diabetes mellitus (14.4%). The most prevalent pathogen was *Trichophyton rubrum* (53.1%), followed by *T. mentagrophytes* (7.5%), *Microsporum canis* (6.9%), *T. tonsurans* (5.6%), *T. interdigitale* (5.0%) and *T. violaceum* (3.8%). Genetic mutations, identified in 23 (14.4%) patients, included 22 autosomal recessive *CARD9* mutations and one heterozygous *STAT3* mutation. Patients with these mutations were more likely than those without mutations to have mixed infections involving two or more dermatophytes (17.4% versus 2.8%, $p<0.05$). The overall mortality rate due to invasive dermatophytosis was 7.9% (17.4% and 5.5% in those with and without mutations, respectively). Most patients without mutations responded well to oral antifungal therapy, with complete resolution of infection seen in 84.3%. The prognosis was poorer in patients with mutations, who were more likely to require lifelong combined antifungal therapy to stabilize the infection.

CONCLUSIONS: Early recognition and treatment of invasive dermatophytosis is important. Superficial dermatophytosis, immunosuppression and genetic mutations are predisposing factors, and such patients should receive preventive therapy.

THE GLOBAL INCIDENCE AND DIAGNOSIS OF FUNGAL KERATITIS

The Lancet Infectious Diseases, 2020 October 22; Epub ahead of print

AUTHORS: Brown L, Leck AK, Gichangi M, Burton MJ, Denning DW
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BACKGROUND & AIM: Fungal keratitis (mycotic keratitis/keratomycosis/oculomycosis) is a severe infection of the cornea that, if not treated, can lead to mono-ocular blindness and eye loss. Early diagnosis and treatment can dramatically improve the prognosis for infected patients and can preserve vision. The disease is most prevalent in tropical and subtropical locations, and affected individuals tend to be young agricultural workers of low socioeconomic status who have suffered an injury to the eye. Although it is common, the global incidence of fungal keratitis has yet to be determined. The aim of this review was to evaluate the diagnosis, incidence and global burden of fungal keratitis.

ARTICLE TYPE: Review.

FINDINGS: A systematic literature search identified 116 studies reporting the incidence of fungal keratitis as a proportion of microbial keratitis and 18 reporting the incidence in a defined population. Using an adapted GRADE score, the authors estimated the minimum incidence of fungal keratitis to be 1,051,787 cases (±30%) per year, with an annual incidence rate of 23.6 per 100,000 population. The highest incidence rates were in Asia and Africa. If all culture-negative cases were assumed to be fungal, the incidence would rise to 1,480,916 cases per year.

Diagnosis is based on assessment of the history, symptoms, preceding events and risk factors. Symptoms (such as blurred vision, eye pain, excessive tearing) are non-specific, but the duration of symptoms associated with fungal infections is typically longer (5–10 days) than for other forms of infectious keratitis.

In most of the studies reviewed, both microscopy and culture were used to diagnose the condition. Among the stains used for microscopic evaluation, calcofluor-white with florescence microscopy has been shown to have greater sensitivity for the diagnosis of fungal keratitis than potassium hydroxide, Giemsa, lactophenol cotton blue and Gram stain.

Patients with fungal keratitis are initially managed medically with specific topical or systemic antifungal drugs and non-specific supportive measures. The use of topical 5% natamycin is associated with an adequate response in 75% of mild or moderately infected corneas and 60% of those with severe infection. Surgery may be required in some cases. It is estimated that about 100,000 eyes are removed annually because of late diagnosis and inadequate treatment response.

CONCLUSIONS: Fungal keratitis is a debilitating condition associated with high morbidity, but it is usually treatable with generic antifungal therapy provided it is diagnosed early.

THE ONE HEALTH PROBLEM OF AZOLE RESISTANCE IN *ASPERGILLUS FUMIGATUS*:

CURRENT INSIGHTS AND FUTURE RESEARCH AGENDA

Fungal Biology Reviews, 2020; 34(4):202–14

AUTHORS: Verweij PE, Lucas JA, Arendrup MC, Bowyer P, Brinkmann AJ, Denning DW, Dyer PS, Fisher MC, Geenen PL, Gisi U, Hermann D, Hoogendijk A, Kiers E, Lagrou K, Melchers WJ, Rhodes J, Rietveld AG, Schoustra SE, Stenzel K, Zwaan BJ, Fraaije BA
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BACKGROUND & AIM: Azole antifungal agents play an important role in the management of fungal diseases in plants, animals and humans. Evidence of resistance to azole antifungals in *Aspergillus fumigatus* – a common cause of fungal diseases such as invasive aspergillosis – is growing and is of concern. Azole fungicides, such as sterol 14α-demethylation inhibitor (DMI) fungicides, are widely used in the environment, and this has been identified as a possible route for the development of resistance in *A. fumigatus*. In 2019, a meeting was convened during which experts representing a range of interested parties (medical and agricultural researchers, government representatives, public health bodies, fungicide producers and end-users) reviewed current evidence for azole resistance selection. A One-Health problem approach was used to outline research and measures needed in order to retain the effectiveness of the azole class for medical and non-medical applications. This article provided an overview of the findings from the meeting.

ARTICLE TYPE: Review.

FINDINGS: Overall, experts accepted that the selection of azole resistance in *A. fumigatus* is an unintended adverse effect of the use of DMI fungicides in the environment. Given the importance of azole antifungals to medicine, immediate action is required.

However, many questions remain to be answered, including the population dynamics of resistance selection in the environment, and the mutation frequency of *A. fumigatus* within a hotspot environment and how this is related to the specific azole the mould is exposed to. Hotspots are defined as areas in which conditions favour fungal growth and spread (allowing completion of the fungal life cycle) and in which azoles are present. Only a limited number have been identified, including flower bulb waste, green waste processing and wood chippings (all characterized by decaying plant waste). How hotspots contribute to the development of resistance is not fully understood.

Although the relation between DMI usage and azole-resistant *A. fumigatus* infection has yet to be explicitly proven, experts considered the evidence to be sufficient to justify bringing in appropriate interventive measures aimed at reducing the development of azole resistance in the environment. Further work is needed to determine how current practices can be amended to achieve this.

CONCLUSIONS: The development of azole resistance in *A. fumigatus* is a global problem with important medical consequences. The main aim of ongoing research should be to preserve the effectiveness of this class of antifungal agents for medical and environmental applications.

PHARMACODYNAMICS OF POSACONAZOLE IN EXPERIMENTAL INVASIVE PULMONARY ASPERGILLOSIS:

UTILITY OF SERUM GALACTOMANNAN AS A DYNAMIC ENDPOINT OF ANTIFUNGAL EFFICACY

Antimicrobial Agents and Chemotherapy, 2020 November 9; Epub ahead of print

AUTHORS: Gastine S, Hope W, Hempel G, Petraitiene R, Petraitis V, Mickiene D, Bacher J, Walsh TJ, Groll AH
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BACKGROUND & AIM: *Aspergillus* galactomannan antigenemia is an accepted biomarker for the diagnosis of invasive pulmonary aspergillosis (IPA) in neutropenic patients. However, it has yet to be determined whether serum galactomannan index (GMI) can be used as a surrogate marker of the success of antifungal treatment. The aim of this study was to investigate the pharmacokinetics and pharmacodynamics of posaconazole in an experimental model of IPA using GMI as a dynamic endpoint of antifungal response.

STUDY DESIGN: *In vivo* pharmacokinetic study.

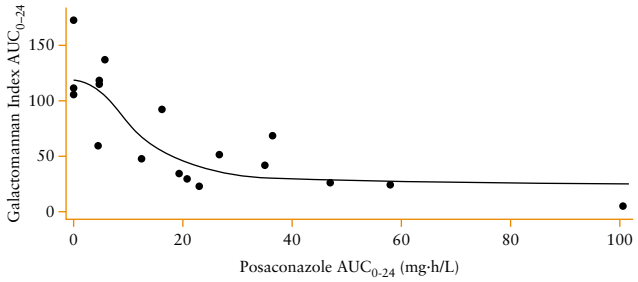
ENDPOINTS: Steady-state pharmacokinetic parameters; serum GMI level.

METHOD: The pharmacokinetics and pharmacodynamics of therapeutic and prophylactic posaconazole at doses of 2–20 mg/kg/day were investigated in a persistently neutropenic rabbit model of *Aspergillus fumigatus* IPA. Steady-state pharmacokinetic data were obtained using sparse plasma sampling. Serum GMI, animal survival and fungal tissue burden were recorded every other day. Data were compiled into a non-parametric pharmacokinetic/pharmacodynamic model.

RESULTS: Posaconazole was effective in the prophylaxis and treatment of experimental IPA. The pharmacokinetics of posaconazole were best described by a one-compartment model with linear elimination. The pharmacokinetic/pharmacodynamic relationship between posaconazole exposure and evolution of the GMI was best described by a Hill function-based dynamic model of growth and kill of *A. fumigatus*. In the treatment setting, estimates of steady-state area under the concentration–time curve from 0 to 24 hours ($AUC_{0–24}$) for posaconazole and GMI revealed that the posaconazole-GMI exposure-response relationship was sigmoidal (figure), with an asymptote forming above an $AUC_{0–24}$ of 30 mg·h/L, associated with significant resolution of the GMI and fungal eradication. In the prophylaxis setting, fungal burden and GMI were controlled by all doses of posaconazole.

CONCLUSIONS: The effects of posaconazole in experimental IPA were adequately described by a non-parametric pharmacokinetic/pharmacodynamic model. A posaconazole $AUC_{0–24}$ of >30 mg·h/L was identified as the threshold for treatment success.

Relationship between posaconazole exposure and the galactomannan index in the treatment of experimental invasive pulmonary aspergillosis



$AUC_{0–24}$ = area under the concentration–time curve from 0 to 24 hours.

ISAVUCONAZOLE THERAPEUTIC DRUG MONITORING DURING LONG-TERM TREATMENT FOR CHRONIC PULMONARY ASPERGILLOSIS

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BACKGROUND & AIMS: Isavuconazole is the newest triazole antifungal approved for the treatment of invasive aspergillosis and mucormycosis. Therapeutic drug monitoring is not currently recommended for isavuconazole because it has predictable pharmacokinetics and plasma concentration does not appear to correlate with efficacy or toxicity. However, the real-world situation may differ from clinical trials. There are also still questions around its safety in the long term and about appropriate drug levels in immunocompetent patients such as those with chronic pulmonary aspergillosis (CPA). This study therefore evaluated the pharmacokinetics and tolerability of isavuconazole in patients with CPA over the long term.

STUDY DESIGN: Retrospective cohort study.

ENDPOINTS: Adverse events and dose adjustments in routine clinical practice.

METHOD: The study included 45 patients (mean age 64 years) diagnosed with CPA and treated with isavuconazole in routine clinical practice between 2015 and 2020, all of whom underwent therapeutic drug monitoring. They were identified from the UK National Aspergillosis Centre database. Adverse events were classified using CTCAE v5.0. Binary logistic regression was used to determine predictors of high drug levels (>6 mg/L) and adverse events, while receiver operating characteristic analysis was used to assess the drug level predictive of toxicity.

RESULTS: Isavuconazole was administered for a mean of 408.5 days (range 18–1473). A total of 285 isavuconazole blood levels were measured in the cohort (mean 6.3 measurements per patient). The mean blood level was 4.1 mg/L overall, 4.6 mg/L in those receiving 200 mg daily and 3.7 mg/L in those receiving 100 mg daily. A high drug level (>6 mg/L) was recorded on 36 occasions (13%), and was more common in older than younger patients, and in those on a daily dose of 200 mg versus 100 mg. Both older age and higher daily dose remained significant independent predictors of a high isavuconazole level on multivariate analysis (p=0.012 and p=0.02, respectively). A total of 25 patients (56%) experienced adverse events. These individuals had a higher mean drug level at the first measurement than did those without adverse events (5.5±2 versus 4.2±1.7 mg/L, p=0.032). The cut-off threshold best predictive of the presence of an adverse event was 4.6 mg/L.

CONCLUSIONS: Isavuconazole was reasonably well tolerated over several years in patients with CPA. A daily dose of 100 mg was tolerated better than the standard dose of 200 mg and was still associated with adequate drug levels.