FramingHam

on systemic fungal infections

Invasive pulmonary aspergillosis goes viral again?
American Journal of Respiratory and Critical Care Medicine, 2021 February 1; 203(3):275–7

Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial
The Lancet, 2021 February 6; 397(10273):499–509

Azole resistance in *Aspergillus fumigatus*: a five-year follow up experience in a tertiary hospital with a special focus on cystic fibrosis
Frontiers in Cellular and Infection Microbiology, 2021 February 18; 10:613774

Factors associated with coinfections in invasive aspergillosis: a retrospective cohort study
Clinical Microbiology and Infection, 2021 March 2: Epub ahead of print

Diagnostic value of galactomannan test in non-immunocompromised critically ill patients with influenza-associated aspergillosis: data from three consecutive influenza seasons
European Journal of Clinical Microbiology & Infectious Diseases, 2021 April 10; Epub ahead of print

Performance of existing definitions and tests for the diagnosis of invasive fungal diseases other than invasive candidiasis and invasive aspergillosis in critically ill, adult patients: a systematic review with qualitative evidence synthesis
Journal of Fungi, 2021 February 28; 7(3):176

Are we ready for nosocomial *Candida auris* infections? Rapid identification and antifungal resistance detection using MALDI-TOF mass spectrometry may be the answer
Frontiers in Cellular and Infection Microbiology, 2021 March 16; 11:645049

MSG07: an international cohort study comparing epidemiology and outcomes of patients with *Cryptococcus neoformans* or *Cryptococcus gattii* infections
Clinical Infectious Diseases, 2021 March 27; Epub ahead of print

ISSUE 2, 2021

Breakthrough mucormycosis developing on Mucorales-active antifungals portrays a poor prognosis in patients with hematologic cancer

Journal of Fungi, 2021 March 17; 7(3):217

COVID-19–associated pulmonary aspergillosis, March–August 2020

Emerging Infectious Diseases, 2021; 27(4):1077–86

COVID-19 associated pulmonary aspergillosis in mechanically ventilated patients

Clinical Infectious Diseases, 2021 March 9; Epub ahead of print

Performance, correlation and kinetic profile of circulating serum fungal biomarkers of invasive aspergillosis in high-risk patients with hematologic malignancies

Journal of Fungi, 2021 March 13; 7(3):211

CURRENT TITLES

Framingham *on anaesthesiology and surgery*

Framingham *on atherosclerosis*

Framingham *on benign haematology*

Framingham *on cystic fibrosis*

Framingham *on dermatology*

Framingham *on diabetes*

Framingham *on fertility*

Framingham *on gastroenterology*

Framingham *on head and neck cancer*

Framingham *on haematological malignancies*

Framingham *on HIV/AIDS*

Framingham *on lung cancer*

Framingham *on multiple myeloma*

Framingham *on multiple sclerosis*

Framingham *on osteoporosis*

Framingham *on ovarian cancer*

Framingham *on rheumatology*

Framingham *on urology*

and many more...

DISCLAIMER

The abstracts in this publication are prepared with care to reflect the views expressed by the author or authors of the original source material. These views are not necessarily those of the publisher or the sponsor. While every care is taken to avoid errors, these cannot always be avoided; readers are advised to independently validate any data and recommendations contained herein before acting on this information. The publisher and the sponsor disclaim any responsibility or liability for the accuracy of such information.

ADVISORY BOARD

OUR PURPOSE

The Framingham series of publications is designed to meet clinical specialists' need for a reliable guide to the most important articles appearing in their field.
Each issue presents an authoritative selection from the recently published literature, with the emphasis on evidence-based medicine. Articles are recommended for inclusion by Framingham's editorial office and an advisory board headed by key opinion leaders in the relevant clinical area.
Framingham's team of medical writers prepares original abstracts of these articles, in a structured format that presents the main points at a glance. Our aim is to convey the essence of each article in a concise but readable style.
Issues are published every three to four months.

Framingham

Editor
Kathy Croom

Medical Writers (this issue)
Stephen Bartlett
Jane Grills
Gill Gummer
Kathy Longley
David Newton

Art Design
Jan van Halm

Layout and Printing
Drukmeesters,
Zwijndrecht, the Netherlands

Publishing Director
Evelien Enter

Publisher
Waldemar H.G. Dobrowolski

Framingham bv
Postbus 1593
1200 BN Hilversum
The Netherlands
www.framinghampublishers.com

Framingham *on systemic fungal infections* is supported by **Gilead Sciences Netherlands BV,** Amsterdam, the Netherlands

INVASIVE PULMONARY ASPERGILLOSIS GOES VIRAL AGAIN?

American Journal of Respiratory and Critical Care Medicine, 2021 February 1; 203(3):275–7

AUTHORS: Wauters J, Lamoth F, Rijnders BJ, Calandra T
CENTRES: Department of Microbiology, Immunology and Transplantation, Catholic University Leuven; Medical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium; Institute of Microbiology; Infectious Diseases Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; and Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands

BACKGROUND & AIM: Influenza infection is a risk factor for the development of invasive pulmonary aspergillosis (IPA) in patients admitted to intensive care units (ICUs) with respiratory failure. Increased awareness of influenza-associated pulmonary aspergillosis (IAPA) and the associated mortality risk has led to concerns about the occurrence of IPA in critically ill patients with COVID-19. Studies have reported incidences of COVID-19–associated pulmonary aspergillosis (CAPA) of 3–33%. A recent retrospective study found probable/putative invasive pulmonary mould infections in 4.8% of mechanically ventilated patients with COVID-19 in an ICU. However, this and previous CAPA studies did not have control groups, meaning that no firm conclusion can yet be made about whether COVID-19 is an independent risk factor for IPA. This article explores the evidence relating to the incidence of CAPA, and how it compares with that of IAPA.

ARTICLE TYPE: Editorial.

FINDINGS: The reported incidence of CAPA has varied between studies, and there are a few possible reasons for this. These include differences in diagnostic criteria, limited availability of galactomannan testing on bronchoalveolar lavage (because of concerns about bronchoscopy in patients with COVID-19), and variability in the use of immune-modulating therapies (which are associated with an increased risk of IPA). Reports on the incidence of IAPA also vary.

There are important clinical and pathophysiological differences between IAPA and CAPA. IAPA is often diagnosed relatively soon after ICU admission (median 3 days), while CAPA tends to occur later in the ICU stay (median 8–10 days). Severe influenza causes destruction of the respiratory epithelium, thereby damaging the epithelial barrier that protects against invasive aspergillosis. In contrast, COVID-19 does not cause as much epithelial damage, but mainly results in diffuse alveolar and endothelial vascular cell damage, leading to congestion, oedema and diffuse inflammatory infiltrates.

Most cases of CAPA do not show an invasive infection, and whereas serum galactomannan is positive in up to 60% of IAPA cases, this is rare in CAPA. It is also notable that CAPA is rarely mentioned in publications on COVID-19 autopsies, although a lack of hyphal invasion could also be due to prolonged administration of antifungal therapy.

CONCLUSIONS: The available evidence suggests that the incidence of CAPA is lower than the incidence of IAPA. However, several questions remain, including whether CAPA is an independent risk factor for ICU mortality, and whether the use of corticosteroids for COVID-19 is a risk factor for CAPA.

https://doi.org/10.1164/rccm.202012-4413ED

POSACONAZOLE VERSUS VORICONAZOLE FOR PRIMARY TREATMENT OF INVASIVE ASPERGILLOSIS:

A PHASE 3, RANDOMISED, CONTROLLED, NON-INFERIORITY TRIAL

The Lancet, 2021 February 6; 397(10273):499–509

AUTHORS: Maertens JA, Rahav G, Lee DG, et al.
CENTRE FOR CORRESPONDENCE: Department of Hematology, University Hospitals Leuven, Leuven, Belgium

BACKGROUND & AIM: Mortality rates in immunosuppressed patients with invasive aspergillosis (IA) remain high despite therapy with voriconazole or isavuconazole, and both drugs can provoke serious adverse events. Posaconazole has been approved for salvage therapy of IA, but has not been investigated for first-line use. The aim of this study was to determine whether posaconazole was non-inferior to voriconazole for the primary treatment of IA.

STUDY DESIGN: Multinational, randomized, double-blind, non-inferiority trial.

ENDPOINTS: The primary endpoint was all-cause mortality up to day 42 in the intention-to-treat (ITT) population. Secondary endpoints included 42-day and 84-day all-cause mortality, IA-related death and clinical response in the full-analysis set (FAS; patients with proven or probable IA).

METHOD: Patients with proven, probable or possible IA were enrolled at 91 sites and assigned 1:1 to therapy with either posaconazole (300 mg/day intravenously or orally) or voriconazole (4 mg/kg intravenously or 200 mg orally twice a day). Oral medications were given using a double-dummy procedure. Patients were evaluated at intervals up to 12 weeks. Non-inferiority of posaconazole was declared if the upper limit of the 95% confidence interval for the between-group difference in mortality at day 42 was <10%.

RESULTS: Among 575 patients who were randomized and received at least one dose of either posaconazole (n=288) or voriconazole (n=287), 163 and 171 had proven or probable IA, respectively, and made up the FAS population. Overall, 56% of posaconazole patients started with intravenous treatment, as did 60% of voriconazole patients. The median length of intravenous therapy was 9 days in both groups. During the first 42 days, 44/288 patients (15%) in the posaconazole group died, as did 59/287 (21%) in the voriconazole group, giving a between-group difference of –5.3% (–11.6% to +1.0%) in mortality in the ITT population, which demonstrated the non-inferiority of posaconazole (p<0.0001). For the FAS population, 42-day all-cause mortality rates were 19% in both groups. Similarly, 84-day mortality and clinical responses at 6 and 12 weeks did not differ significantly between the groups. Posaconazole-treated patients had a lower rate of treatment-related adverse events than those given voriconazole (30% versus 40%) and fewer reported vision-related adverse events (2% versus 10%), a known toxicity of voriconazole.

CONCLUSIONS: Posaconazole was non-inferior to voriconazole as primary therapy for IA and was well tolerated.

https://doi.org/10.1016/S0140-6736(21)00219-1

AZOLE RESISTANCE IN *ASPERGILLUS FUMIGATUS*:

A FIVE-YEAR FOLLOW UP EXPERIENCE IN A TERTIARY HOSPITAL WITH A SPECIAL FOCUS ON CYSTIC FIBROSIS

Frontiers in Cellular and Infection Microbiology, 2021 February 18; 10:613774

AUTHORS: Guegan H, Prat E, Robert-Gangneux F, Gangneux JP
CENTRES: Laboratoire de Parasitologie-Mycologie, Centre Hospitalier Universitaire de Rennes; and Univ Rennes, CHU, Inserm, Irset (Institut de Recherche en santé, environnement et travail) – UMR_S 1085, Rennes, France

BACKGROUND & AIM: *Aspergillus fumigatus* is the leading cause of aspergillosis, including invasive aspergillosis, and is the most common fungal colonizer of the airways of patients with cystic fibrosis (CF). First-line treatments for aspergillosis include the triazole antifungals; however, azole-resistant strains of *A. fumigatus* (AR*Af*) have emerged worldwide. This study estimated the frequency of azole resistance in *A. fumigatus* over a 5-year period in hospitalized patients, with a particular focus on patients with CF.

STUDY DESIGN: Prospective, single-centre, tertiary care study.

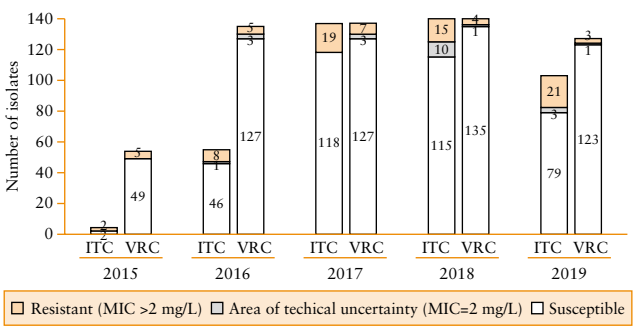
ENDPOINTS: Prevalence rates and longitudinal carriage of AR*Af*; cross resistance between azoles.

METHOD: Between 2015 and 2019, a total of 929 *A. fumigatus* clinical isolates (from 426 patients) were tested for susceptibility to one or more azole. Of these, 595 isolates came from 123 CF patients. The rest were from patients in the intensive care unit (*n*=57), and on pulmonology (*n*=159), haematology (*n*=13) or other clinical wards (*n*=105).

RESULTS: The prevalence rate for itraconazole-resistant *A. fumigatus* isolates for the period 2015–2019 was 14.5% (95 of 656 isolates), recovered from 44 of 308 patients. The corresponding prevalence rate for voriconazole-resistant *A. fumigatus* isolates was 4.1% (38 of 927 isolates), recovered from 21 of 426 patients. Resistance levels remained relatively stable over the 5-year period, but varied according to azole, patient origin and clinical setting. Among voriconazole-resistant isolates, 95% (20/21) were also resistant to itraconazole. In contrast, 27% (20/74) of itraconazole-resistant isolates were resistant to voriconazole. The prevalence rate of AR*Af* was highest in the CF cohort, at 15.1% (90 of 595 isolates); 5% of isolates (27/539) were voriconazole-resistant and 17.9% (78/436) were itraconazole-resistant (figure). Azole resistance among the other patient groups studied was scarce.

CONCLUSIONS: Azole resistance in *A. fumigatus* isolates varied depending on the drug, the clinical setting and the patient's background and type of infection. Patients with CF had higher rates of resistance than other patients.

Number of *Aspergillus fumigatus* isolates resistant to voriconazole (VOR) and itraconazole (ITC) each year from 2015 to 2019 among patients with cystic fibrosis



https://doi.org/10.3389/fcimb.2020.613774

FACTORS ASSOCIATED WITH COINFECTIONS IN INVASIVE ASPERGILLOSIS:
A RETROSPECTIVE COHORT STUDY

Clinical Microbiology and Infection, 2021 March 2: Epub ahead of print

AUTHORS: Danion F, Duval C, Séverac F, et al.
CENTRE FOR CORRESPONDENCE: Department of Haematology, Institut de Cancérologie de Strasbourg (ICANS), Strasbourg, France

BACKGROUND & AIM: Mortality rates are high in invasive aspergillosis (IA) and such patients are frequently infected with other pathogens. Despite this, little is known about the influence of co-infections on mortality. The aim of this study was to delineate the co-infections found in a representative sample of patients with IA and to identify factors affecting co-infection and mortality.

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

ENDPOINTS: Incidences of bacterial, viral, fungal and parasitic protozoal infections identified within ±7 days of the diagnosis of IA.

METHOD: Data on consecutive cases of IA were drawn from the mycology database and hospital diagnosis database of the University Hospital in Strasbourg for the period 1997–2017. IA cases were identified using standard EORTC/MSG criteria with serum galactomannan positivity and thoracic computed tomography findings. Comparisons between patients with and without co-infections were made using a mixed logistic regression model and the effect of co-infection on mortality was evaluated by multivariable Cox regression analysis.

RESULTS: The analysis identified 690 cases of proven (16%), probable (80%) or possible (4%) IA among 661 patients over the 21-year period. Among these cases, 418 involved IA only, while 272 (39%) were episodes of IA with one or more co-infections. In 48% of cases, the site of the co-infection was pulmonary, in 24% blood-borne, and in 28% at other or multiple sites. The most frequent co-infections were bacterial (40%), with viral and fungal co-infections seen in 21% of cases each, and parasites in 2%. Viral infections were diagnosed more frequently after 2009, when a more powerful PCR diagnostic method was introduced by the hospital. Co-infection was independently associated with having undergone allogeneic stem-cell transplantation, having a haematological malignancy, the presence of non-nodular chest CT lesions, low lymphocyte count, high C-reactive protein level, fever, tracheal intubation and infection by more than one *Aspergillus* species, while being aged >65 years reduced the risk. The 12-week survival rate was 46% in those with co-infections and 62% in those with IA mono-infections. Multivariate regression showed that co-infection was an independent predictor of increased 12-week mortality (adjusted hazard ratio 1.5, 95% confidence interval 1.1–1.9, $p<0.01$).

CONCLUSIONS: In this large, non-selective series of patients with IA at a major regional centre, co-infection was common and significantly increased the risk of mortality.

https://doi.org/10.1016/j.cmi.2021.02.021

DIAGNOSTIC VALUE OF GALACTOMANNAN TEST IN NON-IMMUNOCOMPROMISED CRITICALLY ILL PATIENTS WITH INFLUENZA-ASSOCIATED ASPERGILLOSIS:

DATA FROM THREE CONSECUTIVE INFLUENZA SEASONS

European Journal of Clinical Microbiology & Infectious Diseases, 2021 April 10; Epub ahead of print

AUTHORS: Huang L, Zhang Y, Hua L, Zhan Q

CENTRES: Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital; Peking University China-Japan Friendship School of Clinical Medicine; and School of Biomedical Engineering, Capital Medical University, Beijing, People's Republic of China

BACKGROUND & AIM: Influenza-associated invasive aspergillosis (IAA) in critically ill patients has a high mortality rate of 45–61%, but can be difficult to diagnose because of its non-specific symptoms and the low sensitivity of fungal culture. Assessment of galactomannan (GM) in serum and bronchoalveolar lavage fluid (BALF) has diagnostic value in various immunocompromised patient populations, and has been proposed for the identification of IAA in critically ill patients, although most of these are not in an immunocompromised state. The aim of the current study was to investigate the diagnostic value of serum and BALF GM detection in non-immunocompromised, critically ill patients with IAA.

STUDY DESIGN: Retrospective case–control study.

ENDPOINT: Diagnostic performance.

METHOD: The study included 90 patients with severe influenza-induced pneumonia admitted to an intensive care unit (25 with IAA and 65 without IAA) who had at least one BALF GM or fungal culture result, as well as serum GM detection. Analyses of the diagnostic performance of serum GM and BALF GM were performed using four different detection strategies (positive at first test, second test, first or second test, or first and second tests). Appropriate detection timepoints were determined using area under the receiver operating characteristic curve (AUC) analysis.

RESULTS: AUC values were 0.548 and 0.839 for the first and second serum GM tests, respectively, and 0.904 and 0.827 for the first and second BALF GM tests. The AUC value for the first serum test was significantly lower than for the second serum test ($p<0.01$), and lower than for the first ($p<0.01$) and second BALF tests ($p=0.043$). For serum GM testing, detection of at least one positive result on either the first or second tests showed better diagnostic performance (AUC 0.719) than a first positive test (0.419, $p<0.01$) or two consecutive positive tests (0.636, $p=0.014$). There were no differences between these three strategies when considering BALF GM tests. Possible cut-off values for BALF GM were 1.0 or 1.3 (table).

CONCLUSIONS: BALF GM testing may perform better than serum GM testing for the diagnosis of IAA in non-immunocompromised critically ill patients, although finding at least one positive result among two consecutive serum tests may also be useful.

Optimal cut-off values for detection of galactomannan (GM) in serum or bronchoalveolar lavage fluid (BALF) in patients with influenza-associated invasive aspergillosis

	First BALF GM test	Second BALF GM test	Second serum GM test
AUC	0.904	0.827	0.839
Cut-off value	1.335	1.020	0.335
Sensitivity	0.810	0.714	0.762
Specificity	0.857	0.964	0.821
Youden index	0.667	0.679	0.583

https://doi.org/10.1007/s10096-021-04228-z

PERFORMANCE OF EXISTING DEFINITIONS AND TESTS FOR THE DIAGNOSIS OF INVASIVE FUNGAL DISEASES OTHER THAN INVASIVE CANDIDIASIS AND INVASIVE ASPERGILLOSIS IN CRITICALLY ILL, ADULT PATIENTS:

A SYSTEMATIC REVIEW WITH QUALITATIVE EVIDENCE SYNTHESIS

Journal of Fungi, 2021 February 28; 7(3):176

AUTHORS: Giacobbe DR, Cortegiani A, Karaiskos I, Mercier T, Tejada S, Peghin M, Grecchi C, Rebuffi C, Asperges E, Zuccaro V, Scudeller L, Bassetti M, and the FUNDICU Investigators
CENTRES FOR CORRESPONDENCE: Department of Health Sciences, University of Genoa; and Clinica Malattie Infettive, Ospedale Policlinico San Martino-IRCCS, Genoa, Italy

BACKGROUND & AIM: Diagnosing invasive fungal diseases (IFDs) in non-immunocompromised critically ill patients can be challenging due to the frequent absence of a proven diagnosis, the suboptimal performance of definitions that were designed for severely immunocompromised patients, and the lack of consensus over alternative definitions. The Fungal Infections Definitions in Intensive Care Unit patients (FUNDICU) project was launched in order to develop a standard set of definitions for IFDs, including the more frequent invasive candidiasis (IC) and invasive aspergillosis (IA), and less common non-IC and non-IA IFDs such as *Pneumocystis jirovecii* pneumonia (PJP), in non-immunocompromised critically ill adults. As part of the project, a systematic review was undertaken to determine the performance of available definitions and tests for the diagnosis of non-IC and non-IA IFDs in this patient population.

STUDY DESIGN: Systematic review with qualitative synthesis.

ENDPOINTS: Sensitivity, specificity, negative predictive value and positive predictive value.

METHOD: A systematic search of the PubMed, Embase, CINAHL and Cochrane databases from 2003 to 2018 was conducted to identify studies that assessed the diagnostic performance of definitions and/or tests versus a reference definition or reference standard (such as histology or culture from normally sterile sites) for PJP, and for other non-IA, non-IC IFDs, in critically ill adult patients. Studies including solely haematology and/or solid-organ transplant patients, or composed of ≥50% HIV-positive patients (for PJP studies), were excluded.

RESULTS: For PJP, 89 studies were considered eligible for full-text evaluation, but after application of the rigorous criteria of the FUNDICU protocol only two studies were included in the qualitative analysis. These were a prospective cohort study and a retrospective cross-sectional study, both single-centre studies, that assessed the diagnostic performance of polymerase chain reaction versus a reference test for the identification of PJP. Both studies reported high sensitivity (87.2%/100%), high specificity (92.2%/92.4%) and a high negative predictive value (98.7%/100%), but the positive predictive value was relatively low (51.5%/63.4%). For other non-IA, non-IC IFDs, 61 studies underwent full-text evaluation, but none met the minimum standards required for inclusion in the qualitative analysis.

CONCLUSION: This study highlights that there are insufficient data to evaluate the performance of definitions and tests for PJP and other non-IA, non-IC IFDs in non-immunocompromised critically ill adult patients.

https://doi.org/10.3390/jof7030176

ARE WE READY FOR NOSOCOMIAL *CANDIDA AURIS* INFECTIONS? RAPID IDENTIFICATION AND ANTIFUNGAL RESISTANCE DETECTION USING MALDI-TOF MASS SPECTROMETRY MAY BE THE ANSWER

Frontiers in Cellular and Infection Microbiology, 2021 March 16; 11:645049

AUTHORS: De Carolis E, Marchionni F, La Rosa M, Meis JF, Chowdhary A, Posteraro B, Sanguinetti M
CENTRES FOR CORRESPONDENCE: Dipartimento di Scienze di Laboratorio e Infettivologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS; and Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy

BACKGROUND & AIM: Since the emergence of *Candida auris* approximately 10 years ago, multidrug-resistant isolates of this fungal pathogen have been identified worldwide. There is therefore a need for methods that can both accurately and rapidly identify clinical *C. auris* isolates and determine whether they are susceptible or resistant to antifungal drugs. Echinocandins are used as first-line treatment for *C. auris* infections, but resistant isolates can develop. The aim of this study was to develop a fast and reproducible mass spectrometry assay for detecting resistance to the echinocandin antifungal drug anidulafungin in *C. auris* isolates.

STUDY DESIGN: Diagnostic study.

ENDPOINTS: Species identification and classification of resistance.

METHOD: Eight confirmed *C. auris* spectrum profiles were added to the MALDI-TOF mass spectrometry Bruker Daltonics Biotyper® database. Hierarchical cluster analysis was used to generate a score-oriented dendrogram, including spectra from isolates of *C. auris* and other *Candida* and non-*Candida* species, grouping and classifying isolates according to species. A mass spectrometry-based antifungal susceptibility testing (AFST) assay was developed to identify resistant and susceptible isolates. Spectra obtained at null (0 µg/mL), intermediate (0.06 µg/mL) or maximum (64 µg/mL) anidulafungin concentrations were used to create composite correlation index matrices for 18 *C. auris* isolates (six resistant, 12 susceptible). Results were compared with resistance classifications obtained using Sensititre YeastOne (reference).

RESULTS: Using the extended database, reliable species-level identification was obtained for all 18 *C. auris* isolates, based on (log)score values >2.0. When compared with the resistance/susceptibility classification determined by the reference method, the mass spectrometry-based AFST assay correctly classified all six (100%) of the known resistant isolates and 11 (91.7%) of the 12 known susceptible isolates. One isolate which had intermediate susceptibility to anidulafungin (minimum inhibitory concentration 1 µg/mL) was classified as resistant rather than susceptible by the mass spectrometry-based AFST assay.

CONCLUSION: A mass spectrometry-based AFST assay was developed that was able to rapidly and correctly classify resistant and susceptible *C. auris* isolates.

https://doi.org/10.3389/fcimb.2021.645049

MSG07: AN INTERNATIONAL COHORT STUDY COMPARING EPIDEMIOLOGY AND OUTCOMES OF PATIENTS WITH *CRYPTOCOCCUS NEOFORMANS* OR *CRYPTOCOCCUS GATTII* INFECTIONS

Clinical Infectious Diseases, 2021 March 27; Epub ahead of print

AUTHORS: Baddley JW, Chen SC, Huisingh C, Benedict K, DeBess EE, Galanis E, Jackson BR, MacDougall L, Marsden-Haug N, Oltean H, Perfect JR, Phillips P, Sorrell TC, Pappas PG
CENTRE FOR CORRESPONDENCE: Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA

BACKGROUND & AIM: The two main species of *Cryptococcus* that infect humans are *C. neoformans* and *C. gattii*. There are marked differences in the geographical distributions of these two species, as well as in the populations typically affected, and the features and severity of the disease caused by each organism. For example, *C. neoformans* often causes opportunistic infections in immunosuppressed individuals, while *C. gattii* is more likely to affect people with normal immune systems, and is associated with a higher frequency of pulmonary disease than seen with *C. neoformans*. The aim of this study was to compare the epidemiology and outcomes of patients with *C. neoformans* and those with *C. gattii* infection.

STUDY DESIGN: Retrospective cohort study.

ENDPOINTS: Underlying diseases, clinical manifestations, treatment and outcomes.

METHOD: The study included 709 patients with culture-proven cryptococcosis between 1995 and 2013. The participants comprised 452 with *C. neoformans* infection and 257 with *C. gattii* infection, all coming from one of five centres in North America and Australia. Data on clinical presentation, underlying medical conditions, test results, antifungal treatment and outcomes were compared between the two groups of patients.

RESULTS: Patients with *C. gattii* infection tended to have a longer time before diagnosis than those with *C. neoformans* infection (mean 52.2 versus 36.0 days, $p<0.003$), and were more likely to have no underlying disease (40.5% versus 10.2%, $p<0.0001$). Overall, the most common sites of *Cryptococcus* infection were the central nervous system (CNS, 59.1%), lung (42.5%) and blood (24.5%). Pulmonary infection was more common with *C. gattii* than with *C. neoformans* (60.7% versus 32.1%, $p<0.0001$), while *C. neoformans* was associated with higher incidences of CNS (64.4% versus 49.8%, $p=0.0001$), blood (34.1% versus 7.8%, $p<0.0001$) and skin infections (4.0% versus 0.0%, $p=0.0012$). Overall, 76.4% of patients with CNS disease were treated with amphotericin plus flucytosine. The crude 12-month all-cause mortality rate was higher in patients with *C. neoformans* compared with *C. gattii* (28.4% versus 20.2%; odds ratio 1.56, 95% confidence interval 1.08–2.26); however, significance was lost after adjustment (aOR 1.46, 95% CI 0.86–2.46). Immune reconstitution inflammatory syndrome was less common in patients with *C. neoformans* (aOR 0.28, 95% CI 0.10–0.82).

CONCLUSIONS: This study has identified a number of differences in the epidemiology and outcomes of patients with cryptococcosis caused by different species, which may help predict prognosis and guide treatment.

https://doi.org/10.1093/cid/ciab268

BREAKTHROUGH MUCORMYCOSIS DEVELOPING ON MUCORALES-ACTIVE ANTIFUNGALS PORTRAYS A POOR PROGNOSIS IN PATIENTS WITH HEMATOLOGIC CANCER

Journal of Fungi, 2021 March 17; 7(3):217

AUTHORS: Axell-House DB, Wurster S, Jiang Y, Kyvernitakis A, Lewis RE, Tarrand JJ, Raad II, Kontoyiannis DP
CENTRES: Department of Infectious Diseases, Infection Control, and Employee Health; Department of Laboratory Medicine, The University of Texas MD Anderson Cancer Center; and Section of Infectious Diseases, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA

BACKGROUND & AIM: Invasive mucormycosis (MCR) is a common mould infection in patients with haematological malignancies and recipients of haematopoietic stem-cell transplantation (HSCT). These patient groups therefore routinely receive antifungal prophylaxis. Breakthrough MCR (BT-MCR) tends to occur in individuals receiving non-Mucorales-active antifungal therapy, but sporadic BT-MCR has also been reported in those receiving Mucorales-active antifungals such as posaconazole or isavuconazole. The aim of this study was to evaluate the characteristics and outcomes of patients with haematological malignancies or HSCT who developed BT-MCR while receiving treatment with mould-active antifungals with or without activity against Mucorales.

STUDY DESIGN: Retrospective cohort study.

ENDPOINTS: The joint primary endpoints were 42-day all-cause mortality from start of treatment and from onset of symptoms.

METHOD: The study included 103 patients with haematological malignancies or HSCT who developed BT-MCR while receiving treatment with mould-active antifungals. Sixteen individuals were receiving Mucorales-active antifungals (nine on isavuconazole, six on posaconazole and one on amphotericin B), while 87 were on other mould-active antifungals with no Mucorales activity (52 on voriconazole, 22 on echinocandins, eight on itraconazole and five on echinocandin plus voriconazole). Data were collected on patient demographics and clinical characteristics, including malignancy status, intensive care unit (ICU) admission and presence of neutropenia. Factors associated with mortality were identified using multivariate Cox regression analysis.

RESULTS: Patients who developed BT-MCR while receiving Mucorales-active antifungal therapy had a higher 42-day mortality rate than those with BT-MCR while on non-Mucorales-active antifungal therapy, and this was true whether measured from treatment initiation (69% versus 39%, p=0.028) or from onset of symptoms (63% versus 25%, p=0.006). Exposure to Mucorales-active antifungals before BT-MCR was an independent predictor of 42-day mortality measured from treatment initiation (hazard ratio 2.40, p=0.015) and from symptom onset (HR 4.63, p<0.001). Other independent predictors of mortality included ICU admission and higher APACHE II score at diagnosis, lack of recovery from severe neutropenia during treatment, active malignancy, and combination amphotericin B/caspofungin treatment.

CONCLUSIONS: The development of BT-MCR while on Mucorales-active antifungal treatment was associated with a poor prognosis in patients with haematological malignancy or HSCT.

https://doi.org/10.3390/jof7030217

COVID-19–ASSOCIATED PULMONARY ASPERGILLOSIS, MARCH–AUGUST 2020

Emerging Infectious Diseases, 2021; 27(4):1077–86

AUTHORS: Salmanton-García J, Sprute R, Stemler J, et al.; for the FungiScope European Confederation of Medical Mycology/The International Society for Human and Animal Mycology Working Group
CENTRE FOR CORRESPONDENCE: University of Cologne, Cologne, Germany

BACKGROUND & AIM: Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), often develop pneumonia. SARS-CoV-2 infection results in severe immunomodulation, and patients are often treated with immunosuppressive drugs, such as dexamethasone. Hence, it is possible that patients with COVID-19 will experience fungal superinfections. This study evaluated baseline conditions, clinical management and outcomes in patients who developed coronavirus disease-associated pulmonary aspergillosis (CAPA).

STUDY DESIGN: Retrospective analysis.

ENDPOINTS: Conditions at baseline, clinical management and mortality, and cumulative incidence of CAPA.

METHOD: Patients (*n*=186) diagnosed with COVID-19 and CAPA during March–August 2020 were identified from the FungiScope registry and academic literature.

RESULTS: Patients came from 17 countries. The median age was 68 years and 72.6% were men. Most (*n*=182, 97.8%) patients who developed CAPA had been admitted to the intensive care unit (ICU) for acute respiratory distress syndrome (*n*=180, 96.8%) and/or mechanical ventilation (*n*=175, 94.1%). Comorbidity was common (table) and 98 patients (52.7%) were receiving corticosteroids. CAPA was diagnosed a median of 10 days after a positive reverse transcription polymerase chain reaction test for SARS-CoV-2, and a median of 8 and 7 days, respectively, after ICU admission or initiation of mechanical ventilation. *Aspergillus fumigatus* was the most common pathogen, detected in 122 patients (65.6%). Most (*n*=98, 52.7%) patients were treated with voriconazole. Five patients had azole-resistant infections. Overall, 97 (52.2%) patients died; death was attributed to CAPA in 32 (17.2%) patients. Half of all patients (*n*=93) died ≤12 weeks after CAPA diagnosis. The cumulative incidence of CAPA in COVID-19 patients admitted to the ICU was 6.9%; rates varied from 1.0% to 39.1% between institutions.

CONCLUSIONS: Most patients with COVID-19 who were diagnosed with CAPA had been admitted to the ICU and had high levels of underlying comorbidity. CAPA contributed to a high mortality rate in patients with COVID-19.

Common comorbid conditions in patients with coronavirus disease-associated pulmonary aspergillosis (*n*=186)

Comorbidity	Number of patients (%)
Chronic cardiovascular disease	94 (50.5%)
Renal failure	74 (39.8%)
Diabetes mellitus	64 (34.4%)
Obesity	47 (25.3%)
Chronic pulmonary disease	40 (21.5%)
Haematological/Oncological disorders	21 (11.3%)
Solid-organ transplantation	4 (2.2%)
Neutropenia	2 (1.1%)

https://doi.org/10.3201/eid2704.204895

COVID-19 ASSOCIATED PULMONARY ASPERGILLOSIS IN MECHANICALLY VENTILATED PATIENTS

Clinical Infectious Diseases, 2021 March 9; Epub ahead of print

AUTHORS: Permpalung N, Chiang TP, Massie AB, Zhang SX, Avery RK, Nematollahi S, Ostrander D, Segev DL, Marr KA
CENTRES: Department of Medicine; Department of Surgery; Department of Epidemiology; Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; and Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

BACKGROUND & AIM: European studies have reported coronavirus disease 2019 (COVID-19)–associated pulmonary aspergillosis (CAPA) occurs in 5–30% of patients with severe COVID-19. The risk factors for, and clinical outcomes of, CAPA in patients on mechanical ventilation are poorly understood, and the criteria used to define the disease vary. Moreover, centres that do not routinely carry out bronchoscopy may underestimate disease burden using currently proposed definitions for 'probable' CAPA. The aim of this study was to describe risk factors and clinical outcomes for CAPA, using expanded definitions of CAPA, in a large cohort of adults hospitalized with severe COVID-19.

STUDY DESIGN: Retrospective cohort study.

ENDPOINTS: Risk factors associated with CAPA; clinical outcomes.

METHOD: The study analysed 396 adult COVID-19 patients admitted to five hospitals in the United States who required mechanical ventilation. Patients with CAPA were identified from the Johns Hopkins COVID-19 registry database using composite clinical criteria to define 'possible' as well as 'probable' cases of CAPA. Clinical outcomes were analysed using Fine and Gray competing risks regression, and longitudinal disease severity scores were compared using multilevel mixed-effects ordinal logistic regression.

RESULTS: A total of 39 patients met the criteria for CAPA. Patients who developed CAPA had a lower median body mass index than those without CAPA (26.6 vs 29.9 kg/m^2, p=0.04), but were more likely than those without CAPA to have underlying pulmonary vascular disease (41% versus 21.6%, p=0.01), liver disease (35.9% versus 18.2%, p=0.02), coagulopathy (51.3% versus 33.1%, p=0.03), solid tumours (25.6% versus 10.9%, p=0.017) or multiple myeloma (5.1% versus 0.3%, p=0.027). Patients with CAPA were more likely than controls to have received corticosteroids during their index hospital admission (66.7% versus 42.6%, p=0.005). The median time from COVID-19 diagnosis to CAPA diagnosis was 15 days, and from intubation to CAPA diagnosis was 12 days. Outcomes (measured by ordinal severity of disease scores) were significantly worse in patients with CAPA: they took longer to show clinical improvement (p<0.001), progressed to more severe illness almost twice as fast (p<0.001), were intubated for twice as long (p<0.001), and had a significantly longer hospital stay (p<0.001) than those without CAPA. However, mortality did not differ significantly between the groups.

CONCLUSIONS: CAPA was associated with poor clinical outcomes. Risk factors for CAPA include conditions linked to poor clearance of fungus from airways and deficiencies in secondary antifungal defences.

https://doi.org/10.1093/cid/ciab223

PERFORMANCE, CORRELATION AND KINETIC PROFILE OF CIRCULATING SERUM FUNGAL BIOMARKERS OF INVASIVE ASPERGILLOSIS IN HIGH-RISK PATIENTS WITH HEMATOLOGIC MALIGNANCIES

Journal of Fungi, 2021 March 13; 7(3):211

AUTHORS: SIOPI M, KARAKATSANIS S, ROUMPAKIS C, KORANTANIS K, ELDEIK E, SAMBATAKOU H, SIPSAS NV, TSIRIGOTIS P, PAGONI M, MELETIADIS J
CENTRE FOR CORRESPONDENCE: CLINICAL MICROBIOLOGY LABORATORY, "ATTIKON" UNIVERSITY GENERAL HOSPITAL, MEDICAL SCHOOL, NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, ATHENS, GREECE

BACKGROUND & AIM: The diagnosis of invasive aspergillosis (IA) in haematology patients remains challenging, and can delay the initiation of targeted therapy, increasing the risk of death. Conventional microbiological and radiological techniques have limitations. Serum fungal biomarkers of IA, such as *Aspergillus* galactomannan antigen and 1,3-beta-D glucan (BDG), are important adjunctive diagnostic tools. Polymerase chain reaction (PCR)-based assays are also used to help identify probable IA infections. The aim of this study was to evaluate the kinetics and diagnostic performance of circulating galactomannan, BDG and *Aspergillus* DNA (PCR), alone and in combination, in patients with haematological malignancies at high risk of IA.

STUDY DESIGN: Retrospective study.

ENDPOINTS: Positivity rates, time to positivity, and diagnostic performance.

METHOD: Serial serum specimens (n=240) from 93 adults with haematological malignancies at risk of IA (eight with probable, 25 with possible and 60 without IA) were screened for the detection of galactomannan, BDG and *Aspergillus* DNA (PCR).

RESULTS: Positivity rates for biomarkers (alone and in combination) in patients with probable, possible or no IA are shown in the table. Median (interquartile range) time to positivity among patients with probable IA was 0 (18), 7 (10) and 18 (45) days for galactomannan, PCR and BDG, respectively. The highest level of agreement (76%) was found between galactomannan and PCR. A significant negative correlation between galactomannan indices and PCR cycle values was found (r_s= –0.47, p=0.0017). Sensitivity and negative predictive values were higher when biomarkers were combined (75–90% and 93–97%, respectively) than when they were used alone (45–55% and 90–92%). Specificity and positive predictive values decreased when biomarkers were combined.

CONCLUSION: Positivity rates, time to positivity and diagnostic performance differed markedly among fungal biomarkers of IA. The combination of galactomannan and PCR may facilitate early diagnosis.

Positivity rates (%) for biomarkers (alone and in combination) in patients with probable, possible and no invasive aspergillosis (IA)

	Probable IA	Possible IA	No IA	p
GM	88	8	0	<0.001
BDG	62	46	35	0.29
PCR	62	33	27	0.15
GM + BDG	50	4	0	<0.001
GM + PCR	50	4	0	<0.001
BDG + PCR	50	8	22	0.038
GM + BDG + PCR	38	4	0	<0.001

GM=galactomannan antigen, BDG=1,3-beta-D glucan, PCR=polymerase chain reaction.

https://doi.org/10.3390/jof7030211