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COVID-19-ASSOCIATED PULMONARY ASPERGILLOSIS, FUNGEMIA, AND PNEUMOCYSTOSIS IN THE INTENSIVE CARE UNIT:

A RETROSPECTIVE MULTICENTER OBSERVATIONAL COHORT DURING THE FIRST FRENCH PANDEMIC WAVE

Microbiology Spectrum, *2021 October 31; 9(2):e0113821*

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BACKGROUND & AIM: Fungal coinfections, including aspergillosis and yeast infections, have been reported in patients with COVID-19 pneumonia treated in intensive care units (ICUs). This study assessed patterns of invasive fungal disease and clinical outcomes among ICU patients with COVID-19 pneumonia during the first wave of the pandemic.

STUDY DESIGN: Retrospective, multicentre, observational cohort study.

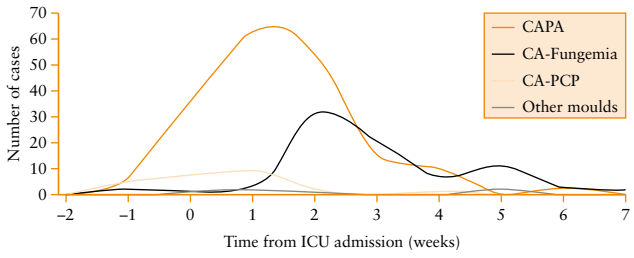
ENDPOINTS: Time to occurrence of fungal coinfection in the ICU; mortality rates.

METHOD: Clinical and laboratory data were collected for cases of COVID-19–associated pulmonary aspergillosis (CAPA), fungaemia (CA-fungaemia) and pneumocystosis (CA-PCP) occurring in patients with COVID-19 pneumonia in the ICUs of 36 centres across France between February and May 2020. Endpoints were compared between different fungal coinfections.

RESULTS: Overall, 244 patients with COVID-19 pneumonia (mean age 64.7 years) experienced 257 episodes of fungal coinfection (154 CAPA, 81 CA-fungaemia, 17 CA-PCP and 5 other moulds). Median time from ICU admission to fungal coinfection was 1 day for CA-PCP, 9 days for CAPA and 16 days for CA-fungaemia ($p<0.0001$); figure. Median length of ICU stay was 16, 26 and 33 days for patients with CA-PCP, CAPA and CA-fungaemia, respectively. Among patients with CAPA, the mortality rate was 76.7% in those with EORTC/MSGERC-defined immunosuppressive factors compared with 45.2% in those with pre-existing pulmonary disease and 36.6% in those with neither ($p=0.001$). The greater the number of positive microbiological diagnostic criteria in CAPA patients, the higher the mortality rate ($p=0.002$). Among patients with CA-fungaemia, 59.3% of episodes were due to *Candida albicans* and 45.7% of patients died. Among patients with CA-PCP, 58.8% of episodes occurred in patients with immunosuppressive risk factors and 29.5% died.

CONCLUSIONS: Fungal coinfections in ICU patients with COVID-19 pneumonia differed with respect to timing and outcomes. The data suggest CAPA was often hospital-acquired and might benefit from early antifungal intervention. CA-fungaemia may be linked to prolonged ICU stays, whereas CA-PCP may develop prior to ICU admission.

Time from ICU admission to diagnosis of fungal coinfection



CA=COVID-19–associated; PA=pulmonary aspergillosis; PCP=pneumocystosis

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ASPERGILLUS INFECTIONS

The New England Journal of Medicine, 2021 October 14; 385(16):1496–509

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BACKGROUND & AIM: Air-born *Aspergillus* conidia (spores) are ubiquitous in the environment. In most people with a healthy immune system, inhalation of these spores will not result in colonization or infection. However, individuals who are affected by the spores can show a wide range of clinical manifestations, from asymptomatic colonization to invasive infection. Invasive aspergillosis (IA) is the most devastating form of the disease and is associated with high morbidity and mortality. Following a previous review by the authors published in 2009, the aim of the current review was to outline more recent progress in the understanding of *Aspergillus* infections. This abstract focuses on IA.

ARTICLE TYPE: Review.

FINDINGS: IA primarily occurs in people with immunosuppression. Advances since 2009 include the recognition of new risk factors for IA, such as an intensive care unit stay, respiratory viral infections (e.g. influenza or severe acute respiratory syndrome coronavirus 2) and chimeric antigen receptor T-cell therapy. Additionally, molecular studies have identified new polymorphisms that predispose some people to IA.

The diagnosis of invasive infection relies on obtaining tissue or bronchoalveolar lavage samples for culture or histopathological assessment, which can be difficult. In patients with suspected disease, non-invasive diagnostic methods (e.g. galactomannan, 1,3-β-D-glucan and polymerase chain reaction) can now be used to supplement radiographic imaging.

Management of patients with IA requires early recognition of infection and the prompt provision of antifungal therapy. Current antifungal options for the treatment of patients with aspergillosis include voriconazole, isavuconazole, posaconazole, itraconazole, lipid amphotericin B formulations, amphotericin B deoxycholate and echinocandins. Voriconazole and isavuconazole are recommended first-line therapies. Evidence supporting posaconazole as a first-line therapy for aspergillosis was provided by a 2021 randomized trial in which this agent demonstrated non-inferiority to voriconazole, with fewer adverse events. Conflicting results have been reported regarding the effect on survival of a voriconazole–echinocandin combination.

High-risk patients (e.g. haematopoietic-cell transplant recipients) should receive antifungal prophylaxis. Posaconazole has shown efficacy in the prevention of aspergillosis in patients undergoing chemotherapy for acute myeloid leukaemia and in those with severe graft-versus-host disease after haematopoietic-cell transplantation.

CONCLUSION: Despite continuing advances in antifungal treatment, prophylaxis and diagnostic testing, the management of patients with IA continues to pose a challenge to physicians.

https://doi.org/10.1056/NEJMra2027424

IMPACT OF CHANGES OF THE 2020 CONSENSUS DEFINITIONS OF INVASIVE ASPERGILLOSIS ON CLINICAL TRIAL DESIGN:

UNINTENDED CONSEQUENCES FOR PREVENTION TRIALS?

Open Forum Infectious Diseases, 2021 September 9; 8(10):ofab441

AUTHORS: Wingard JR, Alexander BD, Baden LR, Chen M, Sugrue MW, Leather HL, Caliendo AM, Clancy CJ, Denning DW, Marty FM, Nguyen MH, Wheat LJ, Logan BR, Horowitz MM, Marr KA
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BACKGROUND & AIM: The 2002 EORTC/MSG criteria for classifying patients with invasive fungal diseases (IFDs) were revised in 2008 and 2020. The 2020 revision made two major changes to invasive aspergillosis (IA) criteria (raising the galactomannan assay threshold for probable IA and allowing diagnosis using PCR testing) that might affect whether patients are classified as having proven, probable or possible IA. This study explored how the change in the galactomannan threshold could affect IA diagnosis and clinical trials of antifungal agents.

STUDY DESIGN: Post hoc analysis.

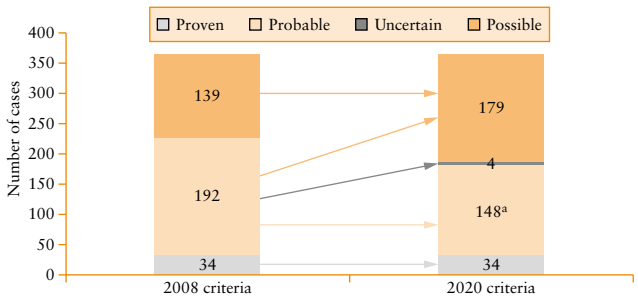
ENDPOINT: Number of patients reclassified.

METHOD: Patients with IA/IFD from two US datasets were classified using both the 2008 and 2020 EORTC/MSG criteria: 277 from the AsTeC Biorepository and 88 haematopoietic-cell transplant (HCT) recipients from the BMT CTN 0101 randomized, double-blind, IFD prevention trial of fluconazole versus voriconazole.

RESULTS: Among the 365 patients (130 haematological malignancies, 194 HCT recipients, 25 lung transplant recipients and 16 'other'), 226 were classified as proven or probable IA and 139 as possible IFD using the 2008 criteria. Applying the 2020 criteria led to 41 patients being reclassified from probable IA to possible IA (n=40) or probable IFD (n=1) (figure), all but one of them in the HCT and malignancy groups. Use of the 2020 criteria led to a delay in establishing a diagnosis of probable IA in 15% of cases, by a median of 3 (range 1–105) days. Similar numbers of patients were reclassified in each of the BMT CTN 0101 trial arms, and reclassification did not affect 12-week survival of either those reclassified or not reclassified.

CONCLUSIONS: Fewer patients met the criteria for probable IA using the more stringent 2020 EORTC/MSG criteria. Use of the new criteria will necessitate more patients being recruited into future prevention trials to maintain statistical power. It could also lead to more severely ill patients being included, hindering comparisons with earlier trials. The analysis did not address PCR testing as this was not performed in the source datasets.

Reclassification of invasive aspergillosis cases using the 2020 EORTC/MSG criteria



[a] Includes one case reclassified as probable IFD

https://doi.org/10.1093/ofid/ofab441

MOLECULAR EPIDEMIOLOGY OF AZOLE RESISTANT *ASPERGILLUS FUMIGATUS* IN FRANCE SHOWS PATIENT AND HEALTHCARE LINKS TO ENVIRONMENTALLY OCCURRING GENOTYPES

Frontiers in Cellular and Infection Microbiology, 2021 September 29; 11:729476

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BACKGROUND & AIM: It is important to understand whether genotypes of azole-resistant *Aspergillus fumigatus* (AR*Af*) are randomly distributed or cluster geographically, and whether a common source of colonization can be identified. The mycology team of Besançon in eastern France has been systematically screening clinical and environmental samples for *A. fumigatus* since the 2000s, and has now collected 1100 strains of the *Aspergilli* complex (*A. fumigatus* and cryptic species) from the region. The aim of this study was to assess the genetic relatedness of a retrospective sample of 225 azole-susceptible (AS*Af*) and AR*Af* samples from that collection by comparing them with worldwide data from genotype databases.

STUDY DESIGN: Genotyping study.

ENDPOINT: Genotype richness (total number of unique multilocus genotypes; MLGs)

METHOD: All 113 AR*Af* isolates obtained between 2012 and 2018 (29 from patients and 84 from the environment) were included in the genetic relatedness analysis, and 112 AS*Af* isolates (five from patients and 107 from the environment) were retrospectively selected from the available collection according to the origin of the AR*Af* isolates. Microsatellite genotyping was performed to assess the genetic relatedness of the 225 AS*Af* and AR*Af* isolates; local TR_{34}/L98H isolates (the most common resistance mechanism) were analysed to determine proximity according to their origin; and local TR_{34}/L98H isolates were compared with those from worldwide data.

RESULTS: AR*Af* samples were generally recovered from patients with cystic fibrosis, while the environmental isolates were from market gardens and sawmills. More than 80% of AR*Af* isolates had the TR_{34}/L98H *cyp51A* allele. The AR*Af* group had less genotypic richness than the AS*Af* group, with a total of 53 versus 102 MLGs. Dominant local TR_{34}/L98H genotypes were found to be isolated in different sample types at different dates (in other words, came from different patients and types of environment), although isolates from hospital air and patients were linked. Genotypes from the various environments were highly diverse. Some identical clonal genotypes were found in both the eastern France region and the rest of the world (mainly Australia), while others were potentially specific to eastern France.

CONCLUSIONS: Reduced genetic diversity of TR_{34}/L98H isolates was found in azole-resistant versus -susceptible strains of *A. fumigatus*, suggesting a more recent emergence of the resistant genotype. Some genotypes found were specific to the area and some were identical to those in other countries.

https://doi.org/10.3389/fcimb.2021.729476

WHEN TO CHANGE TREATMENT OF ACUTE INVASIVE ASPERGILLOSIS:

AN EXPERT VIEWPOINT

The Journal of Antimicrobial Chemotherapy, 2021 December 24; 77(1):16–23

AUTHORS: Slavin MA, Chen YC, Cordonnier C, Cornely OA, Cuenca-Estrella M, Donnelly JP, Groll AH, Lortholary O, Marty FM, Nucci M, Rex JH, Rijnders BJ, Thompson GR, Verweij PE, White PL, Hargreaves R, Harvey E, Maertens JA

CENTRE FOR CORRESPONDENCE: Department of Infectious Diseases, Peter MacCallum Cancer Centre, National Centre for Infections in Cancer, Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia

BACKGROUND & AIM: Current guidelines vary on when and why initial treatment should be changed in immunocompromised patients with invasive aspergillosis (IA). To provide further clarity on this subject, the pharmaceutical company F2G convened an international advisory board of clinicians and scientists (including haematologists, infectious disease specialists, medical mycologists and molecular microbiologists) with expertise in diagnosing and managing invasive fungal diseases (IFDs). One of the goals of the advisory board was to develop criteria for changing antifungal therapy in patients who are receiving prophylaxis or being treated for IA.

ARTICLE TYPE: Advisory group recommendations.

FINDINGS: The group agreed that patients who develop clinical or diagnostic evidence of breakthrough infection after having received mould-active prophylaxis at an adequate drug level for >3 days should have their antifungal therapy changed.

Primary antifungal treatment for IA should be given for ≥8 days to allow an effect to be seen, before the patient can be considered to have refractory disease. Reasons for changing the first-line treatment were broken down by the time since initiation. At any time, the primary antifungal agent should be changed if a pathogen resistant to that therapy is identified. At days 8–14, treatment should be changed if: the serum galactomannan index has not fallen by either 1 unit or to <0.5 units (based on measurements taken ≥7 days apart); positive galactomannan is identified from bronchoalveolar lavage fluid in a patient without a previous positive test; the patient shows clinical deterioration consistent with persisting or progressive IFD, without any other identifiable reason; or clinical or radiological evidence of a distinct new site of infection is found. At ≥15 days after therapy initiation, any of the previous criteria, or the progression of the original lesions on imaging with no change in immune status, should prompt a change in antifungal therapy.

Other than culture of a resistant organism or a new lesion on radiology, there is no single diagnostic test that, in isolation, indicates the need to change therapy. Instead, an approach that integrates clinical, radiological and mycological findings is recommended. An understanding of local epidemiology is required so that an appropriate therapy can be chosen if the patient is switched to a second-line agent in the absence of an identified pathogen.

CONCLUSIONS: The treatment of IA is challenging. An advisory board has provided pragmatic criteria to help clinicians decide when to change therapy for breakthrough or progressive infections.

https://doi.org/10.1093/jac/dkab317

RISK FACTORS FOR INVASIVE *CANDIDA* INFECTION IN CRITICALLY ILL PATIENTS - A SYSTEMATIC REVIEW AND META-ANALYSIS

Chest, 2021 October 18; Epub ahead of print

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BACKGROUND & AIM: *Candida* spp. are responsible for 80% of invasive fungal infections in intensive care units (ICUs). Invasive *Candida* infections (ICI) are associated with a high risk of death, especially in patients with septic shock in whom antifungal therapy has been delayed. As the early identification of ICI is difficult, guidelines recommend empirical antifungal therapy in patients with sepsis. However, many risk factors for ICI have been identified and most are non-specific; hence, their broad application would result in the majority of ICU patients with sepsis being considered eligible for empirical antifungal therapy. The aim of this meta-analysis was to identify the most important risk factors for the development of ICI in adult ICU patients.

STUDY DESIGN: Systematic review and meta-analysis.

ENDPOINTS: Factors associated with the risk of ICI.

METHOD: A search of five electronic databases for cohort and case–control studies involving adults admitted to an ICU that assessed risk factors for the occurrence of ICI identified 34 studies assessing 29 possible risk factors. Pooled adjusted univariate and multivariable odds ratios were calculated using a general inverse variance method with a random-effects model. Heterogeneity between studies was assessed.

RESULTS: In univariate analysis, factors associated with the highest risk of ICI included length of ICU stay, receipt of broad-spectrum antibiotics for >72 hours, blood transfusion, presence of *Candida* colonization or a central venous catheter, and receipt of total parenteral nutrition (table). Significant between-study heterogeneity was observed for 12 risk factors. In adjusted multivariable analyses (involving 17 studies and 15 risk factors), pooled odds ratios were highest for immunosuppression (OR 14.1, 95% CI 0.10–1945.2) and mechanical ventilation (OR 6.6, 95% CI 0.45–95.8) (two studies each), whereas length of ICU stay was not associated with a significant risk of ICI (three studies).

CONCLUSIONS: Numerous factors were associated with the risk of developing ICI in ICU patients. Limited multivariate analysis data and the small number of studies reporting each risk factor restricted the ability to identify risk factors independently associated with ICI.

Factors associated with the highest risk of invasive *Candida* infections in adults admitted to intensive care units (ICUs) in univariate analyses

Risk factor	Unadjusted odds ratio (95% confidence interval)	Number of studies
Length of ICU stay	17.3 (4.1–73.0)	4
Broad-spectrum antibiotics for >72 hours	5.61 (3.56–8.84)	16
Blood transfusion	4.89 (1.46–16.34)	4
Candida colonization	4.74 (1.57–14.25)	12
Central venous catheter	4.66 (2.68–8.10)	18
Total parenteral nutrition	4.56 (3.32–6.26)	24

https://doi.org/10.1016/j.chest.2021.08.081

INVASIVE FUNGAL DISEASE IN PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

Journal of Fungi, 2021 September 15; 7(9):761

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BACKGROUND & AIM: Patients with haematological malignancies, including those with acute myeloid leukaemia (AML), may develop invasive fungal disease (IFD), a complication associated with high morbidity. Although mould-active prophylaxis has been shown to be beneficial in high-risk patients, up to 18% of AML patients experience breakthrough IFD. In recent years, the development of new antifungals and improved formulations of existing agents has led to changes in antifungal prophylaxis strategies for AML patients. The aim of this study was to evaluate the effectiveness of current prophylaxis for preventing IFD in patients with AML.

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

ENDPOINTS: IFD and factors associated with IFD; mortality.

METHOD: The study population comprised 251 adults with newly diagnosed AML (148 primary AML, 76 antecedent myelodysplastic syndrome, 27 secondary AML) who began induction chemotherapy between June 2014 and January 2019. Patients were followed for 1 year after beginning chemotherapy or until death.

RESULTS: Overall, 157 patients (63%) received one cycle of induction chemotherapy and 94 (37%) received two or more cycles. Seventy-five patients (30%) underwent an allogeneic haematopoietic-cell transplant within the first year after starting induction chemotherapy, 52 (69%) of whom developed graft-versus-host disease. Seventeen of the 251 patients (7%) developed proven (*n*=4) or probable (*n*=13) IFD. Twelve of the cases of IFD (71%) were mould infections, including invasive pulmonary aspergillosis (*n*=6), mucormycosis (*n*=3), fusariosis (*n*=3), *Pneumocystis* pneumonia (*n*=3) and invasive candidiasis (*n*=2). Eight cases of breakthrough IFD, seven of them due to moulds, occurred in patients taking antifungal prophylaxis. Compared with patients without IFD, those with proven/probable IFD were significantly older (hazard ratio 1.046, 95% confidence interval 1.002–1.093; *p*=0.04) and had a greater number of cumulative neutropenic days (HR 1.038, 95% CI 1.018–1.059; *p*=0.0001). Cause-specific proportional hazards regression showed that the risk of IFD increased by 3.8% for each day of neutropenia per 100 days of follow-up. The risk of IFD was also significantly elevated in patients with relapsed/refractory AML (HR 7.562, 95% CI 2.585–22.123; *p*=0.0002). Kaplan–Meier survival analysis revealed significantly higher 1-year mortality among patients who developed proven/probable IFD compared with those who did not (76% versus 36%, *p*=0.02).

CONCLUSIONS: Despite the use of antifungal prophylaxis, 7% of AML patients developed IFD, which was associated with an increased risk of mortality.

https://doi.org/10.3390/jof7090761

PATHOGENESIS OF RESPIRATORY VIRAL AND FUNGAL COINFECTIONS

Clinical Microbiology Reviews, 2021 November 17; 35(1):e0009421

AUTHORS: Salazar F, Bignell E, Brown GD, Cook PC, Warris A
CENTRE: Medical Research Council Centre for Medical Mycology, University of Exeter, Exeter, UK

BACKGROUND & AIM: People with severe viral respiratory tract infections, such as pneumonia or COVID-19 infection, are now known to be at high risk of developing a fungal coinfection, often caused by *Aspergillus* species. The aim of this review was to describe the current understanding of the pathogenesis of invasive fungal infection following severe viral pneumonia, in particular influenza-associated pulmonary aspergillosis (IAPA) and COVID-19–associated pulmonary aspergillosis (CAPA).

ARTICLE TYPE: Review.

FINDINGS: Susceptibility to fungal coinfections in individuals suffering from severe viral pneumonia is mediated by several major mechanisms, including innate immunity (with roles for the epithelial barrier, phagocytes and antigen-presenting cells), T-cell responses, and adaptive humoral and cytotoxic responses. The copathogenesis of such infections involves a dynamic interplay between the immune defences and the infecting organisms.

Clinical studies have shown wide variations in the incidence of IAPA and CAPA, probably due to differences in environmental and/or genetic factors, the type of circulating viral strain, treatments given for the critical illness, and the use and availability of fungal diagnostic tools.

Treatment modalities commonly used in severely ill patients, including antibiotics, antivirals and immunomodulatory therapies, can increase susceptibility to respiratory fungal coinfections. For example, studies have reported an association between the use of corticosteroids and the incidence of invasive pulmonary aspergillosis in critically ill patients with COVID-19. Recent clinical trials have also indicated that, although adding the anti–interleukin-6 agent tocilizumab to corticosteroids can improve outcomes in patients with severe COVID-19 infection, such patients are at increased risk of developing CAPA and may then be at increased risk of dying. Further work is needed to understand whether tocilizumab increases susceptibility to respiratory fungal coinfections and worsens outcomes. In addition, meta-analyses of retrospective studies may help to clarify the role of immunosuppressive therapies in the risk of fungal coinfection in patients with COVID-19.

CONCLUSIONS: Coinfection with viral and fungal pathogens is increasingly being recognized, and mortality is increased among patients with IAPA or CAPA. Various immune pathways are implicated in the pathogenesis of such coinfections. Comprehensive epidemiological data on coinfections are needed, in order to better determine the incidence, clinical features and characteristics of secondary fungal infections in patients with influenza or COVID-19.

https://doi.org/10.1128/CMR.00094-21

REAL-LIFE CONSIDERATIONS ON ANTIFUNGAL TREATMENT COMBINATIONS FOR THE MANAGEMENT OF INVASIVE MOLD INFECTIONS AFTER ALLOGENEIC CELL TRANSPLANTATION

Journal of Fungi, 2021 September 28; 7(10):811

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BACKGROUND & AIM: Invasive mould infections (IMIs) increase the risk of mortality in patients undergoing allogeneic hematopoietic-cell transplant (HCT). Combination antifungal therapy could potentially be more effective than monotherapy, but prospective trials have not shown this. The current study examined usage of combination therapy in a tertiary hospital to shed light on how and when it was used in clinical practice.

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

ENDPOINTS: Primary: frequency of, and indications for, combination therapy. Secondary: therapy duration and 12-week and 1-year mortality.

METHOD: The study analysed records for 515 patients who underwent allogeneic HCT between January 2010 and January 2020 and subsequently developed proven or probable IMI and were followed up for ≥1 year, distinguishing between those with invasive aspergillosis (IA) and those with other IMIs. Combination therapy was defined as treatment with two or more antifungals for ≥3 days.

RESULTS: Overall, 47 (9.1%) patients were treated for 48 episodes of IMI, of which 33/48 (68.7%) were IA and 15/48 (31.3%) were non-IA infections. Overall, 23 (49%) patients received monotherapy only, 4 (9%) received combination therapy only and 20 (42%) received both monotherapy and combination therapy. This therapy split did not vary between IA versus non-IA infections, nor did the median time to start of combination therapy (9 days versus 6 days, p=0.46). The main reasons for starting combination therapy were severe infection (38%) and lack of antifungal susceptibility data (30%). Both IA and non-IA patients who received combination therapy were given a median of two courses. Combination therapy duration tended to be longer in non-IA patients (median 28 days versus 14 days for IA). The most common drug combinations used were liposomal amphotericin B plus either an azole (28%) or echinocandin (21%), with no striking differences between IA and non-IA patients. Overall, 14 (30%) patients died in the first 12 weeks and 30 (64%) died within 1 year, with a median time from diagnosis to death of 123 days for IA patients and 150 days for non-IA patients. Those given ≥50% of treatment as combination therapy were more likely to die in the first 12 weeks, especially if they had non-IA infections, which may indicate that this group received combination therapy because they had a worse prognosis.

CONCLUSIONS: Combination antifungal therapy was used in highly variable ways in the treatment of IMI after allogeneic HCT at this tertiary centre, and no evidence emerged of superiority over monotherapy.

https://doi.org/10.3390/jof7100811

CRYPTOCOCCUS GATTII SPECIES COMPLEX AS AN OPPORTUNISTIC PATHOGEN:

UNDERLYING MEDICAL CONDITIONS ASSOCIATED WITH THE INFECTION

mBio, 2021 October 26; 12(5):e0270821

AUTHORS: Yang DH, England MR, Salvator H, Anjum S, Park YD, Marr KA, Chu LA, Govender NP, Lockhart SR, Desnos-Ollivier M, Chen S, Halliday C, Kan A, Chen J, Wollenberg KR, Zelazny A, Perfect JR, Chang YC, Bennett JE, Holland SM, Meyer W, Williamson PR, Kwon-Chung KJ
CENTRE FOR CORRESPONDENCE: National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, USA

BACKGROUND & AIM: Cryptococcosis is caused by *Cryptococcus neoformans* and *C. gattii* species complexes. *C. neotransformans* is an opportunistic pathogen primarily infecting immunocompromised individuals, whereas *C. gattii* is currently considered to be a primary pathogen as it has a high infection frequency in seemingly immunocompetent individuals. The aim of this study was to investigate host and microbial characteristics in a worldwide sample of patients infected with *C. gattii*, and to identify potential risk factors for this fungal infection.

STUDY DESIGN: Retrospective clinical study.

ENDPOINTS: Molecular type of *C. gattii*; immune status; comorbidity; serum granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies.

METHOD: The study included 135 patients from Africa (*n*=40), America (*n*=50), Asia (*n*=12), Australia (*n*=26) and Europe (*n*=7) infected with *C. gattii* who had a documented medical history. Clinical data and *C. gattii* types were assessed. In addition, plasma samples were available for 32 patients; these were tested for the presence of GM-CSF autoantibodies, a known hidden risk factor for *C. gattii* infection.

RESULTS: Forty-nine of the patients were known to be immunocompromised and 86 were considered immunocompetent (although some had underlying health conditions). The immunocompromised patients had risk factors similar to those seen for *C. neotransformans* infection (e.g. HIV infection, cancer, diabetes mellitus, corticosteroid treatment). Among the 32 patients with plasma samples available, three had known immunosuppressive disorders and 29 were previously healthy with no known immunosuppression, although four had other medical conditions. Among the 29 patients who were considered immunocompetent, 20 (69%) had GM-CSF autoantibodies present in their serum. Among the 25 immunocompetent patients with no comorbidities, 19 (76%) had GM-CSF autoantibodies present. The *C. gattii* isolates from the 135 patients represented all four major lineages for this organism (VGI to VGIV). The frequency of each molecular type correlated with the geographical region of origin. No relationship was found between molecular type and underlying medical conditions, other than over-representation of VGIV among HIV-positive patients due to its high prevalence in Africa.

CONCLUSIONS: This study confirms that the presence of GM-CSF autoantibodies is an important hidden risk factor for *C. gattii* infection. *C. gattii* species complex should be recognized as an opportunistic fungal pathogen that affects not only immunocompromised patients but also apparently immunocompetent individuals who have GM-CSF autoantibodies in their serum.

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ANTIFUNGAL PROPHYLAXIS FOR PREVENTION OF COVID-19-ASSOCIATED PULMONARY ASPERGILLOSIS IN CRITICALLY ILL PATIENTS:

AN OBSERVATIONAL STUDY

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BACKGROUND & AIM: In patients who develop COVID-19–associated severe acute respiratory failure, COVID-19–associated pulmonary aspergillosis (CAPA) has emerged as an important fungal complication, affecting an average of 8.9% of patients admitted to intensive care units (ICUs). It is currently not known whether mould-active antifungal prophylaxis (MAFP) can prevent CAPA in this patient population. The aim of this study was to determine whether MAFP prevented CAPA and improved survival in critical-care patients with COVID-19–associated acute respiratory failure.

STUDY DESIGN: Single-centre, observational study.

ENDPOINTS: Primary endpoint: incidence of CAPA within 30 days of ICU admission. Secondary endpoint: 30-day ICU overall survival.

METHOD: The study included 132 consecutive adults (median age 65 years, 36% female) with COVID-19–associated acute respiratory failure who were admitted to an ICU between September 2020 and May 2021. CAPA incidence and overall survival were compared between patients who received MAFP (n=75) and those who did not (n=57). ECMM/ISHAM consensus criteria were used to classify CAPA cases. Between-group differences in baseline characteristics were accounted for by performing propensity score adjustment, which was transformed into inverse-probability-of-treatment-weight (IPTW) to allow for adjusted statistical analyses with IPTW-weighted data.

RESULTS: In the MAFP group, treatment was administered within 48 hours after ICU admission (98% received intravenous posaconazole). Ten cases of CAPA were diagnosed during the first 30 days after ICU admission, including one in the MAFP group and nine in the non-prophylaxis group. In the adjusted analysis, the 30-day CAPA incidence estimates were 1.1% and 15.8% in the MAFP and non-prophylaxis groups, respectively (Gray's test p=0.001). The corresponding subdistributional hazard ratio for administration of MAFP was 0.07 (95% confidence interval 0.01–0.57, p=0.013). However, there was no improvement in 30-day ICU overall survival in the MAFP group versus the non-prophylaxis group, with 30-day survival rates of 62.7% versus 63.1%, respectively.

CONCLUSIONS: Mould-active antifungal prophylaxis significantly reduced the incidence of CAPA in patients with COVID-19–associated acute respiratory failure admitted to ICU, but did not result in improved survival.

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FUNGAL INFECTIONS IN MECHANICALLY VENTILATED PATIENTS WITH COVID-19 DURING THE FIRST WAVE:

THE FRENCH MULTICENTRE MYCOVID STUDY

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BACKGROUND & AIM: There is evidence that patients with COVID-19 are at increased risk of fungal infections. However, the estimated prevalence of COVID-19–associated pulmonary aspergillosis (CAPA) ranges from <5% to >30% and the prevalence of candidaemia and other fungal infections is even less clear. This study characterized the prevalence and outcomes of invasive fungal infections (IFIs) in mechanically ventilated ICU patients with COVID-19.

STUDY DESIGN: Multicentre, observational, cohort study.

ENDPOINTS: Primary endpoint: prevalence of IFIs. Secondary endpoints: risk factors for proven or probable (pr/pb) CAPA, and ICU mortality.

METHOD: Adults with COVID-19 who required mechanical ventilation for acute respiratory distress syndrome were retrospectively and prospectively enrolled during the first wave of COVID-19 infection in France in 2020 and systematically screened for respiratory fungal micro-organisms once or twice per week until ICU discharge. The analysis included patients with at least three screening samples (*n*=509).

RESULTS: The mean age of participants was 59.4±12.5 years and 79% were male. The mean duration of ICU stay was 32.7±24.1 days. In total, 138 episodes of pr/pb or possible IFIs were experienced by 128 patients (25%), 76 of whom (15%) fulfilled the ECMM/ISHAM criteria for pr/pb CAPA. Other pr/pb IFIs were recorded for 38 patients (7%): candidaemia, *n*=32 (6%); invasive mucormycosis, *n*=6 (1%); and invasive fusariosis, *n*=1 (<1%). At ICU discharge, overall ICU mortality was significantly higher in patients with pr/pb CAPA than in those without (61.8% versus 32.1%, $p<0.0001$). Multivariate analysis revealed that age >62 years, treatment with dexamethasone plus anti–interleukin-6, and mechanical ventilation for >14 days were associated with pr/pb CAPA (table). Multivariate analysis adjusted for candidaemia found that age >62 years, solid-organ transplantation and pr/pb CAPA were independently associated with mortality.

CONCLUSIONS: The prevalence of invasive pulmonary aspergillosis and candidaemia was high among mechanically ventilated patients with COVID-19. A high mortality rate was observed for patients with pr/pb CAPA.

Factors independently associated with pr/pb CAPA or with mortality in mechanically ventilated COVID-19 patients

Outcome	Risk factor	OR or HR (95% CI)	*p*
pr/pb CAPA	Age >62 years	OR 2.34 (1.39–3.92)	0.0013
	Dexamethasone plus anti–IL-6	OR 2.71 (1.12–6.56)	0.027
	Mechanical ventilation >14 days	OR 2.16 (1.14–4.09)	0.019
Mortality	Age >62 years	HR 1.71 (1.26–2.32)[a]	0.0005
	Solid-organ transplantation	HR 2.46 (1.53–3.95)[a]	0.0002
	pr/pb CAPA	HR 1.45 (1.03–2.03)[a]	0.033

[a] Analysis adjusted for candidaemia. CAPA=COVID-19–associated pulmonary aspergillosis, CI=confidence interval, HR=hazard ratio, IL-6=interleukin-6, OR=odds ratio, pr/pb=proven or probable.

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