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on systemic fungal infections

Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis

Intensive Care Medicine, 2021 August; 47(8):819–34

Azole-resistant *Aspergillus fumigatus* in the environment: identifying key reservoirs and hotspots of antifungal resistance

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Clinical Infectious Diseases, 2021 July 20; Epub ahead of print

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Intensive Care Medicine, 2021 June; 47(6):674–86

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Transplantation and Cellular Therapy, 2021 September; 27(9):781.e1–5

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TASKFORCE REPORT ON THE DIAGNOSIS AND CLINICAL MANAGEMENT OF COVID-19 ASSOCIATED PULMONARY ASPERGILLOSIS

Intensive Care Medicine, 2021 August; 47(8):819–34

AUTHORS: Verweij PE, Brüggemann RJ, Azoulay E, et al.
CENTRE FOR CORRESPONDENCE: Department of Medical Microbiology, Radboudumc Center for Infectious Diseases (RCI), Radboud University Medical Center, Nijmegen, the Netherlands

BACKGROUND & AIM: Coronavirus-associated pulmonary aspergillosis (CAPA) has emerged during the COVID-19 pandemic. CAPA has different characteristics to influenza-associated pulmonary aspergillosis (IAPA) but, like IAPA, is associated with high mortality. A group of 28 international experts, many with experience of formulating IAPA guidelines, was convened to evaluate existing knowledge about CAPA and to propose practical, evidence-based, guidelines for its diagnosis and management.

ARTICLE TYPE: Expert review and practice guidance.

FINDINGS: Recommendations on the management of patients with CAPA were formulated based on published literature and expert opinion, and an outline management algorithm was provided. With respect to a standardized case definition, the panel found that the consensus definition published by ISHAM/ECMM in 2020 provided the most useful starting point for identifying CAPA, although discrepant features of CAPA, including non-typical radiological findings, mean that it may not cover all cases effectively.

Although the quality of existing evidence was mostly low, the panel strongly endorsed the use of bronchoscopy with bronchoalveolar lavage (BAL) for diagnosis. BAL fluid should be analysed using microscopy, *Aspergillus* culture, galactomannan or PCR testing. Azole resistance testing should also be done. They cautioned that serum galactomannan and β-D-glucan tests and standard CT imaging were not helpful. Many radiological findings that might indicate CAPA may also be a result of coronavirus infection and thus lack diagnostic specificity.

The prevalence of CAPA in ICU patients varied from 0% to 33% in 15 published case series, with a mean of 9.3%. However, most cases were rated probable or possible rather than proven, as only one series used gold-standard bronchoscopy for diagnosis. Few CAPA patients have classical host-related risk factors such as malignancy or solid organ transplantation, but some studies have identified long-term/high-dose steroid treatment as a predisposing risk.

The panel recommended the use of empirical antifungal therapy in CAPA patients, with later discontinuation if BAL testing was negative. Antifungal selection should follow national/international guidelines. A strong recommendation for therapeutic drug monitoring of triazole therapy was made. Despite very low quality evidence, the panel found that stopping concomitant dexamethasone or corticosteroid therapy in CAPA was probably not justified. However, discontinuation or tapering could be considered in patients who did not respond to antifungal therapy.

CONCLUSIONS: This report summarizes practical recommendations for the management of CAPA.

https://doi.org/10.1007/s00134-021-06449-4

AZOLE-RESISTANT *ASPERGILLUS FUMIGATUS* IN THE ENVIRONMENT:

IDENTIFYING KEY RESERVOIRS AND HOTSPOTS OF ANTIFUNGAL RESISTANCE

PLoS Pathogens, 2021 July 29; 17(7):e1009711

AUTHORS: Burks C, Darby A, Gómez Londoño L, Momany M, Brewer MT
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BACKGROUND & AIM: Aspergillosis is caused by fungal spores from the *Aspergillus* species, most commonly *A. fumigatus*, which is found in the environment on decaying plant matter. Aspergillosis is primarily treated with azoles, which are also used in agriculture to treat plant pathogenic fungi. There have been increasing reports of azole-naïve patients presenting with pan-azole–resistant strains of *A. fumigatus*, most commonly involving the TR34/L98H and TR46/Y121F/T289A alleles in the *cyp51A* gene. One study suggests that these resistant isolates are likely to have moved from the environment into human hosts (although it has not yet been proved conclusively), and this has prompted multiple investigations to identify sources of azole-resistant *A. fumigatus* in the environment. This article summarizes the findings of these studies.

ARTICLE TYPE: Review.

FINDINGS: The authors present a world map indicating locations where resistant isolates have been detected, and in what type of setting they occurred (agricultural, developed or other environments, or in commercial products). Based on 52 studies, azole-resistant *A. fumigatus* has been reported in every continent except Antarctica, with the largest number of reports from Europe (56.7%). The greatest number of resistant isolates were detected in soil (56.7%), followed by air (16.5%), plant debris (11.4%) and compost (9.4%).

A total of 53.9% of studies found azole-resistant isolates in developed environments, mostly in the soil (52.1%) or air (33.0%). More than half of these isolates (58%) were from hospital environments (including 27.1% from inside and 31.9% from outside). Overall, 32.6% of isolates from developed environments were found in gardens and plant-pots. The second most common source of azole-resistant *A. fumigatus* was soil sampled from agricultural settings.

Most resistant isolates had either the TR34/L98H allele (60.7%) or the TR46/Y121F/T289A allele (15.0%). TR34/L98H was the most common in all regions except South America where TR46/Y121F/T289A predominated. Most isolates with TR34/L98H alleles were found in Europe (71.1%), followed by the Middle East (8.2%) and India (7.8%). TR46/Y121F/T289A was prevalent in Europe (46.1%), as well as South America (23.6%) and East Asia (14.0%).

It is important to note that this survey may have been influenced by sampling bias, since some regions and environments have been more extensively sampled than others, and are therefore more likely to show greater azole resistance.

CONCLUSIONS: Azole resistant *A. fumigatus* has been found in multiple environments worldwide. Additional sampling from under-represented locations is needed.

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CASE SERIES OF FOUR SECONDARY MUCORMYCOSIS INFECTIONS IN COVID-19 PATIENTS, THE NETHERLANDS, DECEMBER 2020 TO MAY 2021

Eurosurveillance, 2021 June 10; 26(23):2100510

AUTHORS: Buil JB, van Zanten AR, Bentvelsen RG, Rijpstra TA, Goorhuis B, van der Voort S, Wammes LJ, Janson JA, Melchers M, Heusinkveld M, Melchers WJ, Kuijper EJ, Verweij PE
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BACKGROUND & AIM: Mucormycosis is a rare fungal disease which is most often found in immunocompromised individuals, patients with diabetes mellitus and patients receiving corticosteroids. Multiple cases of mucormycosis have been reported in patients with severe COVID-19, most commonly in the presence of poorly controlled diabetes and/or concomitant use of systemic corticosteroids. This article reports four cases of COVID-19–associated mucormycosis (CAM) from the Netherlands, diagnosed between December 2020 and May 2021.

ARTICLE TYPE: Case series.

FINDINGS: All four cases involved men aged between their late 50s and mid-70s who were receiving corticosteroids. Two had underlying diseases: one had chronic lymphocytic leukaemia as well as diabetes mellitus and obesity, and the other had poorly controlled diabetes mellitus and a recent cerebrovascular stroke. The other two had no underlying conditions. Three patients had been admitted to the intensive care unit, while one had not.

CAM presented variously as pulmonary, rhino-orbital cerebral and disseminated infection. One patient developed bilateral consolidations with no typical radiological signs of fungal infection, one had pulmonary cavities and a reversed halo sign, one experienced respiratory deterioration and acute-onset kidney failure, and one had extensive sinusitis with intracranial necrosis and infarction.

The diagnosis of CAM can be difficult because there is no specific biomarker, and tests for Mucorales are not always available. In three of these cases, computed tomography was not helpful for the diagnosis of CAM because of the presence of extensive COVID-19 lesions. Mucorales was first cultured from sputum in the three ICU patients.

All patients received appropriate antifungal therapy (including variously liposomal amphotericin B, posaconazole, voriconazole, isavuconazole and interferon-γ), but three subsequently died, while one was still receiving antifungal treatment and mechanical ventilation at the time of writing. Three patients had received the anti-interleukin-6 receptor monoclonal antibody tocilizumab, but it is not yet clear whether immunotherapy is a risk factor for the development of secondary invasive fungal infections.

CONCLUSIONS: It is important to be aware of the possibility of invasive mucormycosis in patients with COVID-19, particularly those receiving corticosteroids and/or with poorly controlled diabetes mellitus. When invasive mucormycosis is diagnosed, aggressive management is recommended.

https://doi.org/10.2807/1560-7917.ES.2021.26.23.2100510

TREATMENT PRACTICES FOR ADULTS WITH CANDIDEMIA AT NINE ACTIVE SURVEILLANCE SITES – UNITED STATES, 2017–2018

Clinical Infectious Diseases, 2021 June 3; Epub ahead of print

AUTHORS: Gold JA, Seagle EE, Nadle J, et al.
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BACKGROUND & AIM: A growing prevalence of non-*albicans Candida* species and increase in antifungal resistance led in 2016 to changed recommendations by the Infectious Diseases Society of America (IDSA) for the treatment of candidaemia, favouring early use of echinocandins and greater adoption of antifungal susceptibility testing (AFST). The aim of this study was to characterize initial and subsequent therapy of candidaemia cases and discover whether the updated guidelines had been generally adopted.

STUDY DESIGN: Population-based, multicentre, epidemiological survey.

ENDPOINTS: Type of initial and subsequent therapy, use of AFST, in-hospital mortality.

METHOD: Data on 2271 initial (index) candidaemia cases among adult patients in nine geographically distributed areas of the USA during the period January 2017 to December 2018 were gathered using standardized methodology to record the *Candida* species identified, use of AFST, initial and subsequent antifungal treatment, patient characteristics and mortality.

RESULTS: Initial therapy was with an echinocandin in 1258 (68.6%) of index cases, fluconazole in 543 (29.6%), and another antifungal in 34 cases; no therapy was given in 436 cases. Among the 1801 cases initially treated with either an echinocandin or fluconazole, treatment continued unchanged in approximately half of cases. If therapy was switched, this occurred after a median of 3 (echinocandin) or 2 days (fluconazole), principally to the other agent. Multivariate regression showed that initial treatment was more likely to be with an echinocandin if the patient had cirrhosis (odds ratio 2.06), and was less likely if they had been hospitalized within 90 days (OR 0.80). Moreover, the likelihood of initial treatment with an echinocandin varied widely by geographical location (by a factor of up to three). Fluconazole AFST was carried out in 53.7% of cases overall, but varied widely between sites (11.5– 95.1%). AFST for echinocandin susceptibility was less common (40.0%) but showed similar variation between sites. Among the 543 patients started on fluconazole, 56.0% were found to have non-*albicans* candidaemia and 10.6% of those tested had fluconazole-resistant strains. Despite this, in-hospital mortality was greater in those given initial echinocandin therapy (28.3% versus 16.1%, $p<0.0001$), possibly because of confounding factors such as echinocandin use being more likely in critically ill patients.

CONCLUSIONS: Regional practice appeared to be the most important determinant of choice of therapy and use of AFST in patients with candidaemia in the USA, with only partial adherence to the revised IDSA guidelines.

https://doi.org/10.1093/cid/ciab512

DIAGNOSIS AND TREATMENT OF COVID-19 ASSOCIATED PULMONARY APERGILLOSIS IN CRITICALLY ILL PATIENTS:

RESULTS FROM A EUROPEAN CONFEDERATION OF MEDICAL MYCOLOGY REGISTRY

Intensive Care Medicine, 2021 July 16; Epub ahead of print

AUTHORS: Prattes J, Wauters J, Giacobbe DR, Lagrou K, Hoenigl M, for the ECMM-CAPA Study Group
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BACKGROUND & AIM: COVID-19–associated pulmonary aspergillosis (CAPA) has become a significant complication in patients with acute respiratory failure caused by SARS-CoV-2. The diagnosis of CAPA relies on microbiological testing, including culture of lower respiratory tract samples and detection of bronchoalveolar lavage fluid galactomannan (BALF-GM). The aim of this study was to assess approaches to the diagnosis and treatment of CAPA, as well as the prevalence of CAPA, across nine countries.

STUDY DESIGN: Multinational cohort study.

ENDPOINTS: Diagnostic approach and treatment of CAPA.

METHOD: Twenty centres provided data on consecutive patients with COVID-19 admitted to the intensive care unit (ICU) due to respiratory failure, with or without CAPA. Information was collected on their diagnostic work-up, treatment and outcome, and cases were classified according to the 2020 ECMM/ISHAM consensus criteria on the definition and management of CAPA. The study included 592 cases, 98.5% of whom were from Europe.

RESULTS: A total of 11 patients (1.9%) had proven CAPA, 80 (13.5%) had probable CAPA and 18 (3%) had possible CAPA, giving an overall prevalence for probable/proven CAPA of 15.4% in this cohort. The median BALF-GM optical density index (ODI) in patients with CAPA was 2.74 (from a sample of 83 patients), while 2.4% of patients without CAPA (from a sample of 170) had a BALF-GM ODI greater than 1.0. Other diagnostic approaches included serum GM, tracheal aspirate GM, *Aspergillus* spp. culture and *Aspergillus* PCR (table). A total of 99 patients received systemic antifungal treatment (including voriconazole, isavuconazole and amphotericin B). A total of 261 deaths occurred. The ICU mortality rates for CAPA patients were 1%, 16% and 20% at 1, 15 and 90 days, respectively.

CONCLUSIONS: The diagnosis of CAPA is challenging. Serum GM has limited sensitivity for this complication, and lower respiratory sampling or tracheal, bronchial or lung biopsy are required for confirmation. ICU mortality is high in patients with CAPA despite antifungal treatment.

Diagnostic characteristics of patients with COVID-19–associated pulmonary aspergillosis

Test	Positivity rate, n/N (%)
BALF galactomannan >1.0 ODI	64/83 (77)
Serum galactomannan >0.5 ODI	16/85 (19)
Tracheal aspirate galactomannan >1.2 ODI	16/21 (76)
BALF-positive *Aspergillus* spp. culture	45/85 (53)
Bronchial aspiration positive *Aspergillus* spp. culture	14/32 (44)
Tracheal aspiration positive *Aspergillus* spp. culture	42/68 (62)
Sputum-positive *Aspergillus* spp. culture	4/29 (14)
BALF-positive *Aspergillus* PCR	24/33 (73)
Tracheal aspiration positive *Aspergillus* PCR	7/32 (22)

BALF, bronchoalveolar lavage fluid; ODI, optical density index.

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CEREBRAL MUCORMYCOSIS: NEUROIMAGING FINDINGS AND HISTOPATHOLOGICAL CORRELATION

Journal of Neurology, 2021 July 8; Epub ahead of print

AUTHORS: Lersy F, Royer-Leblond J, Lhermitte B, Chammas A, Schneider F, Hansmann Y, Lefebvre N, Denis J, Sabou M, Lafitte F, Cotton F, Boncoeur-Martel MP, Tourdias T, Pruvo JP, Cottier JP, Herbrecht R, Kremer S

CENTRE FOR CORRESPONDENCE: Service d'imagerie 2, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

BACKGROUND & AIM: Mucormycoses are rare, opportunistic infections caused by Mucorales fungi that typically affect immunocompromised or diabetic patients and are often fatal. Involvement of the central nervous system in mucormycoses is associated with increased mortality. Prompt diagnosis and treatment is important. The aim of this study was to analyse the neuroimaging and histopathological findings of cerebral mucormycosis.

STUDY DESIGN: Retrospective study.

ENDPOINTS: Neuroimaging and histopathological findings.

METHOD: The analysis included neuroimaging findings from 18 patients with mucormycosis seen across five French university hospitals between 2008 and 2018. Histopathological analysis was performed in four of these patients. The radiological findings were obtained from computed tomography (CT) and magnetic resonance imaging (MRI) scans.

RESULTS: The patients were aged 3–74 years and were all immunocompromised and/or diabetic. The radiological presentation depended on the dissemination pathway (haematogenous versus direct posterior extension with/without perineural spread). Haematogenous dissemination affected 15 patients and manifested mainly as brain abscesses (59 lesions) and cortical, cortical–subcortical or basal ganglia involvement, with the presence of a halo on diffusion-weighted imaging seen in lesions >1.6 cm. T1-weighted enhancement after gadolinium administration was visualized in only two patients (seven lesions). Ischaemia and haemorrhagic areas were also observed. Five patients had vascular lesions, such as stenosis and thrombosis. Six patients had direct posterior sinonasal and perineural extension lesions, which appeared as bifrontal basal hypodensities on CT and as restricted diffusion without enhancement on MRI. Two patients presented with perineural spread along the trigeminal nerve. All four patients with histopathology data had endovascular lesions with complete or incomplete destruction of vessel walls, microbleeding around vessels, and acute and chronic inflammation.

CONCLUSIONS: Among patients with mucormycosis affecting the central nervous system, neuroimaging findings were dependent on the dissemination pathway. MRI was the most sensitive technique. The most common finding was brain abscess, with halo on diffusion-weighted imaging seen in large lesions. Histopathological findings were similar in all patients evaluated and were consistent with angioinvasive activity.

https://doi.org/10.1007/s00415-021-10701-8

EPIDEMIOLOGY, CLINICAL PROFILE, MANAGEMENT, AND OUTCOME OF COVID-19-ASSOCIATED RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS IN 2826 PATIENTS IN INDIA –

COLLABORATIVE OPAI-IJO STUDY ON MUCORMYCOSIS IN COVID-19 (COSMIC), REPORT 1

Indian Journal of Ophthalmology, 2021 July; 69(7):1670–92

AUTHORS: Sen M, Honavar SG, Bansal R, et al., for the Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC) Study Group
CENTRE FOR CORRESPONDENCE: Ophthalmic Plastic Surgery and Ocular Oncology, Centre for Sight, Ashoka Capitol, Telangana, India

BACKGROUND & AIM: The prevalence of mucormycosis is much higher in India compared with other parts of the world. During India's second wave of the COVID-19 pandemic, the occurrence of rhino-orbital-cerebral mucormycosis (ROCM) associated with COVID-19 reached epidemic proportions. The aim of this study was to determine the characteristics and management of patients with ROCM associated with COVID-19 in India.

STUDY DESIGN: Retrospective, multicentre, observational study.

ENDPOINTS: Demographics, clinical characteristics, risk factors, therapy and outcomes.

METHOD: The analysis included data from 2826 patients with possible, probable or proven ROCM associated with COVID-19 infection who were treated by ophthalmologists in India.

RESULTS: The patients had a median age of 53 (range 12–88) years, were mostly men (71%), and 78% had diabetes mellitus. Overall, 72% required hospitalization, 57% required oxygen support and 87% received systemic corticosteroids. Symptoms of ROCM developed a mean of 14.5±10 days after COVID-19 diagnosis. Involvement of the orbit (stage 3) occurred in 72% of the patients, most of whom presented with stage 3c (extensive sino-orbital) disease. Treatment included intravenous amphotericin B in 73% of patients for a median of 7 (range 1–60) days, functional endoscopic sinus surgery (FESS)/paranasal sinus (PNS) debridement in 67%, orbital exenteration in 15% and both FESS/PNS debridement and orbital exenteration in 17%. Intraorbital amphotericin B was administered to 22% of patients. Among 2218 patients with outcome data, 305 (14%) died. Prognosis was poor in patients with stage 3c or worse, with mortality/disease progression seen in 39% of these patients compared with 12% of those with stage 3b (limited sino-orbital) disease or better ($p<0.05$). In patients with stage 4 disease (intracranial extension/central nervous system involvement), mortality/disease progression decreased from 67% to 39% after PNS debridement ($p<0.05$) and from 52% to 39% after orbital exenteration ($p<0.05$).

CONCLUSIONS: Patients with ROCM associated with COVID-19 were mostly middle-aged men with diabetes or receiving corticosteroids. ROCM developed on average 2 weeks after the diagnosis of COVID-19. Intravenous amphotericin B was the drug of choice in most cases, and aggressive surgical debridement was often necessary. The prognosis was particularly poor in patients with stage 3c or worse disease.

https://doi.org/10.4103/ijo.IJO_1565_21

INVASIVE MOULD DISEASE IN FATAL COVID-19:
A SYSTEMATIC REVIEW OF AUTOPSIES

The Lancet Microbe, 2021 August; 2(8):e405–14

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BACKGROUND & AIMS: Invasive mould disease (IMD) such as pulmonary aspergillosis has been reported in a significant proportion of critically ill patients with COVID-19, and is associated with increased mortality. The diagnosis of IMD is challenging in this context because it can be difficult to obtain tissue samples, and host factors needed for a definition of IMD are often absent in patients in the intensive care unit (ICU). Rates of COVID-19–associated pulmonary aspergillosis (CAPA) reported in ICU cohort studies may therefore not represent true tissue-invasive disease. The aim of the current systematic review was to assess the prevalence of autopsy-proven tissue-invasive IMD in decedents with fatal COVID-19 and identify potential risk factors.

STUDY DESIGN: Systematic review.

ENDPOINT: Autopsy-proven IMD.

METHOD: A literature search identified 50 studies that reported autopsy results for a total of 677 decedents with fatal COVID-19; individual-level data were available for 443 decedents (32 studies). All studies were retrospective or prospective case series reporting on at least three decedents with confirmed SARS-CoV-2 infection, and including histopathological investigation of the lungs. Cases of autopsy-proven IMD were recorded, including the type of mould if available. Data on clinical characteristics and treatment were also collected.

RESULTS: Of the 443 decedents (median age 70.0 years) for whom individual-level data were available, 30% had diabetes, 22% had pre-existing lung disease, 14% had cancer and 6% were immunocompromised. A total of 58% of decedents had received invasive mechanical ventilation (320/548 for whom this information was available). Sixty patients were treated with immunomodulatory agents and 50 with antifungal drugs. A total of 11/677 COVID-19 decedents (2%) had autopsy-proven IMD, of whom eight had CAPA, two had unspecified IMD and one had disseminated mucormycosis. IMD was reported in 6 of the 320 decedents who had received mechanical ventilation (2%). The characteristics of decedents with or without IMD are summarized in the table.

CONCLUSIONS: Autopsy-proven IMD is relatively rare among decedents with COVID-19.

Clinical characteristics of decedents with COVID-19 with or without invasive mould disease (IMD)

Factor	IMD (*n*=10)	No IMD (*n*=433)
Median age	60 years	70 years
Male	100%	66%
Pre-existing lung disease	11%	24%
Immunocompromised	11%	6%
Median time from symptom onset to death	9 days	14 days
Median length of hospital stay	14 days	10 days
Received mechanical ventilation	60%	51%
Median ventilation time	7 days	9 days
Immunomodulatory therapy for COVID-19	11%	14%

https://doi.org/10.1016/S2666-5247(21)00091-4

REMEDIATION OF MUCORALES-CONTAMINATED HEALTHCARE LINENS AT A LAUNDRY FACILITY FOLLOWING AN INVESTIGATION OF A CASE CLUSTER OF HOSPITAL-ACQUIRED MUCORMYCOSIS

Clinical Infectious Diseases, 2021 July 20; Epub ahead of print

AUTHORS: Sundermann AJ, Clancy CJ, Pasculle AW, Liu G, Cheng S, Cumbie RB, Driscoll E, Ayres A, Donahue L, Buck M, Streifel A, Muto CA, Nguyen MH
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BACKGROUND & AIM: Mucormycosis generally affects immunocompromised people, and generally manifests as respiratory tract, cutaneous or gastrointestinal infections. Outbreaks of mucormycosis in healthcare settings have been reported, and are often due to contaminated supplies or environmental reservoirs. Exposure to healthcare linens (HCLs) with Mucorales contamination has been reported, prompting the authors to call for a better understanding of the risks posed to patients by the laundering, storage and use of HCLs. This article describes the systematic investigation of potential sources of HCL Mucorales contamination after four cases of healthcare-associated mucormycosis occurred at a single centre.

ARTICLE TYPE: Epidemiological investigation.

FINDINGS: Four solid-organ transplant recipients were diagnosed with likely healthcare-associated mucormycosis at a single centre over an 11-month period. Two were infected with *Rhizopus microsporus*, one with *R. arrhizus* var *delemar* and one with *Lichtheimia corymbifera*. The Infection Prevention team identified HCLs as the likely source of infection, with surveillance cultures of freshly laundered HCLs showing contamination with *Rhizopus*, *Lichtheimia* and other Mucorales. Cultures from environments and supplies not associated with HCLs were rarely contaminated with fungi.

A dedicated team made several unannounced site visits to the HCL facility to inspect the layout and laundering process, and to perform cultures at different stations of this process. The layout, processes and workflow were all consistent with current industrial standards and guidelines. HCL fungal positivity was detected at several stations of the laundry process, with a significant increase seen in the post-wash stage. Inspection of the laundry roof revealed considerable lint accumulation, especially around the air ventilation system, including the intake vents which delivered unfiltered air into the driers. Culture of this lint grew confluent Mucorales and other moulds,

Remediation targeted the intake and exhaust vents, including installation of a filter, movement of the intake vents away from the exhaust vents, frequent lint removal from the roof, and increased attention to lint removal from floors, walls and ceilings. In addition, covers were introduced for carts containing laundered HCL awaiting transportation. These steps led to elimination of lint contamination on the roof, and a reduction in mean culture positivity for HCLs arriving at the hospital from 20% to 0.3% (p=0.0001).

CONCLUSION: Collaboration between a healthcare infection prevention team and a commercial laundry resulted in effective remediation of Mucorales-contaminated HCLs.

https://doi.org/10.1093/cid/ciab638

THE HUMAN GUT MYCOBIOME AND THE SPECIFIC ROLE OF *CANDIDA ALBICANS*: WHERE DO WE STAND, AS CLINICIANS?

Clinical Microbiology and Infection, 2021 August 4; Epub ahead of print

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BACKGROUND & AIM: Within the human gut microbiota, the mycobiome (fungi) represents a significant biomass which is potentially involved in several physiological and pathological processes. However, there is not yet any consensus on what constitutes a normal mycobiome, because of its instability and variability, as well as a lack of standardized investigative methods. This article reviews current knowledge of the human gut mycobiome, particularly the role of *Candida albicans*.

ARTICLE TYPE: Review.

FINDINGS: The structure and population of the human gut mycobiome appears to be influenced by several factors, including diet (e.g. *Candida spp*. may be related to carbohydrate ingestion), gender (a higher prevalence of *Candida spp*. is found in samples from females), age, comorbidities, medications, immune status and inter-kingdom interactions. The mycobiome is involved in physiological processes such as training the immune system. There is a high prevalence of *C. albicans* in the gastrointestinal tract of humans, and this may be relevant when considering its potential beneficial effects, such as training the immune system against candidiasis and other infections.

Alterations in the gut mycobiome have been demonstrated in a variety of conditions, including metabolic disorders such as obesity and diabetes (in which an increased prevalence of *C. albicans* in the intestine has been reported), immunological/inflammatory disorders, psychiatric conditions, chronic viral infections and SARS-CoV-2 infection. Furthermore, an increased ratio of *Basidiomycota* to *Ascomycota* (due partly to an increase of *C. albicans*) has been demonstrated in patients with inflammatory bowel disease. *Candida spp*. have also been implicated in graft-versus-host disease and in the development of some tumours.

It is difficult to foresee whether current or future understanding of the mycobiome will have any influence on clinical practice, partly because of the lack of standard investigational techniques. However, the mycobiome does play a role in health, and one possibility is to modulate *C. albicans* physiology in the gut via diet. In addition, a gut mycobiome signature could be used as a possible screening biomarker in certain conditions such as Alzheimer's disease and intestinal adenomas. It is also important to consider the interaction between antibiotic use and the gut mycobiome.

CONCLUSIONS: Despite an increase in understanding, many questions remain about the human gut mycobiome, including the role of *C. albicans*.

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POSACONAZOLE FOR PREVENTION OF INVASIVE PULMONARY ASPERGILLOSIS IN CRITICALLY ILL INFLUENZA PATIENTS (POSA-FLU):

A RANDOMISED, OPEN-LABEL, PROOF-OF-CONCEPT TRIAL

Intensive Care Medicine, 2021 June; 47(6):674–86

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BACKGROUND & AIM: Influenza-associated pulmonary aspergillosis (IAPA) affects about 20% of patients admitted to Dutch and Belgian intensive care units (ICUs) and is often fatal. Early diagnosis is difficult and resistance of *Aspergillus fumigatus* to antifungals may complicate its therapy. This study evaluated prophylaxis with posaconazole for the prevention of IAPA in an ICU context.

STUDY DESIGN: Multicentre, randomized, non-blinded trial.

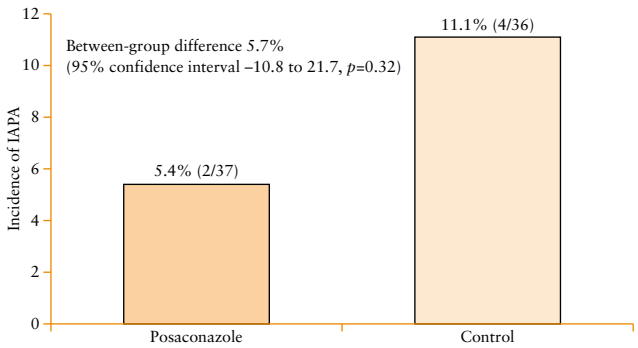
ENDPOINTS: Incidence of IAPA during ICU stay (in patients who did not have IAPA within 48 hours of ICU admission); ICU and hospital length of stay and mortality, and 90-day mortality.

METHOD: The study was conducted in 12 centres in Belgium, the Netherlands and France. Adults with PCR-confirmed influenza admitted to the ICU were randomized within 48 hours of admission 1:1 between prophylaxis with intravenous posaconazole (300 mg/day for 7 days) or standard-of-care (control) treatment. Patients were evaluated for invasive fungal infection within 48 hours of ICU admission and those with evidence of IAPA in this workup were excluded from the main analysis.

RESULTS: Of 252 critically ill influenza patients, 88 were eligible for randomization. Among 21 patients who developed IAPA during the study, 15 (71%) were diagnosed within the first 48 hours after ICU admission (early IAPA) and were excluded from the main analysis. During follow-up of the evaluable population, there was no significant difference in the incidence of IAPA between the posaconazole group and the control group (figure). Length of ICU and hospital stay and mortality rates did not differ between the two arms. Both of the IAPA cases in the posaconazole arm occurred after completing prophylaxis and were in patients receiving corticosteroids, of whom one died. Three of the four IAPA cases in the control group died in the ICU. Among the 15 early IAPA cases, all required ventilation and eight (53%) died in the ICU.

CONCLUSIONS: While this study was found to be insufficiently powered to show an effect of posaconazole prophylaxis, such use seems reasonable in view of the high mortality rate of ICU patients who develop IAPA.

Incidence of influenza-associated pulmonary aspergillosis (IAPA) during intensive care unit stay



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ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IS FEASIBLE IN PEDIATRIC PATIENTS WITH AN ACTIVE OR RECENTLY DIAGNOSED INVASIVE FUNGAL INFECTION

Transplantation and Cellular Therapy, 2021 September; 27(9):781.e1–5

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BACKGROUND & AIM: Recently diagnosed mould infection is a contraindication for allogeneic haematopoietic stem-cell transplantation (HSCT) because of the documented risk of post-transplant relapse. However, the only published study exclusively involving children found no increased risk. The aim of this study was to report outcomes of allogeneic HSCT in paediatric patients with active or recent invasive mould infections (IMIs) at a major transplant unit in the Netherlands.

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

ENDPOINTS: Post-transplant incidence of mould infection and 1-year survival.

METHOD: Electronic health records of children with active IMI or recent history (<6 months) of such infection before undergoing allogeneic HSCT at a single centre between January 2012 and June 2020 were analysed.

RESULTS: Among 317 children who underwent allogeneic HSCT at the unit during the period, 23 patients (median age 12.7 years, range 1.6–17.6) had a proven (4/23) or probable (19/23) IMI, of whom nine were receiving antifungal treatment for an active infection and 14 were receiving secondary prophylaxis (because of a recent IMI) at the time of transplant. Infections were due to *Aspergillus* species in 20 cases, including three patients with mixed infections. The most common site of infection was the lungs (22/23), with brain involvement in six patients. Seventeen patients were being transplanted because of an underlying malignancy and six for a non-malignant condition. Most patients (13/23) received cord blood while the remainder had a bone-marrow transplant. Among the 23 patients, nine developed graft-versus-host disease (GVHD) after transplantation. After 1 year, 18/23 patients (78.3%) were alive. Among the five children who died, in only one case was it because of an IMI (uncontrolled pulmonary aspergillosis complicated by GVHD). These five children all had significant comorbidities at the time of transplantation. Among the nine children with active IMI who underwent transplantation, two developed a new IMI after transplantation and two had reactivation of ongoing infection, of whom one (with GVHD) died. Of the 14 children on secondary prophylaxis at the time of transplantation, only one developed an IMI afterwards.

CONCLUSIONS: The experience with this cohort suggests that active IMI or a recent history of infection need not be a contraindication to allogeneic HSCT in paediatric patients. One-year survival was encouraging, even though four of nine children with active IMI at the time of transplantation experienced a new or reactivated IMI after transplantation.

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