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on systemic fungal infections

Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study

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PLoS Pathogens, 2020 April 2; 16(4):e1008353

ISSUE 2, 2020

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Thorax, 2020 June; 75(6): 513–16

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Clinical Infectious Diseases, 2020 March 19; Epub ahead of print

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Clinical Infectious Diseases, 2020 February 28; Epub ahead of print

Diagnosing COVID-19-associated pulmonary aspergillosis

The Lancet Microbe, 2020 June; 1(2):e53–5

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Stephen Bartlett
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Art Design
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Layout and Printing
Drukmeesters,
Zwijndrecht, the Netherlands

Publishing Director
Evelien Enter

Publisher
Waldemar H.G. Dobrowolski

Framingham bv
Amalialaan 126 G
3743 KJ Baarn
The Netherlands
framingham@framingham.nl

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

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EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF 99 CASES OF 2019 NOVEL CORONAVIRUS PNEUMONIA IN WUHAN, CHINA:

A DESCRIPTIVE STUDY

The Lancet, 2020 February 15; 395(10223):507–13

AUTHORS: Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L

CENTRES FOR CORRESPONDENCE: Tuberculosis and Respiratory Department, Wuhan Jinyintan Hospital, Wuhan; and Research Laboratory of Clinical Virology, Ruijin Hospital and Ruijin Hospital North, Shanghai Jiaotong University School of Medicine, Shanghai, China

BACKGROUND & AIM: Cases of pneumonia associated with a new coronavirus (2019-nCoV) were observed in a specialist infectious disease hospital in Wuhan, China, starting in December 2019. Case records of the series of initial patients were reviewed to throw light on the epidemiology and clinical features of this novel infection.

STUDY DESIGN: Retrospective, single-centre, case review.

ENDPOINTS: Epidemiological, demographic, clinical and radiographic parameters and outcomes.

METHOD: All adult patients admitted to Jinyintan Hospital between 1 and 20 January 2020 and diagnosed as having 2019-nCoV infection according to interim WHO criteria were included. Records for these patients were evaluated for the period up to 25 January 2020. The presence of 2019-nCoV was confirmed by RT-PCR, and other respiratory viruses were also tested for using this technique. All patients had chest X-rays or CT scans.

RESULTS: The study included 99 patients (68% male, mean age 55.5 years, 51% with a chronic medical condition), of whom 49% had a history of exposure to the Huanan seafood and live animal market. Chronic comorbid conditions were primarily cardiovascular/cerebrovascular disease (40 cases) and diabetes (12 cases). At admission, 83% of patients had fever, 82% had a cough and 31% had shortness of breath, while 15% had all three symptoms. Overall, 75% of patients had bilateral pneumonia and 25% had unilateral pneumonia. Seventeen patients (17%) developed acute respiratory distress syndrome. During the study period, 23% of patients were admitted to intensive care, 76% were given oxygen therapy, 13% received non-invasive mechanical ventilation and 4% invasive mechanical ventilation. No other respiratory viruses were detected; four cases of concomitant fungal infection were found. Lymphocytes were reduced in 35% of patients, while 86% (63/73 patients) had elevated C-reactive protein, 52% had an elevated interleukin-6 level and 63% had raised serum ferritin. Overall, 76% of patients were given one or more antiviral agent (oseltamivir, ganciclovir, lopinavir/ritonavir), 71% received antibiotics and 15% antifungal therapy. On 25 January, 31% had been discharged, 11% had died (seven of them aged >60 years) and 58% remained in hospital.

CONCLUSIONS: This study gives expanded insight into the first patients in Wuhan who had confirmed 2019-nCoV infection. It showed a clustered onset, appeared most likely to infect older men with comorbidities, and could result in potentially fatal respiratory disease.

CLINICAL AND VIROLOGICAL DATA OF THE FIRST CASES OF COVID-19 IN EUROPE:

A CASE SERIES

The Lancet Infectious Diseases, 2020 June; 20(6):697–706

AUTHORS: Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, Gaymard A, Bouscambert-Duchamp M, Donati F, Le Hingrat Q, Enouf V, Houhou-Fidouh N, Valette M, Mailles A, Lucet JC, Mentre F, Duval X, Descamps D, Malvy D, Timsit JF, Lina B, van-der-Werf S, Yazdanpanah Y
CENTRE FOR CORRESPONDENCE: Department of Infectious and Tropical Diseases, Assistance Publique–Hôpitaux de Paris, Bichat-Claude Bernard University Hospital, Paris, France

BACKGROUND & AIM: The coronavirus disease 2019 (COVID-19) pandemic began in Wuhan, China at the end of 2019. In Europe, the first patient with COVID-19 was diagnosed in France on 24 January 2020. This paper described the clinical course of the first five patients diagnosed with COVID-19 in France, three of whom were treated with the investigational anti-viral drug remdesivir.

STUDY DESIGN: Case series.

ENDPOINT: Clinical course of COVID-19 infection.

METHOD: Five Chinese patients were admitted to one of two French hospitals with COVID-19, having arrived from China in mid-January. Three patients with severe disease according to WHO criteria were treated with intravenous remdesivir (recommended regimen: loading dose 200 mg, followed by a maintenance daily dose of 100 mg for a total 10 days).

RESULTS: Patient 1 was a 31-year-old man diagnosed with COVID-19 on 24 January (illness day 6), 5 days after arriving in France. His symptoms worsened on ill-ness day 10, and remdesivir was started, but was discontinued after 5 days due to elevated alanine aminotransferase and a maculopapular rash. The patient recovered (discharged 12 February). Patient 2 was a 48-year-old man diagnosed with COVID-19 on 24 January (illness day 9), 2 days after arriving in France. Two days later he was transferred to the intensive care unit (ICU) with worsening symptoms, including fever and skin mottling suggestive of sepsis. Remdesivir was administered for 10 days, starting on illness day 15. He made a full recovery (discharged 14 February). Patient 3 was an 80-year-old male with previous thyroid cancer who was diagnosed with COVID-19 on 28 January (illness day 7), 11 days after arriving in Europe and 2 days after being admitted to the ICU with acute respiratory failure, which was followed by multiple organ failure. Remdesivir was started but discontinued after a single dose because it contains cyclodextrin and, as the patient required renal replacement therapy, there was a risk of cyclodextrin accumulation. Remdesivir was restarted 6 days later because of the illness severity and persistent viral detection. Treatment was also given for *Acinetobacter baumannii* and *Aspergillus flavus* infection. The patient died on 14 February (illness day 24). Patient 4 (wife of Patient 1) and Patient 5 (daughter of Patient 3) had mild disease that resolved without specific treatment.

CONCLUSIONS: Three different clinical courses of COVID-19 were identified (mild, mild with deterioration by day 10–11, and rapidly severe). No firm conclusions could be drawn regarding the efficacy of remdesivir treatment.

RISK FACTORS FOR CANDIDEMIA:
A PROSPECTIVE MATCHED CASE-CONTROL STUDY

Critical Care, 2020 March 18; 24(1):109

AUTHORS: Poissy J, Damonti L, Bignon A, et al.; for the FUNGINOS and Allfun French Study Groups
CENTRE FOR CORRESPONDENCE: Infectious Diseases Service, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

BACKGROUND & AIM: Nosocomial candidaemia is becoming more common and causes significant mortality. Prophylactic or early empirical antifungal treatment is often used in high-risk patients while awaiting diagnostic culture results, but risks encouraging drug resistance. The aim of this study was to identify factors that increase the risk of candidaemia, both within and outside the intensive care unit (ICU), to enable more appropriate use of antifungals.

STUDY DESIGN: Multicentre, case–control study.

ENDPOINTS: Risk factors for candidaemia and in-hospital mortality.

METHOD: Adult patients with a positive blood culture for *Candida* species were enrolled at six hospitals in France and Switzerland between 2013 and 2017. Each was matched with up to three *Candida*-negative control patients from the same ward with a similar duration of hospitalization. Demographic and clinical data, including use of antibiotics and antifungal drugs within 4 weeks prior to candidaemia diagnosis, were captured. Multivariable regression was used to identify factors associated with candidaemia and mortality.

RESULTS: The study enrolled 603 patients (192 cases and 411 matched controls), of whom 47% were located in an ICU and 53% in other wards. Candidaemia developed a median of 16 days after admission and *C. albicans* was the most common pathogen (61%), followed by *C. glabrata* (16%). Within the ICU setting, regression analysis showed that the main independent risk factors for candidaemia were total parenteral nutrition (odds ratio 6.75, $p<0.001$), acute kidney injury (OR 4.77, $p<0.001$), heart disease (OR 3.78, $p=0.006$), previous septic shock (OR 2.39, $p=0.02$) and exposure to aminoglycosides (OR 2.28, $p=0.05$). In contrast, in a non-ICU setting, independent risk factors for candidaemia were the presence of a central venous catheter (OR 9.77, $p<0.001$), total parenteral nutrition (OR 3.29, $p=0.003$), and exposure to glycopeptide (OR 3.31, $p=0.04$) or nitroimidazole (OR 3.12, $p=0.04$) antibiotics. Acute kidney injury and septic shock were independent risk factors for mortality in both ICU and non-ICU settings. Based on these findings, separate risk score models were developed for predicting the risk of candidaemia in ICU and non-ICU settings.

CONCLUSIONS: Factors predisposing towards the risk of developing candidaemia differed between the ICU and non-ICU settings. Risk models based on these findings need testing in larger studies to validate their usefulness.

A MULTICENTER, LONGITUDINAL COHORT STUDY OF CRYPTOCOCCOSIS IN HUMAN IMMUNODEFICIENCY VIRUS-NEGATIVE PEOPLE IN THE UNITED STATES

Clinical Infectious Diseases, 2020 January 2; 70(2):252–61

AUTHORS: Marr KA, Sun Y, Spec A, Lu N, Panackal A, Bennett J, Pappas P, Ostrander D, Datta K, Zhang SX, Williamson PR; for the Cryptococcus Infection Network Cohort Study Working Group
CENTRE FOR CORRESPONDENCE: Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

BACKGROUND & AIM: Cryptococcosis is a recognised complication of infection with human immunodeficiency virus (HIV), but is now increasingly detected in people given biological immunosuppressive treatment for various conditions. Little is known, however, about the clinical features, treatment and outcomes in such patients. The aim of this study was to improve understanding of cryptococcosis in non-HIV patients.

STUDY DESIGN: Multicentre, prospective, cohort study.

ENDPOINTS: Presenting symptoms, therapy choices, and clinical and microbial outcomes.

METHOD: HIV-negative patients with proven, probable or possible cryptococcosis were recruited at 20 centres in the USA and followed for 2 years. Demographic and clinical data, treatment details and outcomes were collected. Subjects were assessed 3-monthly during the first year and 6-monthly in the second year of follow-up.

RESULTS: The study enrolled 145 patients, with longitudinal data available for 138. Seventeen participants were lost to follow-up or withdrew and were excluded from outcome assessments. Patients had a mean age of 56.8 years, 33.8% had had a solid organ transplant, 15.9% had an autoimmune disease and 11.7% had a haematological malignancy. Diagnosis of cryptococcosis was delayed by >1 month after symptom onset in 30 (23.6%) patients. Only 40 (27.6%) patients presented with fever. The causative organism was identified as *Cryptococcus gattii* in five subjects. The CNS was involved in 71 (49%) patients. Patients with CNS infection typically had higher baseline cryptococcal antigen levels, were more likely to present with headache, reported lower quality of life, and had more cognitive impairment than those without CNS involvement. Patients with CNS involvement were typically given initial therapy with amphotericin B and 5-flucytosine (71.8%), while those without CNS involvement most often received azole monotherapy (58.1%). Patients with CNS involvement required more extensive interventions (such as multiple lumbar punctures) during follow-up, showed more evidence of neurological impairment and had reduced survival. Among the whole cohort, multivariate regression analysis suggested that age was the main predictor of higher mortality, while solid organ transplant and haematological malignancy were associated with lower mortality.

CONCLUSIONS: CNS involvement is common in HIV-negative cryptococcosis patients and is associated with long-term neurological impairment and increased mortality risk.

RE-DRAWING THE MAPS FOR ENDEMIC MYCOSES

Mycopathologia, 2020 February 10; Epub ahead of print

AUTHORS: Ashraf N, Kubat RC, Poplin V, Adenis AA, Denning DW, Wright L, McCotter O, Schwartz IS, Jackson BR, Chiller T, Bahr NC
CENTRE FOR CORRESPONDENCE: Division of Infectious Diseases, Department of Internal Medicine, University of Kansas, Kansas City, Kansas, USA

BACKGROUND & AIM: Endemic mycoses – such as histoplasmosis, coccidioidomycosis and blastomycosis – are so called because they occur regularly within limited geographical areas. However, in recent years there have been increasing reports of these fungal infections being diagnosed outside their areas of known endemicity, suggesting that our understanding of their distribution needs to be updated. This article reviews the changing geographical landscape of endemic mycoses.

ARTICLE TYPE: Review.

FINDINGS: Histoplasmosis is caused by varieties of *Histoplasma capsulatum*. It is associated with soil containing bird or bat guano. The disease is known to be endemic in the Ohio and Mississippi River Valleys in the USA, and in Central and South America, and differences between isolates from different regions suggest they may be distinct *Histoplasma* species. However, recent findings show that histoplasmosis actually has a more global distribution and is endemic in much of the world. Cases have been reported throughout west, central and eastern Africa, specific areas of Asia, the Caribbean, Italy, and outside known endemic areas in the USA. Histoplasmosis is likely to be underdiagnosed in most settings due to a lack of tests and/or clinician awareness.

Coccidioidomycosis is caused by two species: *Coccidioides immitis* is most commonly found in the Central Valley of California and further north in the USA, while *C. posadasii* is found in the desert areas of Arizona, Texas, Utah, Mexico, and Central and South America. Cases often occur following disruption of the soil, including construction work, earthquakes and military manoeuvres. In the USA, the incidence of coccidioidomycosis has risen in the last 20 years, in both endemic and non-endemic areas. A number of geographically isolated areas of endemicity have been identified in South America (including regions of Colombia, Venezuela, Argentina, Paraguay and Brazil) and Central America.

Blastomycosis is caused by *Blastomyces dermatitidis* (including *B. gilchristi*) and *B. helicus*, which are typically found in woodland with damp soil near lakes, waterways and rivers. The disease often occurs as a result of excavation and construction in endemic areas. *B. dermatitidis* is endemic in mid-western, eastern and central areas of the USA, as well as in parts of Canada and much of Africa, with cases also reported in India. Understanding of the epidemiology of blastomycosis has been hampered by a lack of public reporting and reliable tests.

CONCLUSIONS: Recent years have seen marked shifts in the geographical distribution of endemic mycoses worldwide.

IMPACT OF THE BETA-GLUCAN TEST ON MANAGEMENT OF INTENSIVE CARE UNIT PATIENTS AT RISK OF INVASIVE CANDIDIASIS

Journal of Clinical Microbiology, 2020 May 26; 58(6):e01996–19

AUTHORS: Kritikos A, Poissy J, Croxatto A, Bochud PY, Pagani JL, Lamoth F
CENTRES: Infectious Diseases Service, Department of Medicine; Institute of Microbiology, Department of Laboratories; and Service of Intensive Care Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; and Intensive Care Unit and Hyperbaric Center, Lille University Hospital, Lille, France

BACKGROUND & AIM: Invasive candidiasis (IC) occurs frequently in intensive care units (ICUs) and is associated with high mortality. It is important to diagnose it early and initiate antifungal (AF) therapy promptly. However, such action is associated with significant costs. The 1,3-β-D-glucan (BDG) test is used to diagnose IC, but whether it affects the prescription of AF therapy is unclear. The aim of this study was to evaluate the impact of BDG test results on therapeutic decisions for patients at risk of IC.

STUDY DESIGN: Single-centre observational study.

ENDPOINTS: BDG test performance; effect of BDG testing on AF prescribing.

METHOD: The study included all ICU patients for whom BDG tests were ordered during two 6-month periods. During period 1, decisions to order BDG tests were at the discretion of the physicians. During period 2, physicians received a pocket card bearing an algorithm outlining the indications for, and interpretation of, BDG tests. All treatment decisions were at the discretion of physicians.

RESULTS: Among all 72 patients for whom a BDG test was ordered, 14 (19%) were diagnosed with IC. BDG test results influenced therapeutic decisions in 41 cases (57%). The impact was considered positive in 30/41 (73%) cases, including avoidance/interruption of AF treatment following a negative BDG test (n=27), and initiation/continuation of AF treatment following a positive BDG test with subsequent confirmation of IC (n=3). BDG testing had an undetermined effect in 10 patients (24%), in whom a positive BDG test resulted in initiation/continuation of AF treatment with no further evidence of IC. The impact of testing was negative (avoidance of AF treatment based on a negative BDG test with subsequent diagnosis of IC) in one case (2%). The positive predictive value of the BDG test was higher when performed in selected high-risk patients according to the algorithm (80% versus 36% for the overall population); however, the negative predictive value was lower (79% versus 90%). Overall, only 19 cases (26%) fulfilled the BDG testing indications specified in the algorithm (34% in period 1 and 20% in period 2; p=0.12). AF prescribing rates did not differ significantly between periods 1 and 2 (69% versus 45%).

CONCLUSIONS: BDG test results guided therapeutic decisions in just over half of patients at risk of IC. Targeted BDG testing in high-risk patients may be beneficial but appeared to be difficult to implement in daily ICU practice.

INVASIVE PULMONARY ASPERGILLOSIS TREATMENT DURATION IN HAEMATOLOGY PATIENTS IN EUROPE:

AN EFISG, IDWP-EBMT, EORTC-IDG AND SEIFEM SURVEY

Mycoses, 2020 May; 63(5):420–9

AUTHORS: Lanternier F, Seidel D, Pagano L, et al.
CENTRE FOR CORRESPONDENCE: Service de Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris (APHP), Université de Paris, Paris, France

BACKGROUND & AIM: The optimal duration of antifungal treatment for invasive pulmonary aspergillosis (IPA) has not been established, and so guidelines do not currently offer any recommendations. Most clinicians treat pulmonary infections until clinical and radiographic manifestations are resolved or stabilized, often leading to prolonged antifungal administration, which can be associated with complications and the emergence of resistant strains. This survey assessed current IPA management practices in European haematology centres.

STUDY DESIGN: Questionnaire survey.

ENDPOINTS: Treatment duration; management tools.

METHOD: Four international scientific societies and groups were involved in conducting this cross-sectional, internet-based, survey, which comprised 20 questions regarding the characteristics of respondents and their centre, tools used for the diagnosis, follow-up and discontinuation of IPA in haematology patients, and timepoints chosen for re-evaluation. The questionnaire was emailed to physicians in 16 European countries, and responses were received from 112 individuals in 14 countries.

RESULTS: Common diagnostic tools included galactomannan (GM) antigen in serum/plasma (95% of centres) or in bronchoalveolar lavage (87%), whereas quantitative *Aspergillus* PCR was available in only 24% of centres, β-D-glucan in 21% and PET in 45%. Treatment response was commonly evaluated using chest CT (98%) and serum/plasma GM antigen (74%), with CT evaluations performed after a median of 2 and 4 weeks in clinically stable patients. In patients with AML or graft-versus-host-disease (GvHD), treatment discontinuation was commonly guided by clinical response (81% and 72% of centres) and chest CT lesion resolution (72% and 74%) or lesion reduction (52% and 32%), with GM antigen index used in 60% and 50% of centres, and *Aspergillus* PCR, β-D-glucan and PET in <10%. The median duration of antifungal treatment varied according to the underlying disorder (table). Treatment duration differed significantly between countries for the same underlying disease (p=0.0001 for AML and GvHD, and p=0.0003 for lymphoproliferative disease), and was shortest in Poland for all disorders.

CONCLUSION: The duration of antifungal treatment for IPA in haematology patients varies considerably across Europe, highlighting the importance of developing guidelines.

Median duration of antifungal treatment for invasive pulmonary aspergillosis in Europe, by haematological disorder

Haematological disorder	Median duration of antifungal treatment (interquartile range)
Acute myeloid leukaemia	6 (3–12) weeks
Graft-versus-host disease after allogeneic stem-cell transplantation	11 (4–12) weeks
Lymphoproliferative disease	6 (3–12) weeks

THE GUT MYCOBIOME:

THE OVERLOOKED CONSTITUENT OF CLINICAL OUTCOMES AND TREATMENT COMPLICATIONS IN PATIENTS WITH CANCER AND OTHER IMMUNOSUPPRESSIVE CONDITIONS

PLoS Pathogens, 2020 April 2; 16(4):e1008353

AUTHORS: Galloway-Peña JR, Kontoyiannis DP
CENTRES: Department of Genomic Medicine; and Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

BACKGROUND & AIM: The bacteriome makes up more than 99% of the intestinal microbiome, and research has focused on the immunomodulatory role of the bacteriome in gastrointestinal disorders, cancer therapy-related toxicity and stem-cell transplantation outcomes. However, the mycobiome – which comprises the commensal fungi – also has an influence on immunomodulation, although this has not been well researched. The aim of this article was to review the role of the gut mycobiome with respect to clinical outcomes and treatment complications in patients with cancer or other immunosuppressive conditions.

ARTICLE TYPE: Review.

FINDINGS: Fungal colonization of the gut is normally limited by the presence of commensal bacteria, but a number of factors – including antibiotic treatment and high-intensity chemotherapy – can lead to an increase in fungal burden. This increase may have an impact on cancer treatment-related complications and oncological outcomes, and patients with *Candida* colonization have been reported to have an increased incidence of graft-versus-host disease after haematopoietic stem-cell transplantation.

The gut mycobiome may also have an impact on patients with inflammatory gastrointestinal disorders, in whom increased intestinal colonization with *C. albicans* has been reported. Animal studies have suggested that the mycobiome is involved in the initiation of inflammation and pathogenesis of inflammatory bowel disorders, and *C. tropicalis* exacerbated colitis severity in dectin-1–deficient mice.

There is evidence to suggest that fungi colonizing the gastrointestinal tract have an immunomodulatory role relating to both innate and adaptive immunity. Gut colonization with *Candida* or other fungi produces Th17 and Th1 responses, while *Saccharomyces cerevisiae* yeasts induce Th1 CD4 differentiation, and *S. cerevisiae* spores promote Th17 CD4 expansion. Furthermore, inoculation with *S. cerevisiae* and *C. albicans* improved severe colitis in antibiotic-treated mice infected with influenza virus. In other work, gut mycobiota (particularly *Malassezia* species) have been implicated in the pathogenesis of pancreatic adenocarcinoma by promoting pancreatic inflammation.

The immunomodulatory role of the mycobiome could affect the response to chemotherapy or immunotherapy, the persistence of leukaemia, and the occurrence of infectious complications.

CONCLUSIONS: The impact of the gut mycobiome on clinical outcomes and treatment complications in patients with cancer or other immunosuppressive conditions has been under-investigated. Many questions are still to be answered, which may help in the provision of personalized medicine.

INTERFERON GAMMA REPLACEMENT AS SALVAGE THERAPY IN CHRONIC PULMONARY ASPERGILLOSIS:

EFFECTS ON FREQUENCY OF ACUTE EXACERBATION AND ALL-CAUSE HOSPITAL ADMISSION

Thorax, 2020 June; 75(6): 513–16

AUTHORS: Monk EJ, Harris C, Döffinger R, Hayes G, Denning DW, Kosmidis C
CENTRE FOR CORRESPONDENCE: National Aspergillosis Centre, Manchester University NHS Foundation Trust, Manchester, UK

BACKGROUND & AIM: Impaired production of interferon gamma (IFNγ) has been implicated in chronic pulmonary aspergillosis (CPA), and supplementation with IFNγ has been tried as salvage therapy in patients with severe CPA and impaired IFNγ production. The aim of this study was to gather evidence on the impact of such treatment.

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

ENDPOINTS: Incidence of acute exacerbations and all-cause hospital admission.

METHOD: Records were reviewed for all CPA patients who were refractory to antifungal therapy and had impaired production of IFNγ or interleukin-12, and who received IFNγ salvage therapy (50 µg subcutaneously, three times per week), at the National Aspergillosis Centre in Manchester between January 2011 and September 2018. Patients with data available for at least 12 months after starting IFNγ treatment were included in the study. The frequency of exacerbations and hospital admissions were compared between the 12 months before and after initiation of IFNγ, using the Wilcoxon matched-pairs signed-rank test.

RESULTS: The study included 36 patients (median age 56 years, 36% with bronchiectasis and 22% with chronic obstructive pulmonary disease). Most patients received concomitant antifungal therapy. Eight discontinued IFNγ treatment within 6 months due to adverse effects, eight died within 12 months of initiating IFNγ, and 20 received IFNγ for >12 months. In an analysis of all participants, the death rate was not significantly greater on IFNγ therapy than off therapy (0.16/year versus 0.12/year, p=0.6). Among the 20 patients who received IFNγ for >12 months, both the frequency of acute exacerbations and the frequency of hospital admissions were significantly lower in the 12 months following the start of IFNγ therapy compared with the 12 months before treatment (mean exacerbations 1.4 versus 3.1, p=0.006; mean admissions 0.3 versus 0.8, p=0.04). No significant difference was seen in either parameter for those who received <6 months of IFNγ supplementation. IFNγ treatment did not appear to affect *Aspergillus* serology, lung imaging or the nature of pathogens isolated from sputum culture.

CONCLUSIONS: Among patients with refractory CPA and impaired IFNγ production, IFNγ salvage therapy reduced the frequency of acute exacerbations and the number of hospital admissions in those who received the treatment for >12 months. Larger, prospective, studies are needed to further assess the value of this therapy.

PROSPECTIVE EVALUATION OF THE TURBIDIMETRIC β-D-GLUCAN ASSAY AND TWO LATERAL FLOW ASSAYS ON SERUM IN INVASIVE ASPERGILLOSIS

Clinical Infectious Diseases, 2020 March 19; Epub ahead of print

AUTHORS: Mercier T, Guldentops E, Lagrou K, Maertens J
CENTRES: KU Leuven, Department of Microbiology, Immunology and Transplantation; University Hospitals Leuven, Department of Hematology; and Department of Laboratory Medicine and National Reference Centre for Mycosis, Leuven, Belgium

BACKGROUND & AIM: Immunocompromised patients are at risk of developing invasive aspergillosis (IA), a potentially fatal infection. Patients are often diagnosed late in the disease course, if at all. Consequently, the initiation of appropriate antifungal therapy is often delayed, which can affect patient survival. More sensitive and rapid diagnostic tools are needed. Recently approved diagnostic tests include an *Aspergillus*-specific lateral flow device (LFD), an *Aspergillus*-specific lateral flow assay (LFA) and a turbidimetric β-D-glucan assay. The aims of this study were to compare the performance of these tests in diagnosing IA using serum samples from patients at risk of IA, and to determine whether they added value to the current diagnostic method (serum galactomannan detection).

STUDY DESIGN: Diagnostic performance study.

ENDPOINTS: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

METHOD: The study included patients with underlying haematological disorders who were evaluated for IA, and were classified as proven IA (*n*=5), probable IA (*n*=36) or suspected IA that ultimately lacked evidence (*n*=188, controls). Serum samples taken before the start of any antifungal therapy were used to investigate diagnostic test performance for the LFA, LFD and β-D-glucan tests, as well as for serum galactomannan. Diagnostic performance was estimated using area under the curve (AUC)/receiver operating characteristic curve analysis.

RESULTS: The best overall performance was seen with the serum galactomannan and LFA tests (AUC 0.83 and 0.82, respectively). LFA demonstrated the highest sensitivity and NPV, while serum galactomannan had the highest specificity and PPV (table). Sensitivity did not differ significantly between these two tests (p=0.18). The LFD performed least well amongst the tests for all parameters. When used in combination, the highest sensitivity and NPV was seen in patients with a positive LFA or β-D-glucan (≥2.359 pg/mL), but specificity was low. The highest PPV amongst combinations was seen in patients with both a positive LFA and positive β-D-glucan.

CONCLUSIONS: In an at-risk population, the LFA test was as effective as serum galactomannan detection for the diagnosis of IA. Combining LFA or serum galactomannan with β-D-glucan may be optimal.

Diagnostic performance in patients with proven or probable invasive aspergillosis versus controls

	Sensitivity	Specificity	Negative predictive value	Positive predictive value
Serum galactomannan	0.44	0.99	0.89	0.93
Lateral flow assay	0.49	0.95	0.90	0.69
Lateral flow device	0.24	0.89	0.84	0.33
β-D-glucan ≥2.359 pg/mL	0.46	0.90	0.89	0.51

BURDEN OF CANDIDEMIA IN THE UNITED STATES, 2017

Clinical Infectious Diseases, 2020 February 28; Epub ahead of print

AUTHORS: TSAY SV, MU Y, WILLIAMS S, EPSON E, NADLE J, BAMBERG WM, BARTER DM, JOHNSTON HL, FARLEY MM, HARB S, THOMAS S, BONNER LA, HARRISON LH, HOLLICK R, MARCEAUX K, MODY RK, PATTEE B, SHRUM DAVIS S, PHIPPS EC, TESINI BL, GELLERT AB, ZHANG AY, SCHAFFNER W, HILLIS S, NDI D, GRABER CR, JACKSON BR, CHILLER T, MAGILL S, VALLABHANENI S
CENTRE FOR CORRESPONDENCE: MYCOTIC DISEASES BRANCH, CDC, ATLANTA, GEORGIA, USA

BACKGROUND & AIM: Blood-borne *Candida* infections are common in the USA, for example in patients who are critically ill, have malignancies, have undergone haematopoietic stem cell or solid organ transplantation, have had recent abdominal surgery or are undergoing haemodialysis. Nevertheless, estimates of the healthcare burden posed by candidaemia in the USA are lacking. The aim of this study was to use surveillance data from the Centers for Disease Control and Prevention (CDC) to estimate the national burden of candidaemia in the USA in 2017.

STUDY DESIGN: Surveillance study.

ENDPOINTS: Rates of *Candida* incidence, all-cause in-hospital mortality within 7 days of confirmed candidaemia, and all-cause in-hospital mortality during the entire candidaemia-associated hospitalization.

METHOD: In 2017, the Emerging Infections Program (EIP) of the CDC conducted active population-based surveillance for candidaemia in 45 counties across nine states in the USA, encompassing approximately 17 million people (5% of the US population). Candidaemia was identified using a standard case definition. Surveillance data were extrapolated to estimate national numbers using 2017 national census data.

RESULTS: EIP surveillance data identified a total of 1226 candidaemia cases in 2017, which were extrapolated to an estimated 22,660 (95% confidence interval 20,210–25,110) cases across the USA (table). The overall estimated incidence case rate was 7.0 per 100,000 people. Incidence rates were higher than average in those aged ≥65 years, people of black race and males. The most frequent *Candida* species isolated from culture were *Candida albicans* (38%) and *C. glabrata* (30%). Across the EIP surveillance sites, 15% of patients died within 7 days of a positive *Candida* blood culture, corresponding to an estimated 3380 deaths nationally. The all-cause in-hospital mortality rate during the entire candidaemia-associated hospitalization was 25%, corresponding to 5628 deaths across the USA.

CONCLUSION: Candidaemia was associated with a substantial burden in the USA, based on population-based surveillance data from 2017.

Estimated number of cases and incidence rates for candidemia in the USA in 2017

	Number of surveillance cases	Estimated national number of cases (95% confidence interval)	Estimated incidence rate per 100,000 population
Total	1226	22,660 (20,210–25,110)	7.0
Sex			
Male	676	12,625 (10,674–14,577)	7.9
Female	550	10,035 (8554–11,516)	6.1
Race			
Black	388	5366 (4055–6677)	12.3
White	785	16,515 (14,455–18,574)	6.6
Other[a]	53	779 (490–1069)	2.4
Age group (years)			
<1	18	303 (238–368)	7.7
1–18	14	242 (195–290)	0.3
19–44	271	4629 (3816–5441)	4.1
45–64	414	7281 (5966–8596)	8.6
≥65	509	10,205 (8305–12,104)	20.1

[a] Asian, Native Hawaiian/Pacific Islander or American Indian/Alaska Native.

DIAGNOSING COVID-19-ASSOCIATED PULMONARY ASPERGILLOSIS

The Lancet Microbe, 2020 June; 1(2):e53–5

AUTHORS: Verweij PE, Gangneux JP, Bassetti M, Brüggemann RJ, Cornely OA, Koehler P, Lass-Flörl C, van de Veerdonk FL, Chakrabarti A, Hoenigl M
CENTRE FOR CORRESPONDENCE: Department of Medical Microbiology, Radboud University Medical Centre, Nijmegen, the Netherlands

BACKGROUND & AIM: There is evidence to suggest that patients with coronavirus disease 2019 (COVID-19) may be vulnerable to co-infection with invasive pulmonary aspergillosis (IPA). In a French cohort of 27 patients with COVID-19 admitted to the intensive care unit (ICU), nine (33%) were reported to have IPA, while equivalent figures in a German cohort were five out of 19 (26%) patients admitted to the ICU. These figures are similar to those for influenza-associated co-infection. This article discusses the diagnosis of COVID-19-associated pulmonary aspergillosis.

ARTICLE TYPE: Review.

FINDINGS: Serum galactomannan (GM) testing appears to have a lower sensitivity as a diagnostic marker in patients with COVID-19 than in those with influenza, and in one study only three of 14 patients (21%) with COVID-19-associated pulmonary aspergillosis were positive for serum GM, compared with 65% in those with influenza-associated pulmonary aspergillosis. The reasons for this insensitivity are not known, but the performance of the test may be influenced by treatment with chloroquine or antifungals, while a negative test may indicate that *Aspergillus* hyphae cannot cause angioinvasive growth and release GM into the blood.

Bronchoalveolar lavage GM testing is important for the diagnosis of IPA in the ICU. However, bronchoscopy is not generally recommended in patients with COVID-19 (except when it may be life-saving) because it generates aerosols that put patients and staff at risk of infection. In these cases, testing of upper respiratory samples is preferred, plus tracheal aspirates and non-bronchoscopic alveolar lavage samples in intubated patients. However, GM testing has not been validated for upper respiratory tract samples, and the presence of *Aspergillus* species in sputum and tracheal aspirates may reflect oropharyngeal colonization.

Histopathological evidence that IPA occurs in patients with COVID-19 can only come from autopsies. Further research into the diagnosis of COVID-19-associated pulmonary aspergillosis should consider the sensitivity of testing samples from the upper respiratory tract, the potential value of alternative blood tests, and whether radiological signs differ between COVID-19 patients with and without pulmonary aspergillosis. Research also needs to address the prophylaxis and treatment of COVID-19-associated pulmonary aspergillosis, and the influence of underlying immunological and host factors.

CONCLUSIONS: Diagnosing COVID-19-associated pulmonary aspergillosis can be difficult. The authors believe that COVID-19 patients with evidence of *Aspergillus* species in bronchoalveolar lavage or serum should receive antifungal therapy.