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on systemic fungal infections

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Clinical Infectious Diseases, 2022 November 11; Epub ahead of print

Survival outcome of empirical antifungal therapy and the value of early initiation: a review of the last decade

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Emerging Microbes & Infections, 2022 December 27; 12(1):2155584

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Journal of Fungi, 2022 November 21; 8(11):1228

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Emerging Microbes & Infections, 2022 December 24; 12(1):2153086

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LUNG EPITHELIAL AND MYELOID INNATE IMMUNITY IN INFLUENZA-ASSOCIATED OR COVID-19-ASSOCIATED PULMONARY ASPERGILLOSIS:

AN OBSERVATIONAL STUDY

The Lancet Respiratory Medicine, 2022 December; 10(12):1147–59

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BACKGROUND & AIM: There are currently limited data on the pathophysiology of influenza-associated pulmonary aspergillosis (IAPA) and COVID-19–associated pulmonary aspergillosis (CAPA). These conditions are difficult to diagnose and are associated with a higher mortality rate than either viral infection alone. The aim of this study was to investigate the pathogenesis of these viral–fungal coinfections, focusing on the role of lung epithelial and myeloid innate immunity.

STUDY DESIGN: Observational study.

ENDPOINTS: Differential gene expression, and proportions of immune and epithelial cell types.

METHOD: Biobanked bronchoalveolar lavage samples were collected from 166 patients admitted to intensive care requiring ventilation due to severe influenza or COVID-19 with or without aspergillosis. Samples underwent nCounter gene expression analysis of 755 genes linked to myeloid innate immunity, and protein analysis of 47 growth factors, cytokines and chemokines. Gene expression data were then used to estimate cell fractions for immune and epithelial cell types using CIBERSORTx, to perform gene set enrichment and hypergeometric enrichment pathway analysis, and to calculate pathway module scores for the interleukin-1β, tumour necrosis factor-α, and type I and II interferon (IFN) pathways. Biobanked tracheobronchial samples retrieved from four patients with IAPA or CAPA who had invasive *Aspergillus* tracheobronchitis were analysed using RNAScope and spatial transcriptomics.

RESULTS: Lower neutrophil and higher epithelial cell fractions were observed in patients with CAPA versus COVID-19 only (statistically significant differences) and IAPA versus influenza only (numerical differences). Several fibrosis-related growth factor concentrations were significantly elevated in patients with IAPA or CAPA versus those with viral infection only. Genes associated with antifungal effector functions were downregulated in patients with IAPA or (to a lesser extent) CAPA. Expression of several genes encoding proteins involved in opsonization, recognition and killing of *Aspergillus* conidia, and the IFNγ signalling pathway were downregulated in those with IAPA or CAPA versus influenza or COVID-19 only. Differential expression of several genes related to LC3-associated phagocytosis, autophagy or both were also observed. Disruption of the epithelial barrier by active or very recent SARS-CoV-2 infection facilitated tissue-invasive aspergillosis in one patient with CAPA.

CONCLUSION: Factors predisposing to the development of IAPA and CAPA consist of a three-level breach in innate antifungal immunity affecting neutrophils, macrophages and the lung epithelium.

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LIPOSOMAL AMPHOTERICIN B–THE PAST

Journal of Antimicrobial Chemotherapy, 2022 November 25; 77(Suppl 2):ii3–10

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BACKGROUND & AIM: The broad-spectrum, polyene antifungal compound amphotericin B (AMB) was discovered in 1953, and the development of a liposomal drug delivery system has allowed it to be used to successfully treat systemic fungal infections for several decades. The aim of this article was to summarize the history and nature of the liposomal formulation, including key clinical studies evaluating pharmacokinetics, safety and efficacy, and available microbiological data for liposomal AMB.

TYPE OF ARTICLE: Review.

FINDINGS: AMB was originally combined with the bile acid deoxycholate to enable intravenous administration, but its use is limited due to toxicity. The liposomal formulation entrapped amphotericin B in a stable, cholesterol-containing phospholipid bilayer, allowing it to pass through the fungal cell wall and bind to the fungal membrane surface. The presence of cholesterol in the liposome resulted in a low propensity to transfer AMB to mammalian membranes, and this, combined with the higher binding avidity of AMB for the fungal membrane sterol ergosterol, substantially reduced the toxicity of liposomal AMB relative to AMB deoxycholate. Preclinical studies demonstrated that liposomal AMB substantially increased drug concentrations in plasma and tissue, while markedly reducing toxicity.

Early clinical studies demonstrated non-linear pharmacokinetics, with exposure increasing disproportionately with increasing dose. Maximum exposure values occurred at 10 mg/kg, but the pivotal dose-finding trial AmBiLoad demonstrated that 3 mg/kg performed as effectively as 10 mg/kg in haematology patients, with lower adverse event rates. This lower dose of 3 mg/kg is now internationally recommended for the treatment of *Aspergillus* infections, including pulmonary aspergillosis. Pharmacokinetic data were similar in children and they can be given identical dosages to adults; however, data remain limited in patients with renal and hepatic impairment.

Liposomal AMB is successfully used to treat severe systemic and/or deep mycoses, such as candidiasis and aspergillosis, in adults and children (from age 1 month), as well as presumed fungal infections in patients with febrile neutropenia, and visceral leishmaniasis in immunocompetent patients. It has a broad spectrum of activity and the development of resistance is uncommon and slow, meaning this is not a major factor in the treatment of patients.

CONCLUSION: The development of liposomal AMB allowed AMB to be used successfully to treat a wide range of systemic fungal infections while substantially reducing toxicity.

https://doi.org/10.1093/jac/dkac351

REZAFUNGIN VERSUS CASPOFUNGIN FOR TREATMENT OF CANDIDAEMIA AND INVASIVE CANDIDIASIS (RESTORE):

A MULTICENTRE, DOUBLE-BLIND, DOUBLE-DUMMY, RANDOMISED PHASE 3 TRIAL

The Lancet, 2023 January 7; 401 (10370):49–59

AUTHORS: Thompson GR 3rd, Soriano A, Cornely OA, Kullberg BJ, Kollef M, Vazquez J, Honore PM, Bassetti M, Pullman J, Chayakulkeeree M, Poromanski I, Dignani C, Das AF, Sandison T, Pappas PG; for the ReSTORE trial investigators
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BACKGROUND & AIM: Invasive candidiasis is a significant cause of morbidity and mortality. Echinocandins are recommended as first-line therapy for most types of invasive candidiasis. However, the change in epidemiology towards non-*albicans Candida* spp., unpredictable dose–exposure relationships for current echinocandins and increasing resistance to antifungal drugs emphasize the need for new drugs. Rezafungin is a novel broad-spectrum echinocandin with a prolonged half-life that allows once-weekly dosing and provides high plasma drug concentrations early in therapy. This study compared the efficacy and safety of intravenous rezafungin versus intravenous caspofungin in patients with candidaemia or invasive candidiasis.

STUDY DESIGN: Multinational, randomized, double-blind, non-inferiority, phase 3 study.

ENDPOINTS: Global cure (clinical cure, radiological cure and mycological eradication) at day 14, and 30-day all-cause mortality; adverse events (AEs).

METHOD: Adults with systemic signs and mycological confirmation of candidaemia or invasive candidiasis were randomized to receive intravenous rezafungin once a week (400 mg in week 1, followed by 200 mg weekly; *n*=100) or intravenous caspofungin (70 mg on day 1, followed by 50 mg daily; *n*=99) for a maximum of 4 weeks. Non-inferiority of rezafungin was demonstrated if the lower bound of the 95% confidence interval (CI) for the treatment difference was above –20% for global cure, and if the upper bound was below 20% for mortality.

RESULTS: The mean age of the study population was 61 years and 59% were men. The most common species isolated was *Candida albicans*. The median duration of intravenous treatment was 14 days in both groups. Global cure rates at day 14 were 59% in the rezafungin group and 61% in the caspofungin group (weighted treatment difference –1.1%, 95% CI –14.9 to 12.7). All-cause mortality at day 30 was 24% in the rezafungin group and 21% in the caspofungin group (treatment difference 2.4%, 95% CI –9.7 to 14.4). Thus, rezafungin was non-inferior to caspofungin for both efficacy endpoints. Most patients experienced at least one treatment-related AE (rezafungin 91% versus caspofungin 85%). The most common in the rezafungin group were pyrexia, hypokalaemia, pneumonia and septic shock. Serious AEs occurred in 56% of the rezafungin group and 53% of the caspofungin group.

CONCLUSION: Once-weekly rezafungin was non-inferior to daily caspofungin with regard to day 14 global cure and 30-day all-cause mortality in patients with candidaemia and invasive candidiasis.

https://doi.org/10.1016/S0140-6736(22)02324-8

THE GEOGRAPHIC DISTRIBUTION OF DIMORPHIC MYCOSES IN THE UNITED STATES FOR THE MODERN ERA

Clinical Infectious Diseases, 2022 November 11; Epub ahead of print

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BACKGROUND & AIM: The dimorphic fungal genera of *Histoplasma*, *Coccidioides* and *Blastomyces* are considered endemic mycoses of the USA, owing to their presence in ecological niches within specific geographical areas. Maps describing their distributions in the USA were last compiled more than 50 years ago and need to be updated because these pathogens are increasingly being diagnosed outside of their historical distributions. Therefore, the aim of this study was to update the distribution maps for dimorphic mycoses, using geographically granular data from more recent times.

STUDY DESIGN: Retrospective analysis of individual-patient-level data.

ENDPOINTS: Incidence of histoplasmosis, coccidioidomycosis and blastomycosis in each US county.

METHOD: Claims data for more than 45 million Medicare fee-for-service beneficiaries for the period 2007–2016 were used to create a retrospective cohort of persons aged ≥65 years. Those with diagnoses of histoplasmosis, coccidioidomycosis or blastomycosis were identified based on ICD 9/10 codes, and incidences per county were calculated. Counties with ≤5 cases of histoplasmosis, ≤3 cases of coccidioidomycosis or ≤1 case of blastomycosis were considered to have zero cases. Incidences were defined as clinically meaningful if there were >100 cases per 100,000 person-years for histoplasmosis and coccidioidomycosis, and >50 cases per 100,000 person-years for blastomycosis.

RESULTS: Across 3143 US counties, the total number of incident diagnoses in unique persons during the study was 79,749 for histoplasmosis, 37,726 for coccidioidomycosis and 6109 for blastomycosis. The numbers of counties with cases are summarized in the table. Among the 50 states plus Washington DC, 94% (48/51) had at least one county with a clinically meaningful incidence of histoplasmosis, as did 69% (35/51) for coccidioidomycosis, and 78% (40/51) for blastomycosis. The distributions extended beyond the historical boundaries mapped half a century ago.

CONCLUSIONS: A systematic update of the geographical distribution of dimorphic mycoses in the USA has been undertaken. Most states had at least one county with a clinically meaningful incidence of each of the dimorphic mycoses. Therefore, such a diagnosis should be considered based on clinical presentation rather than relying on geographical exposure.

Number of US counties with cases of dimorphic mycoses

	Number of counties with cases[a]	Counties with clinically meaningful incidence[b]
Histoplasmosis	1971	92% (1806/1971)
Coccidioidomycosis	839	40% (339/839)
Blastomycosis	1602	34% (547/1602)

Total number of US counties=3143.
[a] Counties with ≤5 cases of histoplasmosis, ≤3 cases of coccidioidomycosis or ≤1 case of blastomycosis were considered to have zero cases.
[b] Defined as >100 cases per 100,000 person-years for histoplasmosis and coccidioidomycosis, and >50 cases per 100,000 person-years for blastomycosis.

https://doi.org/10.1093/cid/ciac882

SURVIVAL OUTCOME OF EMPIRICAL ANTIFUNGAL THERAPY AND THE VALUE OF EARLY INITIATION:

A REVIEW OF THE LAST DECADE

Journal of Fungi, 2022 October 29; 8(11):1146

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BACKGROUND & AIM: Due to the association between invasive fungal infections and high morbidity and mortality rates, many clinicians continue to prescribe empirical antifungal therapy (EAFT) in a variety of settings. As delaying treatment can significantly worsen patient outcomes, most clinicians also prefer to commence treatment early. However, evidence on the use of EAFT is conflicting, and there remains uncertainty as to whether early EAFT is the best approach. The aim of this study was to analyse evidence from the last decade on the outcomes associated with EAFT and the value of early treatment initiation.

STUDY DESIGN: Rapid systematic review.

ENDPOINTS: Survival rate in patients who received EAFT, and any independent correlation between EAFT and survival rate.

METHOD: The Scopus, Medline (Ovid), PubMed, Embase and Cochrane Library databases were systematically searched for randomized controlled trials (RCTs) and cohort studies published in the last decade (2012–2022) that reported survival rates among immunocompromised or critically ill patients treated with EAFT and/or the association between early EAFT treatment and survival rate. Studies including patients with a confirmed diagnosis prior to treatment were excluded. Meta-analysis was not conducted due to high study heterogeneity.

RESULTS: A total of 16 original studies were identified, including two RCTs, 13 retrospective cohort studies and one prospective cohort study. Fourteen studies were in an intensive care unit setting and two were in a haematological malignancy setting. Overall, 10 studies found no statistically significant association between EAFT and survival rate, while the other six studies found that early EAFT was superior to diagnostic-based treatment. For example, the two RCTs found no survival improvement in critically ill patients at increased risk of invasive fungal infection who were treated with empirical echinocandin therapy, whereas a cohort study involving patients with haematological malignancies found that early appropriate EAFT was independently associated with reduced all-cause in-hospital mortality (adjusted odds ratio 0.31, p=0.011) and 28-day all-cause mortality (adjusted hazard ratio 0.469, p=0.03).

CONCLUSIONS: There remains a lack of strong evidence that EAFT improves survival rates in immunocompromised and critically ill patients. Several studies support early initiation of EAFT, but further evidence is needed to confirm this. Insights from global and regional experts on the use of EAFT may benefit the medical community until additional data from larger, well-designed studies becomes available.

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PERFORMANCE OF EXISTING CLINICAL SCORES AND LABORATORY TESTS FOR THE DIAGNOSIS OF INVASIVE CANDIDIASIS IN CRITICALLY ILL, NONNEUTROPENIC, ADULT PATIENTS:

A SYSTEMATIC REVIEW WITH QUALITATIVE EVIDENCE SYNTHESIS

Mycoses, 2022 December; 65(12):1073–111

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BACKGROUND & AIM: The most frequent fungal disease to develop in non-neutropenic, critically ill adults in the intensive care unit (ICU) is invasive candidiasis (IC), but currently there are no standard definitions of IC in this patient population. The Fungal Infections Definitions in ICU patients (FUNDICU) project is developing standard sets of definitions for invasive fungal diseases in critically ill adults, starting by reviewing available diagnostic criteria and laboratory tests. As part of the project, this study reviewed the performance of available clinical scores and laboratory tests for diagnosing IC in non-neutropenic, critically ill adults in the ICU.

STUDY DESIGN: Systematic review with qualitative evidence synthesis.

ENDPOINTS: Negative predictive value (NPV) and positive predictive value (PPV).

METHOD: The databases PubMed, Embase, CINAHL and the Cochrane Library were searched from 2003 to 2022 for studies assessing the diagnostic performance of predictive scores and/or laboratory tests for IC compared with a reference standard or a reference definition in non-neutropenic, critically ill adults in the ICU. Studies with a population that included ≥50% neutropenic patients or with <10 IC episodes were excluded. Studies could be cross-sectional, prospective or retrospective longitudinal cohorts, randomized controlled trials, single-arm studies or quasi-experimental studies.

RESULTS: A total of 35 studies were included in the qualitative synthesis. Diagnostic performance of existing clinical scores was evaluated in 16 studies, in which the prevalence of IC ranged from 1% to 42%. Despite heterogeneity of IC prevalences and study populations, existing clinical scores consistently demonstrated a high NPV (>90% in the majority cases) and a low PPV (<50% in almost all cases) in the target population. Most of the studies evaluating the performance of fungal antigen-based biomarkers assessed serum beta-D-glucan and demonstrated a similar high NPV (>90%), but with a higher PPV than that of clinical scores. The higher PPV showed substantial heterogeneity across studies, which could have reflected use of the tests in patients with a consistent clinical picture but with differing baseline risk factors for IC.

CONCLUSION: These results provide a structured evidence-based summary of the diagnostic ability of clinical scores and laboratory tests for IC in critically ill, non-neutropenic adults in the ICU. Both clinical scores and laboratory tests showed high NPV. The findings will be used to guide discussions of the FUNDICU expert panel during the development of definitions for IC in this patient population.

https://doi.org/10.1111/myc.13515

INFLUENZA VACCINATION IS ASSOCIATED WITH A REDUCED RISK OF INVASIVE ASPERGILLOSIS IN HIGH-RISK INDIVIDUALS IN TAIWAN:

A POPULATION-BASED COHORT STUDY

Emerging Microbes & Infections, 2022 December 27; 12(1):2155584

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BACKGROUND & AIM: Invasive aspergillosis (IA) is a life-threatening disease, particularly among immunocompromised individuals, including those with neutropenia, inherited immune dysfunction, transplant recipients with graft-versus-host disease, and people receiving immunosuppressant therapies. Because influenza virus infection is an independent risk factor for IA, vaccination against influenza might reduce the risk of IA, although evidence for this is sparse. Therefore, the aim of this study was to evaluate the association between influenza vaccination and the risk of IA in individuals at high risk for IA.

STUDY DESIGN: Population-based cohort study.

ENDPOINT: Incidence of IA.

METHOD: The cohort included individuals at high risk for IA and who were eligible to receive government-funded influenza vaccination for the three influenza seasons between 2016 and 2019. Participants' influenza vaccination status and IA diagnosis status were obtained from the Taiwan National Health Insurance Research Database. Incidence of IA among individuals vaccinated against influenza (*n*=3,136,477) was compared with that of unvaccinated individuals (*n*=5,407,974), using multivariable logistic regression analysis to calculate the risk difference.

RESULTS: During the study period, 412 (0.013%) vaccinated individuals and 767 (0.014%) unvaccinated individuals developed IA. Vaccinated individuals had a 21% lower risk of developing IA versus unvaccinated individuals (adjusted odds ratio 0.79, 95% confidence interval 0.70–0.90). Influenza vaccination was associated with a lower risk of IA versus non-vaccination among males (but not females), and in individuals with immunosuppressive conditions, malignancy or diabetes (table). Influenza vaccination was associated with a reduced risk of IA regardless of patient age or the presence/absence of EORTC/MSGERC host factors (table).

CONCLUSIONS: Influenza vaccination significantly reduced the risk of IA in high-risk individuals, particularly among males and people with immunosuppressive conditions, malignancy or diabetes.

Subgroups in which there was a significant association between influenza vaccination and reduced risk of invasive aspergillosis

Subgroup	Adjusted odds ratio (95% confidence interval)
Males	0.78 (0.67–0.92)
Immunosuppressive conditions	0.76 (0.61–0.95)
Malignancy	0.80 (0.64–0.99)
Diabetes	0.76 (0.63–0.93)
Age <65 years	0.63 (0.50–0.79)
Age ≥65 years	0.85 (0.73–0.99)
With EORTC/MSGERC host factors	0.78 (0.63–0.97)
Without EORTC/MSGERC host factors	0.79 (0.67–0.92)

EORTC/MSGERC=European Organization for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium.

https://doi.org/10.1080/22221751.2022.2155584

LIPOSOMAL AMPHOTERICIN B EXPOSURE IN CRITICALLY ILL PATIENTS:
A PROSPECTIVE PHARMACOKINETIC STUDY

Medical Mycology, 2022 October 12; 60(10):myac074

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BACKGROUND & AIM: Liposomal amphotericin B (LAmB) has been in use for more than 20 years for treating invasive fungal infections, but its pharmacokinetic (PK) properties are poorly understood, particularly in critically ill patients. The aim of this study was to gather PK data and evaluate the LAmB dose/exposure relationship in such patients.

STUDY DESIGN: Single-centre, prospective study.

ENDPOINTS: PK parameters, including peak (C_{max}) and trough (C_{min}) levels and exposure ($AUC_{0–24}$).

METHOD: The study enrolled critically ill adult patients treated with LAmB in either the intensive care unit (ICU) or haematology ward at a single hospital between 2016 and 2020. Patients were given 120-minute infusions of LAmB at a dose chosen by the clinician, and blood samples were taken before and 1, 2, 4, 8, 12, 16, 20 and 24 hours after dosing on an early treatment day (day 2–3) and on a later treatment day (≥6 days). Daily trough blood samples were collected on all other days for up to 14 days.

RESULTS: Data were available from 31 patients (65% male, median age 59 years). Of these, 26 were treated in the ICU and had a median APACHE II score of 19. The median dose of LAmB was 3.0 mg/kg and this dose was given to 80% of those studied. No significant differences were found in PK parameters between those admitted to the ICU versus the haematology ward. Overall, median C_{max} was 23.2 mg/L and median $AUC_{0–24}$ was 169 mg·h/L. There was considerable interindividual and intraindividual variability in both C_{max} (35% and 42%, respectively) and $AUC_{0–24}$ (48% and 29%, respectively). Regression modelling identified no explanatory factor for this variability other than administered dose. Median trough levels increased with dose, from 2.67 mg/L at a dose of 3 mg/kg to 5.36 mg/L at a dose of 12 mg/kg. There appeared to be some accumulation over time at a given dose level, but this did not reach statistical significance. Patient numbers at higher dose levels were small, limiting conclusions about dose-dependency of PK parameters.

CONCLUSIONS: LAmB PK values in critically ill patients were similar to those reported previously for less ill patients, but there was significant interindividual and intraindividual variability that remains to be explained. Further studies will be needed to establish regimens for optimal exposure to L-AmB.

https://doi.org/10.1093/mmy/myac074

THE CURRENT STATE OF LABORATORY MYCOLOGY AND ACCESS TO ANTIFUNGAL TREATMENT IN EUROPE:

A EUROPEAN CONFEDERATION OF MEDICAL MYCOLOGY SURVEY

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BACKGROUND & AIM: In Europe, the prevalence of invasive fungal infections (IFIs) continues to increase. To achieve early diagnosis and successful clinical management of these infections, access to appropriate diagnostic tools and antifungal treatments is essential. However, differences across European countries in average gross domestic product (GDP) may result in discrepancies in access. The aim of this survey by the European Confederation of Medical Mycology was to describe the IFI diagnostic capacity and access to antifungal treatments within institutions cross Europe, to help clarify the current status and any aspects that need improvement.

TYPE OF ARTICLE: Review.

FINDINGS: Between November 2021 and January 2022, 388 institutions from 45 countries in Europe self-assessed their capability to manage IFIs. Each institution was classified according to their country GDP per capita using three cut-offs (>$45,000; $30,000–45,000; <$30,000), according to the International Monetary Fund for 2021.

For diagnosis of IFIs, most institutions had access to culture media (99%), microscopy (97%) and antigen-detection assays (94%), with a lower percentage having access to molecular tests (85%) and antibody tests (84%). Access to these techniques (with the exception of microscopy) differed considerably between countries according to their GDP. For example, compared with those with a GDP <$30,000, countries with a GDP >$30,000 more commonly had the capability of performing blood cultures when fungaemia was suspected, and access to matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry for species identification. Countries with a GDP >$45,000 more commonly had access to DNA sequencing compared with countries with a lower GDP, and had access to a greater range of antigen-detection tests.

Overall, 94% and 89% of institutions had access to at least one triazole and one echinocandin, respectively, whereas only 78% had access to liposomal amphotericin B. All triazoles (except fluconazole), all echinocandins and liposomal amphotericin B were more readily available in countries with a GDP >$30,000 versus <$30,000. Furthermore, access to therapeutic drug monitoring of azoles was significantly more accessible in countries with a GDP >$45,000 versus <$30,000.

CONCLUSIONS: Institutions in some European countries do not have access to certain diagnostic tools and antifungal drugs. As these tools and drugs are considered essential by the World Health Organization for the management of IFIs, it is vital to overcome these limitations to ensure the best diagnostic and therapeutic management for all patients in Europe.

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CANDIDA GENOTYPING OF BLOOD CULTURE ISOLATES FROM PATIENTS ADMITTED TO 16 HOSPITALS IN MADRID: GENOTYPE SPREADING DURING THE COVID-19 PANDEMIC DRIVEN BY FLUCONAZOLE-RESISTANT *C. PARAPSILOSIS*

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BACKGROUND & AIMS: Invasive candidiasis is usually hospital-acquired, and genotyping isolates from different hospitals may help track the spread of clones. Prior to the COVID-19 pandemic, the emergence of fluconazole-resistant *Candida parapsilosis* was detected in the CANDIMAD study, which assessed *Candida* spp. from patients admitted to 16 hospitals in Madrid in 2019–21. The aims of the present study were to genotype *Candida* isolates from the CANDIMAD study and to determine whether genotype clusters (including antifungal-resistant genotypes) found in blood cultures were also found in intra-abdominal samples.

STUDY DESIGN: Epidemiological study.

ENDPOINTS: Genotypes and antifungal susceptibility

METHOD: Isolates of *C. albicans* (*n*=1041), *C. parapsilosis* (*n*=354) and *C. tropicalis* (*n*=125), from blood cultures (53.8%) and intra-abdominal samples (46.2%) from the CANDIMAD study, were genotyped using species-specific microsatellite markers. Genotypes were categorized as singleton (found in a single patient) or clusters (found in ≥2 patients), including intra-hospital clusters (from patients admitted to the same hospital) and widespread clusters (found in patients admitted to different hospitals).

RESULTS: Overall, 1107 different genotypes were found, either exclusively in blood cultures (*n*=528) or intra-abdominal samples (*n*=479) or in both compartments (*n*=100). A total of 83 clusters were detected in blood cultures, of which 20 were intra-hospital only, 49 were widespread only, and 14 were both intra-hospital and widespread. Intra-hospital clusters (total 34/83 clusters) indicated potential patient-to-patient transmission. Widespread clusters (63/83) were detected mostly in the largest hospitals. Some intra-hospital clusters were first detected before the COVID-19 pandemic, but the number of clusters increased during the pandemic, especially for fluconazole-resistant *C. parapsilosis* genotypes. The proportion of widespread clusters was significantly higher for genotypes found in both compartments versus those found exclusively in either blood or intra-abdominal samples. Resistant *C. albicans* and *C. tropicalis* genotypes were mostly singleton and were found exclusively in either blood cultures or intra-abdominal samples. Fluconazole-resistant *C. parapsilosis* isolates harboured either the Y132F or G458S ERG11p substitutions and generally belonged to intra-hospital clusters, although the dominant cluster (CP-451) was widespread; most resistant isolates were found in blood cultures.

CONCLUSIONS: The number of *Candida* clusters increased during the COVID-19 pandemic. This increase was mainly driven by fluconazole-resistant *C. parapsilosis* genotypes, which were found predominantly in blood cultures.

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DECREASED ECHINOCANDIN SUSCEPTIBILITY IN *CANDIDA PARAPSILOSIS* CAUSING CANDIDEMIA AND EMERGENCE OF A PAN-ECHINOCANDIN RESISTANT CASE IN CHINA

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BACKGROUND & AIMS: *Candida parapsilosis* is an increasingly important cause of invasive candidiasis (IC). Echinocandins are the preferred choice for IC treatment and prophylaxis; however, several countries have reported the emergence of echinocandin-resistant *C. parapsilosis*. The mechanisms underlying this resistance are not clear. Furthermore, little is known about the susceptibility profile of *C. parapsilosis* in China. The aims of this study were to determine *in vitro* echinocandin susceptibility of *C. parapsilosis* isolates collected in China and to explore resistance mechanisms among echinocandin-resistant isolates.

STUDY DESIGN: *In vitro* laboratory study.

ENDPOINTS: Minimum inhibitory concentrations (MICs) and resistance mechanisms.

METHOD: A total of 2523 invasive *C. parapsilosis* clinical isolates were collected from 87 hospitals in China. Susceptibility of the isolates to three echinocandins (micafungin, caspofungin and anidulafungin) was determined *in vitro*. Mechanisms of echinocandin resistance were explored using whole-genome sequencing and single nucleotide polymorphism analyses, and identified mutations were further analysed using bioinformatics and site-directed CRISPR Cas9 technology.

RESULTS: The highest MICs were exhibited by anidulafungin, followed by micafungin, whereas caspofungin demonstrated significantly better activity ($p<0.0001$); table. Blood-derived isolates had significantly higher echinocandin MICs compared with those from other specimens, particularly for caspofungin (1.348 versus 0.478 µg/mL, $p<0.05$). Intermediate phenotypes for at least one echinocandin were found in 20 isolates. One isolate demonstrated resistance to all three echinocandins in addition to fluconazole and voriconazole, resulting in breakthrough IC during long-term exposure to micafungin. This isolate carried a serine to proline substitution at position 656 in the hotspot 1 region of *FKS1*; this S656P mutation may lead to an altered protein conformation. Introduction of this mutation into a *C. parapsilosis* reference strain using CRISPR Cas9 technology resulted in a 64-fold increase in the MICs of all three echinocandins.

CONCLUSIONS: Identification of a multi-azole and pan-echinocandin resistant *C. parapsilosis* isolate harbouring a S656P mutation in *FKS1* underlines the importance of monitoring for fungal susceptibility and the necessity of careful management of antifungal use.

***In vitro* susceptibility of *Candida parapsilosis* clinical isolates to echinocandins**

Echinocandin	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Geometric MIC (µg/mL)
Anidulafungin	1	2	0.948
Micafungin	1	2	0.938
Caspofungin	0.5	1	0.498

MIC=minimum inhibitory concentration, MIC_{50}=MIC that inhibits 50% of isolates, MIC_{90}=MIC that inhibits 90% of isolates.

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RISK FACTORS AND OUTCOME OF PULMONARY ASPERGILLOSIS IN CRITICALLY ILL CORONAVIRUS DISEASE 2019 PATIENTS—

A MULTINATIONAL OBSERVATIONAL STUDY BY THE EUROPEAN CONFEDERATION OF MEDICAL MYCOLOGY

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BACKGROUND & AIMS: COVID-19–associated pulmonary aspergillosis (CAPA) is a potentially life-threatening complication in critically ill patients with COVID-19. The aims of this multinational study were to evaluate the prevalence of CAPA among patients with COVID-19 in the intensive care unit (ICU), risk factors for CAPA and its effect on ICU survival.

STUDY DESIGN: Multinational, observational cohort study.

ENDPOINTS: Prevalence of CAPA; risk factors for CAPA; 90-day ICU survival.

METHOD: The study included 592 adults admitted to the ICU with COVID-19–related acute respiratory failure between March 2020 and May 2021 at 20 centres across nine countries, including Austria (*n*=2), Belgium (*n*=4), France (*n*=3), Germany (*n*=4), Italy (*n*=2), Pakistan (*n*=1), Spain (*n*=1), UK (*n*=1) and USA (*n*=2). Data on demographics, underlying medical conditions, risk factors for invasive fungal infections, diagnostic workups (including radiological and microbiological data), treatments and outcomes were collected. CAPA diagnoses were made according to the 2020 ECMM/ISHAM consensus definitions.

RESULTS: Among the study participants, 11 (1.9%) had histologically confirmed CAPA, 80 (13.5%) had probable CAPA, 18 (3%) had possible CAPA, and the remaining 483 (81.6%) patients did not have CAPA. A diagnosis of CAPA was made at a median of 8 (range 0–31) days after admission to the ICU. The median prevalence of CAPA across all 20 centres was 10.7% (range 1.7–26.8%). In multivariate analysis, independent predictors of CAPA included older age (adjusted hazard ratio 1.04 per year, 95% confidence interval 1.02–1.06), invasive respiratory support (HR 3.4, 95% CI 1.84–6.25) and treatment with tocilizumab (HR 2.45, 95% CI 1.41–4.25). The 90-day ICU survival rate was significantly lower among patients with CAPA versus those without CAPA (29% versus 57%, $p<0.001$). CAPA was confirmed as an independent predictor of ICU mortality after adjustment for other predictors of survival (HR 2.14, 95% CI 1.59–2.87, $p\leq0.001$).

CONCLUSIONS: In this multinational study, the prevalence of CAPA ranged from 1.7% to 26.8%. Risk factors for CAPA included older age, invasive respiratory support and tocilizumab treatment. CAPA was an independent predictor of ICU mortality.

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