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on systemic fungal infections

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LIPOSOMAL AMPHOTERICIN B—THE FUTURE

Journal of Antimicrobial Chemotherapy, 2022 November 25; 77(Suppl 2):ii21–34

AUTHORS: Hoenigl M, Lewis R, van de Veerdonk FL, Verweij PE, Cornely OA
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BACKGROUND & AIM: The importance of empirical or pre-emptive broad-spectrum antifungal treatment is expected to increase in the future, and liposomal amphotericin B will therefore remain a gold standard for the primary treatment of unspecified invasive fungal infections (IFIs) and as a targeted therapy against specific pathogens. The aim of this review was to explore the role of liposomal amphotericin B in the next 30 years.

ARTICLE TYPE: Expert review.

FINDINGS: One major advantage of liposomal amphotericin B is its comparative lack of drug–drug interactions, and this is expected to become even more important as additional therapies emerge for patients at risk of IFIs, such as small-molecule kinase inhibitors (SMKIs) for patients with cancer. At present, there is a lack of robust data on the risk of IFIs in these patients, and the physician's clinical judgement is therefore vital in identifying those patients who should have routine diagnostic screening or antifungal prophylaxis. Nonetheless, it is known that nearly all SMKIs are metabolized through the cytochrome P3A4/A5 system, which means drug–drug interactions with triazole antifungals are likely (coadministration should therefore be avoided where possible), highlighting the need for oral broad-spectrum antifungal therapies that do not inhibit human CYP3A4/A5. In the meantime, intravenous echinocandins are often recommended as prophylaxis to avoid drug interactions.

The past few decades have seen the emergence of resistance to most classes of antifungal therapy – the exception being a low level of acquired resistance to amphotericin B in *Aspergillus* species. In addition, new drug-resistant species (e.g. *Candida auris*) are emerging as a result of both in-host and environmental resistance selection. An initial step in managing drug resistance would be to understand the local epidemiology of azole resistance within specific hospitals, regions or countries. However, this remains poorly documented, and improved surveillance programmes are urgently needed to help guide empirical treatment choices and institutional treatment recommendations for patients with IFIs. In addition, minimum inhibitory concentrations are important in guiding personalized therapy, but often do not correlate with outcomes in clinical practice, and susceptibility testing therefore needs to improve.

CONCLUSION: With its broad range of action, low resistance and low rate of drug–drug interactions, liposomal amphotericin B is expected to remain a mainstay of antifungal treatment in the years to come.

https://doi.org/10.1093/jac/dkac353

PRIMARY PROPHYLAXIS OF INVASIVE FUNGAL DISEASES IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES:

2022 UPDATE OF THE RECOMMENDATIONS OF THE INFECTIOUS DISEASES WORKING PARTY (AGIHO) OF THE GERMAN SOCIETY FOR HAEMATOLOGY AND MEDICAL ONCOLOGY (DGHO)

Journal of Antimicrobial Chemotherapy, 2023 August 2; 78(8):1813–26

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BACKGROUND & AIM: Haematological malignancies are associated with a high risk of invasive fungal disease (IFD), which is a significant cause of morbidity and mortality in these individuals. The risk is highest in patients with long-lasting neutropenia, such as those with acute myeloid leukaemia (AML), myelodysplastic syndrome during remission-induction chemotherapy, or severe aplastic anaemia. The most common pathogens are *Aspergillus* and *Candida* species, and the standard of care for those with long-lasting neutropenia is mould-active antifungal prophylaxis. In 2017, the German Society of Haematology and Medical Oncology published recommendations on the primary prophylaxis of IFDs in patients with haematological malignancies. This article updates those recommendations in light of new evidence on epidemiology and treatment approaches.

ARTICLE TYPE: Clinical recommendations.

FINDINGS: Antifungal prophylaxis is still strongly recommended for patients with haematological malignancies and long-lasting neutropenia (<500 cells/μL for >7 days), regardless of the underlying disease. Individuals with a shorter duration of neutropenia are not at increased risk of IFD and should therefore not receive antifungal prophylaxis. The drug of choice for mould-active prophylaxis is still posaconazole. The results of three large retrospective cohort studies published since 2017 are consistent with previous prospective studies of this drug. Isavuconazole and voriconazole now have moderate support, and there are low recommendations for fluconazole and itraconazole, but other azoles are not recommended.

There is still insufficient evidence to recommend novel treatment options such as CAR-T cell therapy or AML-targeted treatments. However, the results of several recent trials of micafungin prophylaxis mean that the recommendation for this drug's use has been upgraded to moderate. Other new recommendations include the use of non-pharmaceutical measures to help prevent IFD, including high-efficiency particulate air filters, advice to give up smoking, and installation during hospital construction of measures to prevent airborne fungal spread, while neutropenic diets are not recommended. There is a potential for interaction between antifungal prophylaxis and novel targeted therapies, in particular between triazoles which inhibit CYP3A4/5 and drugs that are metabolized via cytochrome p450. Accordingly, the dose of venetoclax should be reduced when used concomitantly with strong CYP3A4-inhibiting antifungals.

CONCLUSION: Updated recommendations are provided on the use of antifungal prophylaxis in patients with haematological malignancies.

https://doi.org/10.1093/jac/dkad143

BREAKTHROUGH INVASIVE FUNGAL INFECTION AMONG PATIENTS WITH HAEMATOLOGIC MALIGNANCIES:

A NATIONAL, PROSPECTIVE, AND MULTICENTRE STUDY

Journal of Infection, 2023 July; 87(1):46–53

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BACKGROUND & AIM: Widespread use of antifungal agents in the treatment of patients with haematological malignancies has been linked to an increased incidence of breakthrough invasive fungal infections (BtIFI). A lack of knowledge regarding the causes of BtIFI may increase the incidence of infections caused by rare fungi and the chance of antifungal resistance developing in causative species. The aim of this study was to characterize the causes and outcomes of BtIFI in a real-world cohort of patients with haematological malignancies.

STUDY DESIGN: Prospective, multicentre, cohort study.

ENDPOINTS: Clinical and microbiological outcomes.

METHOD: All BtIFI episodes in adults with haematological malignancies at 13 Spanish university hospitals were prospectively recorded over 36 months (2017–2020). BtIFI was defined as occurring when there was first clinical suspicion of IFI, according to revised EORTC/MSG definitions, following ≥7 days of antifungal treatment. Fungal isolates were identified in blood and respiratory samples using mass spectrometry or pan-fungal polymerase chain reaction and sequencing analysis. A diagnosis of proven BtIFI followed fungal isolation in blood culture, positive culture of a sterile site with radiological or clinical significance, or histopathological findings from a sterile specimen. Kaplan–Meier survival curves were used to assess mortality.

RESULTS: Among 121 BtIFI episodes, 33.9% were proven, 43.8% were probable and 22.3% were possible. The most common underlying disease was acute myeloid leukaemia (67/121 episodes; 55.4%), and the most common prior antifungals were posaconazole (32.2%) and echinocandins (28.9%). The most frequent BtIFI was invasive aspergillosis (55/121 episodes; 45.5%) followed by candidaemia (19.0%), with 62.1% of *Aspergillus* isolates being identified as non-*fumigatus* and 86.9% of *Candida* species as non-*albicans*. Other causes of BtIFI included mucormycosis (5.8%), other moulds (5.0%) and other yeasts (4.1%). Among proven and probable episodes of BtIFI, the most common cause was lack of activity of prior antifungal treatment (63/94 episodes; 67.0%). In 27/94 (28.7%) of these episodes, the causative fungi were intrinsically resistant to the prior antifungal treatment. The 100-day mortality rate was 47.1%, and BtIFI was the cause of death (or a significant contributory factor) in 61.4% of cases.

CONCLUSIONS: In this Spanish cohort of patients with haematological malignancies, BtIFI were mainly caused by non-*fumigatus* *Aspergillus* and non-*albicans* *Candida* species. Patients had a poor prognosis.

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THE USE OF GALACTOMANNAN ANTIGEN ASSAYS FOR THE DIAGNOSIS OF INVASIVE PULMONARY ASPERGILLOSIS IN THE HEMATOLOGICAL PATIENT:

A SYSTEMATIC REVIEW AND META-ANALYSIS

Journal of Fungi, 2023 June 15; 9(6):674

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BACKGROUND & AIM: Individuals with haematological malignancies are at risk of opportunistic infections such as invasive pulmonary aspergillosis (IPA), and early diagnosis and treatment are important for the best chance of survival. A diagnosis of IPA can be made by looking for galactomannan (an *Aspergillus*-specific marker) in serum and bronchoalveolar lavage (BAL) fluid, but the appropriate cutoff value for the optical density index (ODI) for galactomannan in diagnosing IPA is a matter of debate. The aim of this study was to examine the most recent evidence on ODI cut-off values for diagnosing IPA in patients with haematological malignancies.

STUDY DESIGN: Systematic review and meta-analysis.

ENDPOINTS: Primary: pooled sensitivity and specificity of serum and BAL galactomannan. Secondary: sensitivity and specificity per ODI.

METHOD: A search of the PubMed, Embase and Cochrane databases identified 27 studies that reported the use of galactomannan Platelia ELISA in serum or BAL fluid for diagnosing IPA in adults with haematological malignancies, and used the EORTC/MSG categories of proven/probable/possible/no IPA. Data were extracted from eligible studies and pooled using a generalized linear mixed model with binomial distribution.

RESULTS: Analysis of 15 serum studies (total *n*=2568), regardless of the cutoff value or study design, gave an overall sensitivity of 0.76 and specificity of 0.92 for galactomannan for diagnosing proven/probable IPA versus no IPA, and sensitivity and specificity of 0.45 and 0.91, respectively, for diagnosing proven/probable/possible IPA. There were insufficient studies available for pooled analysis of ODI cutoffs of 1.0 and 1.5, but values for a cutoff of 0.5 are shown in the table. Analysis of 12 BAL studies (total *n*=1090) provided overall sensitivity of 0.80 and specificity of 0.95 for diagnosing proven/probable IPA versus no IPA, and values of 0.49 and 0.95, respectively, for proven/probable/possible IPA. Sensitivity and specificity for ODI cutoffs of 0.5 and 1.0 are shown in the table.

CONCLUSION: Based on available data, galactomannan ODI cutoffs of 0.5 for serum and 1.0 for BAL fluid were most suitable for diagnosing proven/probable IPA in patients with haematological malignancies.

Sensitivity and specificity of galactomannan for diagnosing proven/probable invasive pulmonary aspergillosis (IPA) versus no IPA according to optical density index (ODI) cut-off

		Sensitivity	Specificity
Serum	Overall	0.76	0.92
	ODI cut-off 0.5	0.92	0.84
Bronchoalveolar lavage	Overall	0.80	0.95
	ODI cut-off 0.5	0.75	0.88
	ODI cut-off 1.0	0.75	0.96

https://doi.org/10.3390/jof9060674

ANTICIPATORY ANTIFUNGAL TREATMENT IN CRITICALLY ILL PATIENTS WITH SARS-COV-2 PNEUMONIA

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BACKGROUND & AIM: Invasive pulmonary aspergillosis is associated with a very high mortality rate among critically ill patients, but accurate diagnosis is essential to avoid overtreatment. The reported incidence of COVID-19–associated pulmonary aspergillosis (CAPA) has varied considerably, probably due to differences in diagnostic protocols. The early administration of antifungal treatment might reduce the development of CAPA and improve survival. The aim of this study was therefore to investigate the incidence of CAPA in an at-risk population of critically ill patients, as well as the impact of early antifungal therapy on CAPA incidence.

STUDY DESIGN: Observational study.

ENDPOINT: Incidence of CAPA.

METHOD: The study included 160 critically ill patients with severe SARS-CoV-2 pneumonia requiring invasive mechanical ventilation and bronchoscopic evaluation, all of whom were treated in a mixed intensive care unit (ICU) in a university teaching hospital between March 2020 and June 2022. None had a pneumothorax, oxygen saturation less than 80%, severe acidosis or haemodynamic instability. A diagnosis of pulmonary aspergillosis was based on positive molecular testing, fever and/or impaired respiratory function, the presence of pulmonary infiltrates on a simple chest radiograph, and mycological criteria for infection following fibrobronchoscopy. Overall, 58 patients were seen during a period when no antifungal treatment was administered on admission to the ICU, while the other 102 patients were seen during a period when antifungals were administered at admission (because of concerns about the high incidence of aspergillosis).

RESULTS: The incidence of CAPA was 32.75% among patients who did not receive antifungal therapy, and was lower, at 10.78%, in patients who did receive early antifungal therapy at admission (p=0.001). The 90-day CAPA-associated mortality rate was 63.63% in the group who received early antifungals versus 100% in the group who did not (p=0.015). Laboratory measures did not differ between the two groups of patients, except for inflammation parameters, which were higher in those who did not receive early antifungals. Factors with a significant impact on patient survival included the occurrence of CAPA (odds ratio 1.732, 95% confidence interval 1.081–2.773, p=0.022) and age (OR 1.055, 95% CI 1.03–1.08).

CONCLUSIONS: In patients with SARS-CoV-2 pneumonia receiving invasive mechanical ventilation, anticipatory antifungal therapy was associated with reductions in the incidence of pulmonary aspergillosis and associated mortality.

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MANAGING THE NEXT WAVE OF INFLUENZA AND/OR SARS-COV-2 IN THE ICU:

PRACTICAL RECOMMENDATIONS FROM AN EXPERT GROUP FOR CAPA/IAPA PATIENTS

Journal of Fungi, 2023 March 2; 9(3):312

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BACKGROUND & AIM: During the COVID-19 pandemic, much knowledge was gained on treating patients with COVID-19–associated pulmonary aspergillosis (CAPA). This has potential applications for managing patients with influenza virus-associated invasive pulmonary aspergillosis (IAPA), which is a serious disease in critically ill patients. The aim of this study was to apply the knowledge gained during the COVID-19 pandemic to develop practical recommendations for diagnosing and treating CAPA/IAPA.

ARTICLE TYPE: Practical recommendations.

FINDINGS: Experts in CAPA/IAPA searched PubMed for information on CAPA and IAPA, and consensus recommendations for diagnosis and management were developed. The recommendations were grouped around 12 key questions, covering when CAPA/IAPA should be suspected, diagnostic methods (and alternative approaches), recommended treatments, resistance, treatment monitoring, defining treatment failure, the use of corticosteroids, combination therapy, treatment withdrawal, treatment in those with a positive *Aspergillus* culture and antifungal prophylaxis.

Recommendations include incorporating CAPA/IAPA in the differential diagnosis of respiratory superinfection in patients admitted to the intensive care unit (ICU) with viral pneumonia and unexplained deterioration, with particular consideration in patients with risk factors for fungal infection, prolonged or high-dose steroid therapy, prolonged mechanical ventilation and/or structural lung injury. In addition, *Aspergillus* coinfection should be considered in patients admitted to the ICU with severe respiratory failure caused by severe influenza/COVID-19–related viral pneumonia.

There is no evidence to support the use of any one antifungal agent over another to treat CAPA/IAPA, or that treatment should differ to that given for IPA. As such, current recommendations from national and international guidelines should be followed, taking into account the particular needs of critically ill patients or those with severe viral pneumonia caused by influenza or COVID-19. In general, the duration of therapy should be based on clinical response and immune status, and usually continue for 4–6 weeks. Antifungal prophylaxis is not recommended for patients with severe influenza virus/COVID-19 pneumonia undergoing mechanical ventilation, but studies are needed on the use of CAPA/IAPA prophylaxis in critically ill patients without a haematological malignancy and those who are not transplant recipients.

CONCLUSIONS: Data on managing patients with CAPA/IAPA are limited. Nonetheless, practical recommendations based on the available evidence and expert opinion are presented.

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GUIDELINE FOR THE MANAGEMENT OF FEVER AND NEUTROPENIA IN PEDIATRIC PATIENTS WITH CANCER AND HEMATOPOIETIC CELL TRANSPLANTATION RECIPIENTS:

2023 UPDATE

Journal of Clinical Oncology, 2023 March 20; 41(9):1774–85

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BACKGROUND & AIM: Fever and neutropenia (FN) are common complications of treatments for cancer, but there is heterogeneity in their management between different centres. The International Pediatric Fever and Neutropenia Guideline Panel published a clinical practice guideline in 2012 on the management of FN in paediatric patients with cancer and in haematopoietic cell transplant (HCT) recipients, with an update in 2017. This article presents a further update to this clinical practice guideline, based on a systematic review of randomized, controlled trials.

ARTICLE TYPE: Clinical practice guideline.

FINDINGS: The previous guideline was based on the results of 69 randomized trials; this update includes 10 new trials published since then. It includes updated recommendations related to the initial and ongoing management of FN in paediatric patients, and the use of empirical antifungal therapy.

Blood cultures should be taken from central venous catheters at the onset of FN; peripheral blood cultures and urine analysis and cultures can also be considered. Chest radiography is necessary only in patients with respiratory signs or symptoms. In patients with high-risk FN, empirical antibacterial therapy should be started with an antipseudomonal β-lactam, fourth-generation cephalosporin or carbapenem. A second anti–Gram-negative agent or glycopeptide should be reserved for those who are clinically unstable or when resistance is suspected; this can be discontinued if the patient is responding to therapy and there is no microbiological indication for continued combination therapy. If feasible, initial or step-down outpatient management, with careful monitoring and follow-up, can be considered for low-risk patients.

Empirical antibacterial therapy can be discontinued in patients with high- or low-risk FN who have been clinically well and afebrile for ≥24 hours, if blood cultures remain negative at 48 hours and there is evidence of marrow recovery. This can also be considered in low-risk cases where there is no evidence of marrow recovery.

With regard to empirical antifungal therapy, recommendations are provided on the stratification of patients according to the risk of invasive fungal disease, as well as the biomarker assessments and imaging that should be carried out. Caspofungin or liposomal amphotericin B should be initiated in high-risk patients with prolonged FN unresponsive to broad-spectrum antibacterial therapy. In non-HCT high-risk patients not receiving antimould prophylaxis, clinicians should start antifungal therapy only if invasive fungal disease is suspected.

CONCLUSION: Empirical antibacterial therapy consistent with this guideline should be started as soon as possible in febrile patients who are clinically unstable.

https://doi.org/10.1200/JCO.22.02224

GUIDELINE ADHERENCE AND SURVIVAL OF PATIENTS WITH CANDIDAEMIA IN EUROPE:

RESULTS FROM THE ECMM *CANDIDA* III MULTINATIONAL EUROPEAN OBSERVATIONAL COHORT STUDY

The Lancet Infectious Diseases, 2023 June; 23(6):751–61

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CENTRE FOR CORRESPONDENCE: Division of Infectious Diseases, Department of Internal Medicine, Medical University of Graz, Graz, Austria

BACKGROUND & AIMS: Despite advances in management, invasive candidiasis including candidaemia is associated with high mortality in the hospital setting. The European Confederation of Medical Mycology (ECMM) Quality of Clinical Candidaemia Management (EQUAL *Candida*) scores were developed to measure the quality of disease management as reflected by adherence to guidelines published by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the Infectious Diseases Society of America (IDSA). The aim of the *Candida* III study was to assess how adherence to guidelines for the diagnosis and management of candidaemia correlates with patient outcomes.

STUDY DESIGN: European multicentre observational cohort study.

ENDPOINTS: EQUAL *Candida* score and correlation with outcomes.

METHOD: Data for the first 10 consecutive adult patients who presented with culture-proven candidaemia (defined according to ESCMID criteria) after 1 July 2018 at each of 64 participating hospitals in 20 European countries were entered into the ECMM *Candida* Registry. The number of patients and number of centres per country were stratified by population size. EQUAL *Candida* scores were assessed. Independent predictors of mortality were identified using Cox regression analysis.

RESULTS: Among the 632 participants, the median age was 65 years and 58% were male. The most common risk factors for candidaemia were underlying malignancy (39% of patients), intensive care unit (ICU) admission (37%) and recent major surgery (26%). Overall 90-day mortality was 43%. Independent baseline predictors of mortality were ICU admission (adjusted hazard ratio 1.71), increasing age (aHR 1.37), increases in Charlson comorbidity index scores (aHR 1.09 per point) and the causative pathogen being *Candida tropicalis* (aHR 1.78). Lower EQUAL *Candida* score was an independent predictor of mortality after adjustment for known baseline predictors of mortality. Among patients who survived more than 7 days after diagnosis, a decrease of one point in the EQUAL *Candida* score was associated with an increase in the risk of death of 8% and 9% in patients with or without a central venous catheter, respectively. Lack of performance or completion of ophthalmoscopy (aHR 2.19), echocardiography (aHR 1.77), treatment for ≥14 days after first negative blood culture (aHR 3.64) or step-down therapy to fluconazole (aHR 1.71), as recommended in the guidelines, were also predictors of mortality.

CONCLUSION: A lower EQUAL *Candida* score was an independent predictor of mortality, indicating that greater adherence to clinical guideline recommendations for the diagnosis and management of patients with candidaemia may increase survival.

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HOSPITAL-TREATED SERIOUS AND INVASIVE ASPERGILLOSIS AND CANDIDIASIS INFECTIONS DURING THE COVID-19 PANDEMIC:

A RETROSPECTIVE ANALYSIS OF HOSPITAL EPISODE STATISTICS DATA FROM ENGLAND

BMJ Open, 2023 May 30; 13(5):e070537

AUTHORS: Sung AH, Kiely G, Singh JK, Thomas S, Lough J, Smith M
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BACKGROUND & AIM: Serious and invasive fungal infections, such as invasive aspergillosis (IA) and invasive candidiasis, are linked to adverse outcomes in seriously ill patients, but the burden they impose on the UK healthcare system is not well understood. COVID-19 infection increases patient susceptibility through both direct and indirect effects, such as immunosuppression and a requirement for mechanical ventilation. The aim of this analysis was to investigate the impact of COVID-19 infection on the healthcare burden of invasive aspergillosis and invasive candidiasis in hospitals in England.

STUDY DESIGN: Retrospective analysis of Hospital Episode Statistics (HES).

ENDPOINTS: Patient case numbers, mean length of stay (MLOS), admission to a critical care unit (CCU), length of CCU stay, readmission within 30 days and failed discharge (readmission within 7 days).

METHOD: Anonymized data including patient characteristics, diagnoses, comorbidities and healthcare utilization, including CCU admission and readmissions, for patients with a diagnosis of serious aspergillosis or invasive candidiasis were extracted from NHS Digital HES records for the period March 2018 to October 2021. March 2020 was taken as the starting point of the COVID-19 pandemic period in the UK.

RESULTS: Before the COVID period, 6255 patients were recorded with aspergillosis and 3445 with candidiasis. From March 2020 onwards, there were 4350 aspergillosis patients and 2385 candidiasis patients without COVID-19 and a further 600 patients (8.2%) with either fungal infection who also had a COVID-19 diagnosis. Hospital admissions decreased at the start of the COVID-19 pandemic and monthly patient counts with IA showed a similar drop (24.8%), recovering after 12 months; invasive candidiasis patient counts, however, showed only a small decline (3.2%). Patients with aspergillosis plus COVID-19 infection had a markedly longer MLOS than those with aspergillosis alone (20.2 versus 9.0 days), but the same was not true for invasive candidiasis patients (27.2 versus 28.8 days). Readmissions within 30 days increased for patients with a COVID-19 diagnosis in addition to a fungal infection (from 8.6% to 12.6% for aspergillosis and from 2.5% to 3.7% for candidiasis), as did failed discharges. A COVID-19 diagnosis also increased the proportion of patients admitted to the CCU (from 13.2% to 52.5% for aspergillosis patients and from 37.1% to 60.0% for candidiasis) and the length of stay in the CCU.

CONCLUSIONS: Coinfection with invasive aspergillosis or candidiasis and COVID-19 increased disease burden and the need for critical care and worsened outcomes.

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A PATHOLOGY-BASED CASE SERIES OF INFLUENZA- AND COVID-19–ASSOCIATED PULMONARY ASPERGILLOSIS:

THE PROOF IS IN THE TISSUE

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BACKGROUND & AIM: Influenza-associated pulmonary aspergillosis is a potentially life-threatening invasive disease, often confirmed histopathologically, that develops in up to 25% of influenza patients admitted to intensive care. COVID-19–associated pulmonary aspergillosis is a similar condition, but is supported by less evidence of invasiveness and conflicting findings regarding its incidence. The aim of this study was to compare the two, making use of autopsy and antemortem findings.

STUDY DESIGN: Retrospective, single-centre case series.

ENDPOINTS: Incidence of virus-associated pulmonary aspergillosis (VAPA); histopathological findings.

METHOD: The study examined records and tissue samples of patients with PCR-proven influenza or COVID-19–associated respiratory failure who died after admission to the ICU of a Belgian tertiary care hospital and underwent autopsy. Patients were classified based on clinical and pathological evidence of VAPA.

RESULTS: The study examined samples from a cohort of 44 patients (23 coronavirus-infected and 21 influenza virus-infected) who underwent autopsy. Of these 44 patients, 21 (48%) were classified before death as having "probable VAPA", of whom 11/21 (52%) had evidence of invasive pulmonary fungal disease on autopsy, despite having been given antifungal treatment. Overall, proven VAPA was established at autopsy in 12 patients, six with influenza and six with COVID-19. Two histological patterns of fungal growth were observed: unimpeded fungal bronchopneumonia with a high fungal load and large areas of fungal necrosis (2/11 patients) and impeded fungal bronchopneumonia with a low fungal load and dispersed, fragmented hyphae surrounded by acutely inflamed/necrotic lung tissue (9/11 patients). The pattern observed did not correlate with the underlying virus type. Galactomannan (GM) testing of bronchoalveolar lavage (BAL) fluid was found to be the most sensitive method for detecting VAPA in the antemortem period (92%, with a specificity of 64%), ahead of BAL culture (58%, specificity 93%) and serum GM testing (33%, specificity 94%). The autopsy-proven incidence of VAPA in these patients (12% for influenza-infected patients and 8% for those with coronavirus infection) was somewhat higher than reported elsewhere.

CONCLUSIONS: Invasive fungal infection may be more common in critically ill patients with viral pneumonia (influenza or COVID-19) than previously suspected, as demonstrated by histological findings at autopsy. However, the dispersed pattern of impeded fungal growth commonly seen could make it difficult to detect.

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WORLDWIDE EMERGENCE OF FLUCONAZOLE-RESISTANT *CANDIDA PARAPSILOSIS*:

CURRENT FRAMEWORK AND FUTURE RESEARCH ROADMAP

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BACKGROUND & AIMS: Since 2018, outbreaks of candidaemia caused by fluconazole-resistant strains of *Candida parapsilosis* have been reported. Multidrug-resistant and echinocandin-resistant strains have also been reported since 2020, which could potentially replace strains that are susceptible to current azole-based treatment strategies, posing a public health threat given the limited number of antifungal drugs available for clinical use. The aim of this review was to summarize current knowledge regarding the global emergence of fluconazole-resistant *C. parapsilosis* strains.

ARTICLE TYPE: Review.

FINDINGS: *C. parapsilosis* is one of the most prevalent candidaemia-causing species, with infections primarily occurring in patients admitted to intensive care units, neonates and people with COVID-19, cancer or who have received transplants. Outbreaks are generally caused by horizontal transmission from the environment to patients via the hands of healthcare workers, or via contaminated intravenous solutions.

Over the last 3 years, fluconazole-resistant *C. parapsilosis* strains have been reported to outcompete fluconazole-susceptible ones and persist in hospital settings, causing severe sporadic outbreaks among azole-naive patients and increased mortality compared with patients with fluconazole-susceptible infections. *ERG11* mutations and overexpression of ERG11 are believed to underpin fluconazole resistance, although some studies have reported that >60% of resistant strains do not carry *ERG11* mutations. There is also evidence that strains with intermediate fluconazole minimum inhibitory concentrations (MICs) might develop resistance by increasing the *CDR1* copy number.

Echinocandin-resistant strains often have mutations in the catalytic subunit of β-glucan synthase, and a concept of heteroresistance has been proposed, where a small subpopulation of isolates could tolerate high echinocandin concentrations, reducing the efficacy of prophylaxis. Studies have shown that *TAC1*^{L518F} and *FKS1*^{S656P} polymorphisms in *C. parapsilosis* genes increase the fluconazole MIC and confer pan-echinocandin resistance, respectively. Additionally, some *C. parapsilosis* strains have been shown to form biofilms on abiotic and biotic surfaces that protect them from the host immune response and antifungal drugs.

Regular global monitoring of fluconazole- and echinocandin-resistant *C. parapsilosis* outbreaks, and characterization of the underlying mechanisms, is needed to aid the development of new antifungal agents and molecular assays for environmental screening and skin swab sampling.

CONCLUSION: The emergence of fluconazole- and echinocandin-resistant strains of *C. parapsilosis* emphasizes the need for global monitoring and new classes of antifungal agents.

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WORSENING SPREAD OF *CANDIDA AURIS* IN THE UNITED STATES, 2019 TO 2021

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BACKGROUND & AIM: *Candida auris* infections were first reported in the USA in 2016 and notification of clinically confirmed cases became mandatory in 2019. Nosocomial transmission is a significant problem, and the threat is increased by the emergence of antifungal-resistant cases. The aim of this study was to give a national overview, focusing on *C. auris* spread over the period 2019–2021.

STUDY DESIGN: Retrospective analysis of national surveillance and antimicrobial resistance testing data.

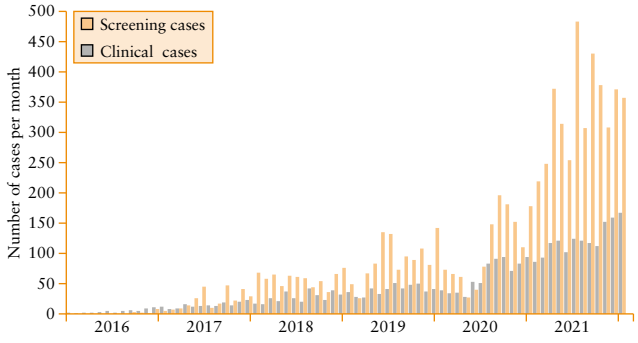
ENDPOINTS: Incidence of *C. auris*-positive cases and antifungal-resistant cases.

METHOD: The study reviewed all confirmed and probable clinical and colonization-screening–derived cases notified to the CDC, state and local health departments from 2013 to the end of 2021. Data on antifungal resistance to azoles, polyenes and echinocandins were obtained from the seven CDC regional testing centres, which have run a *C. auris* testing programme since 2017.

RESULTS: Annual clinical case numbers increased from 53 in 2016 (the year of first report) to 1471 in 2021, with a cumulative total of 3270 cases. Clinical cases increased by 44% from 2018 to 2019, by 59% between 2019 and 2020 and by a further 95% during 2021 (figure). Most positive cases were detected in post–acute-care facilities. In 2020, cases were reported for the first time in eight US states, compared with six states in 2019. Colonization-screening testing increased markedly from 2019 (19,756) to 2021 (>40,000), with a drop in testing during 2020 due to the COVID-19 pandemic, but the positivity rate remained constant at about 8%. A cumulative total of 7413 screening cases were reported (figure). By 2020, 85.7% of isolates were azole-resistant and 25.6% were polyene-resistant. Resistance to echinocandins was still low (1.2%) but had increased significantly since 2018, with the greatest number of resistant cases occurring in the northeastern USA.

CONCLUSIONS: *C. auris* infections are growing numerically and geographically in the US, with an increase in echinocandin-resistance that is potentially concerning. Implementing rigorous infection control protocols is the best means of controlling spread.

Number of clinical and colonization-screening cases of *Candida auris* reported per month in the USA between 2016 and 2021



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