FramingHam

on systemic fungal infections

Exploring European consensus about the remaining treatment challenges and subsequent opportunities to improve the management of invasive fungal infection (IFI) in the intensive care unit

Mycopathologia, 2024 May 5; 189(3):41

Microbiological risk factors, ICU survival, and 1-year survival in hematological patients with pneumonia requiring invasive mechanical ventilation

European Journal of Clinical Microbiology & Infectious Diseases, 2024 September; 43(9):1679–88

Factors associated with poor clinical and microbiologic outcomes in C. *Auris* bloodstream infection: a multicenter retrospective cohort study

Clinical Infectious Diseases, 2024 August 13; Epub ahead of print

Environmental hot spots and resistance-associated application practices for azole-resistant *Aspergillus fumigatus*, Denmark, 2020–2023

Emerging Infectious Diseases, 2024 August; 30(8):1531–41

Insights from three pan-European multicentre studies on invasive *Candida* infections and outlook to ECMM *Candida* IV

Mycopathologia, 2024 August 1; 189(4):70

Treatment outcomes among patients with a positive *candida* culture close to randomization receiving rezafungin or caspofungin in the ReSTORE study

Clinical Infectious Diseases, 2024 July 10; Epub ahead of print

The impact of the fungal priority pathogens list on medical mycology: a northern European perspective

Open Forum Infectious Diseases, 2024 July 1; 11(7):ofae372

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EXPLORING EUROPEAN CONSENSUS ABOUT THE REMAINING TREATMENT CHALLENGES AND SUBSEQUENT OPPORTUNITIES TO IMPROVE THE MANAGEMENT OF INVASIVE FUNGAL INFECTION (IFI) IN THE INTENSIVE CARE UNIT

Mycopathologia, *2024 May 5; 189(3):41*

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BACKGROUND & AIM: The prevalence of invasive fungal infections (IFIs) is increasing around the world, and is a particular problem in the intensive care unit (ICU). *Candida* species are the most common cause of infections, but invasive aspergillosis is also frequently reported. Diagnosis is difficult because of a lack of specific clinical and radiological findings and difficulties with laboratory-based tests, and this affects the ability to provide rapid treatment, which is essential for improving outcomes. Antifungal resistance and the emergence of rare fungal species present additional challenges. The aim of this study was to describe optimal care and identify challenges to the diagnosis and management of IFIs in the ICU by conducting a consensus survey of healthcare professionals.

STUDY DESIGN: Survey.

ENDPOINTS: Consensus statements on the diagnosis and management of IFIs.

METHOD: Modified Delphi methodology was used to develop a set of 44 Likert-scale statements focusing on six main domains relating to the management of IFIs in the ICU. These domains included patient screening, the minimum standard for diagnosis, initiation and change of treatment, termination of treatment, managing side effects, and insights on future research. An online survey was created from these statements, which was distributed to ICU healthcare providers (including intensive care specialists, infectious disease specialists, microbiologists and pharmacists) in France, Germany, Italy, Spain and the UK. All participants had to have at least 2–5 years of experience in their specialty. The threshold for consensus was set at 75%.

RESULTS: There was a total of 335 responses to the survey. Very high agreement (≥90%) was reached for 29 (66%) of the statements, while 11 (25%) had high agreement (75% to <90%), and four (9%) did not reach consensus. There was a strong consensus on the patient characteristics that indicate high suspicion of infection, and that physicians need to be aware of the local incidence of IFIs and rate of azole resistance in their ICUs. The respondents also agreed that treatment should be started as quickly as possible when IFI is suspected, and not delayed to await test results. It was agreed that more evidence is required on the incidence of IFIs in specific patient groups, and the role of antifungal prophylaxis in at-risk ICU populations. Beta-D-glucan testing should be widely available to help guide the cessation of empirical antifungal treatment.

CONCLUSIONS: This survey identified a number of areas that need improvement, and may help guide future research on optimizing the management of IFIs in the ICU.

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MICROBIOLOGICAL RISK FACTORS, ICU SURVIVAL, AND 1-YEAR SURVIVAL IN HEMATOLOGICAL PATIENTS WITH PNEUMONIA REQUIRING INVASIVE MECHANICAL VENTILATION

European Journal of Clinical Microbiology & Infectious Diseases, 2024 September; 43(9):1679–88

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BACKGROUND & AIM: A high proportion of patients with haematological malignancies experience severe infectious complications due to the immune effects of their disease and its treatment. Those who develop pneumonia and consequently require invasive mechanical ventilation have a particularly high mortality rate of up to 70%. To help predict outcomes and improve treatment for this patient population, this study assessed microbiological risk factors associated with intensive care unit (ICU) mortality and 1-year mortality in patients with haematological malignancies and pneumonia requiring invasive mechanical ventilation.

STUDY DESIGN: Retrospective, single-centre study.

ENDPOINTS: ICU mortality and 1-year mortality; associated risk factors.

METHOD: The study included 246 adults with haematological malignancies admitted to the ICU between 2004 and 2016 who required invasive mechanical ventilation because of pneumonia (clinical diagnosis plus pneumonia-suspicious CT findings). Microbiological and radiological data were collected, including the results of lower respiratory tract fluid testing for bacteria, fungi and viruses. Multivariate analysis was used to assess associations between microbiological factors and mortality.

RESULTS: The rates of ICU and 1-year mortality were 63.0% and 81.0%, respectively. Overall, 58.1% of patients had pneumonia-causing pathogens, and 20.7% had multimicrobial infections. The prevalence of fungal, bacterial and viral pathogens was 36.2%, 22.4% and 16.7%, respectively, and 34.6% of patients had concomitant reactivated human herpesviruses. Of note, multimicrobial infection with a combination of respiratory virus infection plus *Aspergillus* species superinfection was associated with high ICU and 1-year mortality rates of 78.9% and 89.5%, respectively. Microbiological risk factors associated with ICU mortality included probable invasive *Aspergillus* disease with positive serum galactomannan, and pulmonary *Cytomegalovirus* reactivation at intubation (table). No associations between type of infection and 1-year mortality were found.

CONCLUSIONS: Mortality rates were high among patients with haematological malignancies on invasive mechanical ventilation due to pneumonia. Risk factors included pulmonary aspergillosis and pulmonary reactivation of *Cytomegalovirus*.

Microbiological risk factors for intensive care unit mortality in patients with haematological malignancies and pneumonia requiring invasive mechanical ventilation (multivariate analysis)

	Odds ratio (95% confidence interval), *p*
Probable invasive *Aspergillus* disease with positive serum galactomannan	3.1 (1.2–8.0), *p*=0.021
Pulmonary *Cytomegalovirus* reactivation at intubation	5.3 (1.1–26.8), *p*=0.043
Viral pneumonia	2.0 (0.8–5.1), *p*=0.136

https://doi.org/10.1007/s10096-024-04883-y

FACTORS ASSOCIATED WITH POOR CLINICAL AND MICROBIOLOGIC OUTCOMES IN *C. AURIS* BLOODSTREAM INFECTION:

A MULTICENTER RETROSPECTIVE COHORT STUDY

Clinical Infectious Diseases, 2024 August 13; Epub ahead of print

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BACKGROUND & AIM: *Candida auris* is a high-priority pathogen with an increasing incidence worldwide and a propensity for invasive infections. Up to 25% of intensive care unit patients with *C. auris* colonization will develop *C. auris* bloodstream infections (BSIs). This study evaluated clinical outcomes of patients with *C. auris* BSI, and explored risk factors for poor outcomes.

STUDY DESIGN: Multicentre, retrospective cohort study.

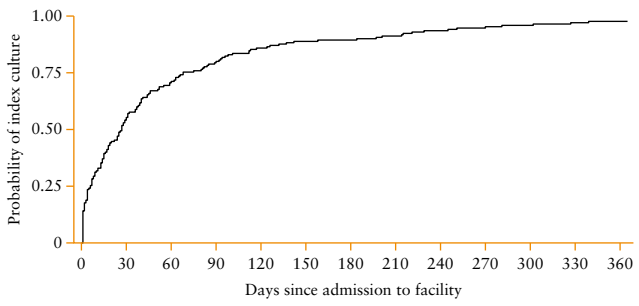
ENDPOINTS: The coprimary endpoints were all-cause mortality during facility admission and blood culture clearance. Time to BSI index culture and time from BSI index culture to death were also investigated.

METHOD: Demographic, clinical and microbiological data were obtained for adult patients with *C. auris* BSI between 2017 and 2022 from two US regions. These were analysed by multivariate logistic regression to determine risk factors for all-cause mortality during facility admission, and blood culture clearance. Patients were stratified by severity of illness based on Pitt bacteraemia score (0, 1–4, 5–8).

RESULTS: Among 187 patients with *C. auris* BSI (43.9% female, 55.6% aged >65 years), the all-cause mortality rate was 54.6%. Among 142 patients with evaluable data, 66.9% achieved blood culture clearance. Bedbound patients (i.e. low palliative performance scale score on admission) and patients with feeding tubes tended to have higher Pitt scores at the time of the index culture. Most patients developed BSI (indicated by index culture) within 30 days of facility admission (see figure), and over half of deaths following BSI occurred within 45 days of the index culture. Pitt bacteraemia score at onset of *C. auris* BSI was associated with mortality (odds ratio 1.19 per 1-point increase, p=0.037). Haemodialysis was also associated with mortality (OR 3.08, p=0.013), as well as with a reduced likelihood of blood culture clearance (OR 0.15, p<0.001).

CONCLUSIONS: Among patients with *C. auris* BSI, Pitt bacteraemia score at onset may help identify those at greatest risk of dying. Prophylactic anti-infection measures could mitigate poor outcomes in those receiving haemodialysis.

Time from admission to index culture indicating *Candida auris* bloodstream infection



https://doi.org/10.1093/cid/ciae411

ENVIRONMENTAL HOT SPOTS AND RESISTANCE-ASSOCIATED APPLICATION PRACTICES FOR AZOLE-RESISTANT *ASPERGILLUS FUMIGATUS*, DENMARK, 2020–2023

Emerging Infectious Diseases, 2024 August; 30(8):1531–41

AUTHORS: Arendrup MC, Hare RK, Jørgensen KM, Bollmann UE, Bech TB, Hansen CC, Heick TM, Jørgensen LN
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BACKGROUND & AIMS: Increasing evidence suggests that selection of azole-resistant *Aspergillus fumigatus* (ARAf) can occur in the environment. In Denmark, nationwide surveillance of clinical *A. fumigatus* between 2018 and 2020 found environmental-origin resistance mutations TR_{34}/L98H or TR_{46}/Y121F/T289A present in 3.6% of clinical isolates. The aims of the current study were to perform extensive environmental sampling to determine hotspots for ARAf, the effect of azole concentrations on resistance development, characterize resistance mechanisms and molecular genotypes, and investigate the potential of various azole fungicides to select for ARAf.

STUDY DESIGN: Environmental sampling study.

ENDPOINT: ARAf in environmental samples.

METHOD: A total of 366 samples were collected from agricultural fields, flowerbeds in parks and private gardens, flower and potato production soil, compost soil/heaps, animal bedding/manure heaps and wood paint-associated soil in Denmark between 2020 and 2023. *A. fumigatus* isolates identified in the samples underwent azole-resistance screening, and any ARAf underwent molecular characterization and genotyping. Azole concentrations used on the environmental samples were determined for eight azole fungicides. Microcosmos and field experiments assessed the potential of various azole fungicides to select for ARAf.

RESULTS: ARAf was found in 20% of the 366 samples (16% TR_{34}/L98H and 4% TR_{46}/Y121F/T289A), and in 4.2% of the 4538 *A. fumigatus* isolates identified. ARAf was found in all of the different environmental sample types, with the highest proportions found in flower- and compost-related samples. The proportions of ARAf in the samples did not correlate with azole-fungicide application concentrations. Using genotyping, a cluster of TR_{34}/L98H was identified that was widely distributed across the country and was found in both clinical and environmental isolates. In the field experiment, poor growth of *A. fumigatus* was observed and there was no change in the proportions of ARAf between prespraying and postspraying samples. However, the microcosmos experiments indicated that some azole fungicides may encourage selection of ARAf in soil, as tebuconazole caused sustained complete inhibition and prothioconazole partial inhibition of wild-type *A. fumigatus* but not of ARAf.

CONCLUSIONS: There is evidence of ARAf in a wide range of environmental samples in Denmark, with compost, flowerbeds and flower production being the main hotspots. Increasing resistance rates will challenge patient management and could possibly be slowed by prioritizing the use of *A. fumigatus*-active azole fungicides.

https://doi.org/10.3201/eid3008.240096

INSIGHTS FROM THREE PAN-EUROPEAN MULTICENTRE STUDIES ON INVASIVE *CANDIDA* INFECTIONS AND OUTLOOK TO ECMM *CANDIDA* IV

Mycopathologia, *2024 August 1; 189(4):70*

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BACKGROUND & AIM: The European Confederation of Medical Mycology (ECMM) conducted three prospective studies across multiple European countries between 1997 and 2022 looking at different features of invasive *Candida* infections, including clinical and microbiological characteristics, antifungal therapy and clinical outcomes. This article reviews key findings.

ARTICLE TYPE: Review.

FINDINGS: *Candida* I (which included 2089 patients with candidaemia based on hospital records) identified *C. albicans* as the most common pathogen (56%), although the incidence of non-*albicans* infections was high versus previous studies. *Candida* II (779 surgical patients with invasive candidiasis in the intensive care unit, ICU) found that most (80.5%) developed *Candida* infections >48 hours after ICU admission (i.e. ICU-acquired infections). In *Candida* III (632 patients with culture-proven candidaemia), the incidence of *C. albicans* infection was 46% and the 90-day mortality rate was 43%. The study identified increasing age, ICU admission, high Charlson comorbidity index score and *C. tropicalis* infection as independent predictors of mortality. First-line echinocandin treatment was associated with improved survival, but also a longer hospital stay due to its parenteral administration.

Risk factors for invasive *Candida* infections identified by the studies included advanced age, major surgery, ICU admission, solid and haematological malignancies, solid-organ transplantation, corticosteroid use, total parenteral nutrition, central venous catheters and burns. Other risk factors identified in *Candida II* (ICU patients) included recent use of broad-spectrum antibiotics, rheumatological disease, recent steroid use and dialysis. The mortality rate was high in all three studies, with a crude 30-day mortality rate of around 38%. *Candida* III also calculated an attributable mortality of 18.1%.

In *Candida* I, 84.5% of patients received antifungal therapy (primarily fluconazole or amphotericin B). In *Candida* II, 16.5% of post-surgical ICU patients received antifungal prophylaxis, most often fluconazole, which was also the most frequent initial antifungal treatment, followed by caspofungin. Antifungal prophylaxis (mainly fluconazole) was also administered to 16.5% of patients in *Candida* III, while echinocandins were the most common initial treatment (56%) and were associated with a lower mortality rate than other antifungals.

CONCLUSIONS: Key findings of the ECMM *Candida* studies include shifts in species distribution, with an increase in non-*albicans* species, and persistently high mortality rates. The article also looks ahead to the forthcoming *Candida IV* study, which will focus on non-*albicans* species.

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TREATMENT OUTCOMES AMONG PATIENTS WITH A POSITIVE *CANDIDA* CULTURE CLOSE TO RANDOMIZATION RECEIVING REZAFUNGIN OR CASPOFUNGIN IN THE RESTORE STUDY

Clinical Infectious Diseases, 2024 July 10; Epub ahead of print

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BACKGROUND & AIM: In the ReSTORE study, a novel, once-weekly echinocandin, rezafungin, was non-inferior to caspofungin in terms of 30-day all-cause mortality and 14-day global cure rate in patients with candidaemia and/or invasive candidiasis. A pre-planned subgroup analysis of ReSTORE participants who had a positive *Candida* culture close to randomization has now been reported.

STUDY DESIGN: Subgroup analysis of a multicentre, randomized, double-blind, double-dummy trial.

ENDPOINTS: Thirty-day all-cause mortality, 14-day global cure rate, 5- and 14-day mycological eradication rates, median time to negative blood culture, and adverse events.

METHOD: The original study randomized adults with candidaemia and/or invasive candidiasis to treatment with once-weekly intravenous rezafungin (400 mg on day 1, then 200 mg) or once-daily intravenous caspofungin (70 mg on day 1, then 50 mg). This subgroup analysis focused on participants who had a positive *Candida* blood culture between 12 hours before and 72 hours after randomization, or a positive culture from another normally sterile site between 48 hours before and 72 hours after randomization.

RESULTS: The analysis included 38 rezafungin recipients and 46 caspofungin recipients. The 30-day all-cause mortality rate, 14-day global cure rate and 14-day mycological eradication rate were similar in both subgroups (table). There was a non-significant trend towards a higher 5-day mycological eradication rate with rezafungin versus caspofungin (table). There was also a non-significant trend towards a shorter median time to negative blood culture with rezafungin versus caspofungin (23.9 versus 60.5 hours, nominal p=0.094). Negative blood culture rates were higher in rezafungin recipients versus caspofungin recipients at 24 hours after treatment initiation (55.2% versus 27.3%, nominal p=0.0162) but not at 48 hours after treatment initiation (58.6% versus 43.8%, nominal p=0.2460). The nature, incidence and severity of adverse events were similar in the two subgroups.

CONCLUSIONS: Among ReSTORE participants with candidaemia and/or invasive candidiasis with a positive *Candida* blood culture close to randomization, rezafungin showed similar efficacy to caspofungin. Rezafungin appeared to provide more rapid clearance of *Candida* infection.

Outcomes with rezafungin versus caspofungin in ReSTORE participants with candidaemia and/or invasive candidiasis with a positive *Candida* blood culture close to randomization

	Rezafungin (%)	Caspofungin (%)	Treatment difference, % points (95% confidence interval)
30-day all-cause mortality rate	26.3	21.7	4.6 (–13.7 to 23.5)
14-day global cure rate	55.3	50.0	5.3 (–16.1 to 26.0)
5-day mycological eradication rate	71.1	50.0	21.1 (–0.2 to 40.2)
14-day mycological eradication rate	63.2	54.3	8.8 (–12.4 to 29.0)

https://doi.org/10.1093/cid/ciae363

THE IMPACT OF THE FUNGAL PRIORITY PATHOGENS LIST ON MEDICAL MYCOLOGY:
A NORTHERN EUROPEAN PERSPECTIVE

Open Forum Infectious Diseases, *2024 July 1; 11(7):ofae372*

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BACKGROUND & AIM: Fungal diseases affect more than 1 billion people globally and antifungal resistance is increasing. In response to this widely overlooked global public health concern, the World Health Organization published the first fungal priority pathogens list (FPPL) in 2022, with the aim of strengthening the global response to fungal diseases and antifungal resistance by focusing research priorities and driving policy interventions. The authors reviewed the impact of FPPL on regional clinical practice by conducting a workshop with key experts from Northern Europe.

ARTICLE TYPE: Review.

FINDINGS: The FPPL has highlighted the challenge of estimating the global burden of fungal diseases and antifungal resistance due to limited surveillance, diagnostic coverage and routine antifungal resistance testing. Current diagnostic methodologies are limited as they require a high level of experience for identifying fungi and can take up to 30 days. Molecular testing is more rapid and sensitive but there are few tests widely available commercially. Broadening access to mycology laboratories and to affordable, high-quality diagnostics is needed to improve fungal disease surveillance as well as early and accurate diagnosis.

Improved surveillance also relies on adequate knowledge and education regarding the clinical presentation of fungal infections and risk factors for infection. Publication of the FPPL is an important first step in raising awareness of fungal pathogens, but increased coverage of fungal diseases in the medical curriculum is needed, along with joint training programmes to educate both clinicians and laboratory technicians in fungal disease management. There is also a need to encourage scientists to specialize in mycology, and for sustainable investment in research and development.

Strategies to tackle antifungal resistance should include increased routine resistance testing, efficient stewardship programmes to limit inappropriate use of antifungal agents, and the One Health approach that can mitigate the use of antimicrobials in the environment. In Northern Europe there is widespread air exposure to azole-resistant *Aspergillus fumigatus*, which accounts for around 40% of resistant infections.

The FPPL is also important for strengthening local guidance on tackling fungal diseases and improving healthcare systems to promote evidence-based therapy.

CONCLUSIONS: The FPPL is a major step in increasing awareness of fungal pathogens, and highlights the importance of strengthening laboratory capacity and surveillance, improving education, and encouraging sustainable investment in research and development and in public health interventions.

https://doi.org/10.1093/ofid/ofae372

THE *ASPERGILLUS* GALACTOMANNAN AG VIRCLIA® MONOTEST AND THE SÕNA *ASPERGILLUS* GALACTOMANNAN LATERAL FLOW ASSAY SHOW COMPARABLE PERFORMANCE FOR THE DIAGNOSIS OF INVASIVE ASPERGILLOSIS

Mycoses, *2024 August; 67(8):e13782*

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BACKGROUND & AIM: Rapid diagnosis is key to reducing mortality in patients with invasive aspergillosis (IA), but existing galactomannan (GM) enzyme immunoassays (EIA) can be a diagnostic bottleneck. The aim of this study was to evaluate the performance of two rapid diagnostic tests – a GM lateral flow assay (GM-LFA) and a recently introduced chemiluminescence immunoassay (GM-Monotest).

STUDY DESIGN: Laboratory study.

ENDPOINTS: Diagnostic performance.

METHOD: The rapid tests were compared on the basis of their performance in analysing retained serum, bronchoalveolar lavage fluid (BALF) or cerebrospinal fluid (CSF) samples from two patient cohorts: (1) patients who had undergone allogeneic haematopoietic stem-cell transplantation (alloHSCT) during 2010 and (2) a cross-sectional cohort of all patients with proven or probable IA diagnosed between 2015 and 2020 at the university hospital in Erlangen. Positive samples were confirmed by re-testing of a second aliquot of the same sample. Testing by the GM-LFA method was carried out with visual evaluation and using a digital cube reader, while for the GM-Monotest an automated analyser was used.

RESULTS: The alloHSCT cohort comprised 101 patients (one proven IA, three probable IA on the basis of GM-EIA) with 527 samples (all sera). A first round of testing with the GM-Monotest and GM-LFA led to 18 and 70 of these sera being rated positive, respectively. Testing of a second aliquot resulted in two (11.1%) of the GM-Monotest samples and 32 (45.7%) of the GM-LFA samples being reclassified as negative. With the GM-LFA assay, 26.3% of sera gave a reading in an "equivocal" zone, where the manufacturer recommends re-testing. Comparison of their receiver operating characteristic curves showed no significant difference between the GM-Monotest and GM-LFA (area under the receiver operating characteristic curve 0.985 versus 0.988, p=0.239) and they both showed good agreement with GM-EIA results. The cross-sectional cohort included 59 patients (six proven IA, 53 probable IA) who generated 184 samples (96 sera, 83 BALF, five CSF). Again, performance of the two rapid assays correlated well with GM-EIA, with Cohen's kappa being 0.89 for the GM-Monotest and 0.82 for the GM-LFA. Both tests had significantly better sensitivity when used to test BALF versus serum.

CONCLUSIONS: The GM-LFA and GM-Monotest rapid diagnostic tests performed similarly to GM-EIA but, due to poor reproducibility, positive GM-LFA tests should always be confirmed by re-testing.

https://doi.org/10.1111/myc.13782

ANTIFUNGAL DRUG USAGE IN EUROPEAN NEONATAL UNITS:

A MULTICENTER WEEKLY POINT PREVALENCE STUDY

The Pediatric Infectious Disease Journal, 2024 June 25; Epub ahead of print

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BACKGROUND & AIM: For critically ill neonatal and paediatric patients, invasive fungal infections represent a major threat. Difficulties in diagnosis in this population and the high morbidity and mortality of invasive fungal infections can lead to increased or excessive antifungal prescribing in neonatal units, and antifungal stewardship programmes are warranted. However, there are limited data on antifungal prescribing patterns for neonatal patients, with published data restricted to single-centre or single-country studies or to 1-day recordings. The aim of this study was to assess longitudinal antifungal usage in neonatal units in Europe.

STUDY DESIGN: Prospective, weekly point-prevalence study.

ENDPOINTS: Antifungal indications, patient risk factors and antifungal regimens.

METHOD: The study was carried out in 18 hospitals across eight European countries during a 12-week period in 2020. The study population comprised all neonatal patients who received systemic antifungal treatment. At the start of the study, ward-specific data on antifungal practices were collected; during the study period, ward- and patient-specific data were collected weekly.

RESULTS: Of the 27 participating neonatal units, 15 (56%) implemented antifungal prophylaxis, with the majority of courses targeted to premature neonates with low (<1500 g) or very low (<1000 g) birthweight plus additional risk factors (e.g. mechanical ventilation). An antifungal stewardship policy was in place in 44% of the neonatal units. Antifungal drugs were given to 174 patients. The median weekly proportion of patients prescribed antifungals was 10.5% (range 6.9–12.6%). Prophylaxis was the indication for prescribing 135 of the 174 antifungal courses (78%), while 39 courses (22%) were prescribed as treatment (69% empirical, 10% pre-emptive, 21% targeted). The most frequently prescribed systemic agent was fluconazole, which was used both for prophylaxis (98.5% of courses) and treatment (38.5% of courses). The most common risk factors in neonates given prophylaxis were premature birth (88%), mechanical ventilation (81%) and central vascular catheterization (66%), whereas only 41% of courses were in patients with gestational age <28 weeks and only 36% were in patients with a birthweight <1000 g. Late-onset sepsis was the most common reason for empirical treatment (63%). All eight of the targeted antifungal courses were prescribed to treat invasive candidiasis.

CONCLUSIONS: In European neonatal units, antifungal usage appeared to be mainly driven by prophylaxis and empirical treatment. In both these settings, fluconazole was the most frequently prescribed antifungal agent.

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ASPERGILLOSIS COINFECTION IN PATIENTS WITH PROVEN MUCORMYCOSIS

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BACKGROUND & AIM: Mucormycosis and aspergillosis are particularly challenging to diagnose and manage because of their similar risk factors and clinical manifestations. Fungal cultures often have low sensitivity, while microscopic findings may be inconsistent, making it difficult to differentiate between them. Several studies have reported cases of mucormycosis and aspergillosis coinfection, and emphasised the importance of distinguishing between them to ensure optimal antifungal therapy. However, this has not yet been investigated systematically. The aim of the current study was therefore to assess aspergillosis coinfection in patients with proven mucormycosis.

STUDY DESIGN: Retrospective review of medical records.

ENDPOINT: Aspergillosis coinfection.

METHOD: The study included 67 adults with proven mucormycosis diagnosed at a tertiary hospital between 2007 and 2023, whose medical records were reviewed, and for whom formalin-fixed paraffin-embedded (FFPE) tissue sections were available for analysis. Proven mucormycosis was defined as the identification of mucormycosis-causing agents from sterile specimens and/or positive mucormycosis immunohistochemistry (IHC) findings. IHC was performed on the tissue sections, and the slides were examined by an experienced pathologist for the identification of aspergillosis coinfection. In addition, polymerase chain reaction (PCR) assays were performed to detect *Aspergillus*- and Mucorales-specific DNA.

RESULTS: Analysing fungal cultures from sterile and non-sterile sites identified *Aspergillus* species growth in nine patients (13%), from two sterile and seven non-sterile cultures. Fungal PCR analyses of the FFPE tissue sections identified Mucorales-specific results in 26 patients (39%), and *Aspergillus*-specific results in five patients (7%). Eight patients (12%) had both positive *Aspergillus*- and Mucorales-specific PCR results. Combining cultures and PCR results, a total of 21 out of 67 patients (31%) with proven mucormycosis had evidence of aspergillosis coinfection. The prevalence of positive blood or bronchoalveolar lavage fluid galactomannan results was higher in patients with coinfection than in those with mucormycosis only (67% versus 37%, p=0.024). There were no significant differences in 30-, 90- or 180-day mortality between the two groups

CONCLUSIONS: Molecular and/or microbiological evidence of aspergillosis coinfection was identified in almost a third of patients with proven mucormycosis. The use of multiple diagnostic methods is needed to identify patients with coinfections, to ensure optimal antifungal therapy.

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GLOBAL GUIDELINE FOR THE DIAGNOSIS AND MANAGEMENT OF CRYPTOCOCCOSIS:

AN INITIATIVE OF THE ECMM AND ISHAM IN COOPERATION WITH THE ASM

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BACKGROUND & AIM: Cryptococcosis is a disseminated invasive fungal infection associated with significant morbidity and mortality. It commonly affects the lungs and central nervous system (CNS), but disseminated disease can involve other organs while appearing to be localized. The disease is particularly common in low- and middle-income countries, including sub-Saharan Africa, where the main risk factor is HIV/AIDS. The most severe form is cryptococcal meningitis, which has a mortality rate of 24–47% at 10 weeks. This article presents a global guideline for the diagnosis and management of cryptococcosis.

ARTICLE TYPE: Clinical guideline.

FINDINGS: The choice and duration of antifungal treatment for cryptococcosis should depend on the specific clinical syndrome, which can be divided into CNS, disseminated disease, isolated pulmonary disease and direct skin inoculation. In high-income countries, the optimal induction therapy for cryptococcal meningitis, disseminated cryptococcosis and severe isolated pulmonary cryptococcosis is liposomal amphotericin B at a dose of 3–4 mg/kg per day plus flucytosine 25 mg/kg four times a day. In low-income settings (where antifungal access, adverse effects and monitoring present challenges), the optimal induction therapy for HIV-associated cryptococcal meningitis is a single dose of liposomal amphotericin B 10 mg/kg, plus 14 days of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg per day. However, there is no clinical trial evidence for this regimen in patients with non–HIV-associated cryptococcal meningitis or other non-CNS cryptococcosis syndromes. There have been no trials of consolidation or maintenance therapy in recent years, but fluconazole 400–800 mg per day for 8 weeks is recommended for consolidation, and fluconazole 200 mg per day for up to 12 months for maintenance.

It is important to provide the most effective antifungal therapy possible to optimize outcomes, and to monitor for and minimize potential toxic effects, in order to avoid having to stop treatment or switch to an inferior regimen unnecessarily. Clinical relapse should be expected and monitored for, so the cause can be properly investigated. Adherence to therapy and the development of drug–drug interactions should also be evaluated throughout treatment. Other recommendations include ensuring that raised intracranial pressure is managed by therapeutic lumbar puncture or surgical decompression as necessary, and investigating potential underlying immunodeficiencies (particularly HIV infection).

CONCLUSIONS: This global guideline provides recommendations on the management of cryptococcosis, but should be adapted to suit local practices.

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