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on systemic fungal infections

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Aspergillus tracheobronchitis in COVID-19 ARDS patients – a cohort study

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Journal of Clinical Microbiology, 2022 April 20; 60(4):e0229821

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RISK FACTORS FOR INTRA-ABDOMINAL CANDIDIASIS IN INTENSIVE CARE UNITS:

RESULTS FROM EUCANDICU STUDY

Infectious Diseases and Therapy, 2022 April; 11(2):827–40

AUTHORS: BASSETTI M, VENA A, GIACOBBE DR, ET AL.; FOR THE STUDY GROUP FOR INFECTIONS IN CRITICALLY ILL PATIENTS (ESGCIP) OF THE EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES (ESCMID)
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BACKGROUND & AIM: Intra-abdominal infections in patients in intensive-care units (ICUs) are associated with high mortality, and up to one third are thought to be caused by *Candida* species. The aim of this study was to identify risk factors for ICU-acquired intra-abdominal candidiasis (IAC).

STUDY DESIGN: Retrospective, multinational, case–control study.

ENDPOINT: Risk factors for IAC starting >48 hours after ICU admission.

METHOD: The study enrolled adults admitted to one of 26 ICUs across 10 European countries in 2015–2016 who developed microbiologically-documented IAC at least 48 hours after ICU admission. Data on potential risk factors were extracted from patient records, starting 30 days before ICU admission. *Candida* infections detected by histology or culture were typed and tested for antifungal susceptibility. Cases were matched 1:1 with control patients admitted to the same ICU for more than 48 hours who tested negative for IAC and were not receiving antifungal prophylaxis. Significant risk factors were identified using a multivariable, conditional logistic regression model.

RESULTS: Among the 101 IAC cases studied the most common *Candida* isolates were *C. albicans* (58.4%), *C. glabrata* (15.8%) and *C. tropicalis* (4%), with more than one species found in 16.8% of patients. Of 64 isolates tested, 17 (26.5%) were resistant to fluconazole. In univariate analyses, IAC cases were associated with severe hepatic failure (p=0.03), prior bacterial infection (p=0.001), prior antibiotic treatment for ≥7 days (p=0.0001), parenteral nutrition (p=0.03), higher median number of abdominal surgical interventions (p=0.04), presence of an abdominal drain (p=0.005), anastomotic leakage (p=0.007), recurrent gastrointestinal perforation (p=0.002), and prior treatment with antifungal drugs for ≥7 days (p=0.02). Those factors that remained significant in the multivariable model are shown in the table; gastrointestinal perforations, anastomotic leakage and an abdominal drain were the most strongly predictive of IAC.

CONCLUSIONS: ICU patients with gastrointestinal perforations, anastomotic leakage, an abdominal drain and prior antimicrobial therapy may be most at risk of developing IAC and might benefit from enhanced surveillance or prophylactic treatment.

Independent predictors of intra-abdominal candidiasis in patients admitted to the intensive care unit

Factor	Odds ratio (95% confidence interval)	p
Antibiotic treatment for ≥7 days	3.78 (1.32–10.52)	0.01
Antifungal treatment for ≥7 days	4.26 (1.04–17.46)	0.04
Abdominal drain	6.58 (1.73–25.06)	0.006
Anastomotic leakage	6.61 (1.98–21.99)	0.002
Recurrent gastrointestinal perforation	13.90 (2.65–72.82)	0.002

https://doi.org/10.1007/s40121-021-00585-6

COMPARISON OF MOLD ACTIVE TRIAZOLES AS PRIMARY ANTIFUNGAL PROPHYLAXIS IN PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA IN THE ERA OF MOLECULARLY TARGETED THERAPIES

Clinical Infectious Diseases, 2022 March 23; Epub ahead of print

AUTHORS: Rausch CR, DiPippo AJ, Jiang Y, DiNardo CD, Kadia T, Maiti A, Montalban-Bravo G, Ravandi F, Kontoyiannis DP
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BACKGROUND & AIM: Patients with acute myeloid leukaemia (AML) and high-risk myelodysplastic syndrome (HR-MDS) frequently experience neutropenia when undergoing remission induction chemotherapy. This puts them at increased risk of invasive fungal infections (IFIs), which is mitigated by primary antifungal prophylaxis (PAP) with a triazole antifungal or an echinocandin. The recent incorporation of targeted leukaemia therapies into the treatment regimens of patients with AML means that the rates and risk factors for breakthrough IFI (bIFI) with agents used for concomitant PAP need to be re-evaluated. This study compared the efficacy and safety of various PAP agents for bIFI prevention in patients with AML or HR-MDS undergoing remission induction chemotherapy.

STUDY DESIGN: Retrospective cohort study.

ENDPOINTS: Incidence of bIFI.

METHOD: The study included 277 adults with newly diagnosed AML or HR-MDS. All were undergoing remission induction chemotherapy with a high-intensity regimen or a low-intensity venetoclax-containing regimen, and received concomitant PAP with posaconazole, voriconazole or isavuconazole for ≥5 days. Prior, but not concomitant, echinocandin use was allowed. IFIs were considered to be bIFI if they occurred after ≥5 days of continuous azole administration or within 14 days of discontinuation.

RESULTS: Overall, 161 (58%) participants received an echinocandin prior to commencing triazole therapy. Eleven (4%) patients developed proven or probable bIFI. Stratifying by triazole type, the bIFI incidence was 2.9% with posaconazole, 4.8% with voriconazole, and 5.7% with isavuconazole (p=0.55). The incidence of bIFI was unaffected by prior echinocandin exposure or by the intensity of the chemotherapy regimen. Absolute neutrophil count recovery to >1000 cells/μL was achieved by 64% of participants with bIFI versus 91% of those without bIFI (p=0.021), and complete remission rates were 18% in participants with bIFI versus 66% in those without bIFI (p=0.002). Overall, 38 (14%) patients discontinued PAP because of toxicity; this was primarily due to hepatotoxicity (13%, 15%, and 13% of patients receiving posaconazole, voriconazole and isavuconazole, respectively).

CONCLUSIONS: The rate of bIFI was low among patients with newly diagnosed AML or HR-MDS undergoing remission induction chemotherapy and receiving concomitant azole-based PAP. Rates of complete remission and recovery of absolute neutrophil count were significantly lower in patients with versus without bIFI.

https://doi.org/10.1093/cid/ciac230

DEFINING COVID-19 ASSOCIATED PULMONARY ASPERGILLOSIS:

SYSTEMATIC REVIEW AND META-ANALYSIS

Clinical Microbiology and Infection, 2022 February 10; Epub ahead of print

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BACKGROUND & AIM: Severe COVID-19 is associated with high morbidity and mortality. Aspergillosis, which has been reported to occur in up to a third of critically ill COVID-19 patients, is a complication that contributes to increased mortality. The lack of a validated definition of COVID-19–associated pulmonary aspergillosis (CAPA) may result in missed or misidentified cases, which can delay appropriate antifungal therapy and contribute to poor outcomes. The aim of this study was to evaluate the prevalence of CAPA and to compare the use of various research definitions of CAPA.

STUDY DESIGN: Systematic review and meta-analysis.

ENDPOINTS: Prevalence of CAPA; concordance between CAPA definitions; outcomes.

METHOD: A search of the PubMed, Embase, Web of Science and MedRxiv databases up to October 2021 identified 45 cohort studies and six case series (reporting on ≥3 patients) that involved adult ICU patients with COVID-19 who were evaluated for pulmonary aspergillosis. Where patient-level data were available (31 studies; *n*=277), patients were reclassified using four research definitions of CAPA.

RESULTS: Among 3297 COVID-19 patients in cohort studies, 313 were diagnosed with CAPA, giving a pooled as-reported CAPA prevalence of 10% (95% confidence interval 8–13%). The pooled prevalence was similar when including only those cohort studies with patient-level data (10%, 95% CI 7–14%). Among the 277 patients with patient-level data, the CAPA definitions of Verweij et al., White et al., Koehler et al. and Bassetti et al. were met by 53.1%, 45.1%, 64.6% and 17.7% of patients, respectively, and the prevalence of CAPA based on these definitions was 4% (95% CI 2–7%), 4% (95% CI 2–6%), 4% (95% CI 2–6%) and 1% (95% CI 0–2%), respectively. Ninety-four patients (33.9%) did not meet the criteria for any of the research definitions of CAPA. The definitions of Koehler et al. and Verweij et al. had a high level of concordance (ρ=0.893, p<0.001), whereas agreement between other definitions was modest (ρ=0.263–0.447, p<0.001). Bronchoscopy was performed in 127 (45.8%) CAPA patients, only four (3.1%) of whom had tracheobronchial abnormalities. Radiographic findings associated with aspergillosis were found in 41 (19.7%) patients. The mortality rate among patients with CAPA was 59.2%. Application of the research definitions of CAPA did not strengthen the association between treatment with mould-active antifungals and survival.

CONCLUSION: The prevalence of CAPA in ICU patients reported in the literature may be overestimated due to the use of non-standard definitions.

https://doi.org/10.1016/j.cmi.2022.01.027

ASPERGILLUS TRACHEOBRONCHITIS IN COVID-19 ARDS PATIENTS – A COHORT STUDY

European Respiratory Journal, 2022 May 5; 59(5):2103142

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BACKGROUND & AIM: Patients with acute respiratory distress syndrome due to COVID-19 are treated with immune modulators, making them susceptible to fungal infections including *Aspergillus* tracheobronchitis (ATB), a sub-entity of COVID-19–associated pulmonary aspergillosis (CAPA). Bronchoscopic findings in ATB include ulcerations, pseudomembranes, plaques, eschars and tracheal stenosis. However, bronchoscopy is not performed routinely in COVID-19 patients because of the risk of SARS-CoV-2 transmission, and samples obtained from tracheal aspirates or non-bronchoscopic lavage have reduced diagnostic quality, making a definitive diagnosis of ATB difficult. This study investigated ATB in a cohort of patients with CAPA managed at a centre that used a stepped CAPA screening strategy.

STUDY DESIGN: Retrospective cohort study.

ENDPOINTS: Characteristics and outcomes of ATB.

METHOD: The study included 69 patients with COVID-19 admitted to the intensive-care unit (ICU) of a single hospital between March 2020 and February 2021. Screening for CAPA included analysis of tracheal aspirates using *Aspergillus*-polymerase chain reaction (PCR), galactomannan and culture combined with serum galactomannan. Bronchoscopy and bronchoalveolar lavage (BAL) were performed in patients with a positive result.

RESULTS: The most common COVID-19 treatment approaches were dexamethasone (*n*=39) and remdesivir (*n*=13), and almost all patients (*n*=66) received antibiotics. Seventeen patients had CAPA, all of whom underwent bronchoscopy, compared with 40/52 (76.9%) of those without CAPA. Eight (47.1%) CAPA patients had a clinical diagnosis of ATB, and this group had a shorter ICU stay than non-ATB CAPA patients (median 14.5 versus 21 days) and a higher 30-day mortality (5/8 patients, 62.5% versus 2/9 patients, 22.2%). Tracheal plaques were reported in all eight (100%) ATB patients, and pseudomembranes, thrombi and a vulnerable or bloody trachea in 87.5%, 50% and 87.5%, respectively. Seven (87.5%) cultures and eight (100%) PCR tests from ATB patients were positive for *Aspergillus*, while only half of the non-ATB patients had positive culture or PCR results. Only one ATB and two non-ATB patients tested positive for serum galactomannan, while six (75%) ATB patients had a positive BAL galactomannan.

CONCLUSIONS: Airways examination is important for the diagnosis of ATB. Patients with ATB have increased mortality, indicating the importance of early identification and treatment. A predefined diagnostic strategy, including indications for bronchoscopy, can help identify ATB in critically ill COVID-19 patients.

https://doi.org/10.1183/13993003.03142-2021

PROGNOSTIC IMPACT OF BRONCHOALVEOLAR LAVAGE FLUID GALACTOMANNAN AND *ASPERGILLUS* CULTURE RESULTS ON SURVIVAL IN COVID-19 INTENSIVE CARE UNIT PATIENTS:

A POST HOC ANALYSIS FROM THE EUROPEAN CONFEDERATION OF MEDICAL MYCOLOGY (ECMM) COVID-19-ASSOCIATED PULMONARY ASPERGILLOSIS STUDY

Journal of Clinical Microbiology, 2022 April 20; 60(4):e0229821

AUTHORS: GIACOBBE DR, PRATTES J, WAUTERS J, DETTORI S, SIGNORI A, SALMANTON-GARCÍA J, MAERTENS J, BOURGEOIS M, REYNDERS M, RUTSAERT L, VAN REGENMORTEL N, LORMANS P, FEYS S, KLIMKO N, SHADRIVOVA O, CORNELY OA, RAUTEMAA-RICHARDSON R, KOEHLER P, LAGROU K, BASSETTI M, HOENIGL M; FOR THE ECMM-CAPA STUDY GROUP

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BACKGROUND & AIM: Patients who are critically ill with COVID-19 can develop COVID-19–associated pulmonary aspergillosis (CAPA), which can increase the risk of mortality. Patients with CAPA who are positive for serum galactomannan (GM) have unfavourable outcomes; however, serum GM-positivity is only observed in a minority of patients, owing to the airway invasive nature of the disease. The aim of this analysis was to determine whether bronchoalveolar lavage fluid (BALF) GM-positivity and/or BALF *Aspergillus* culture can predict outcomes in patients with CAPA who are GM serum-negative.

STUDY DESIGN: Post hoc analysis of a multinational observational study.

ENDPOINT: The primary endpoint was 90-day mortality.

METHOD: The analysis involved a subset of 218 critically ill patients with COVID-19 from an observational study conducted across 20 hospitals worldwide. The subset had both BALF GM and BALF *Aspergillus* culture test results available, and all were GM serum-negative. The differential ability of positive BALF GM (optical density index ≥1.0), positive BALF *Aspergillus* culture, or both, to predict mortality was evaluated using multivariable analysis.

RESULTS: Overall, 56 (26%) of the 218 patients were diagnosed with CAPA (51 probable and 5 proven cases). After data adjustment for between-centre heterogeneity, the final multivariable model demonstrated that a combination of positive BALF GM and positive BALF *Aspergillus* culture was independently associated with 90-day mortality when compared with both tests being negative (table). The same model found that increasing age and active malignant disease were also independent predictors of 90-day mortality (table).

CONCLUSION: Among critically ill patients with COVID-19, the combination of positive BALF GM and positive BALF *Aspergillus* culture was independently associated with 90-day mortality.

Multivariable analysis of factors associated with 90-day mortality in patients with COVID-19–associated pulmonary aspergillosis who were galactomannan serum-negative

Factor	Hazard ratio (95% confidence interval)	*p*
BALF mycology test results		
BALF GM – / BALF culture –	Referent	–
BALF GM + / BALF culture –	1.30 (0.62–2.70)	0.49
BALF GM – / BALF culture +	1.53 (0.42–5.54	0.52
BALF GM + / BALF culture +	2.53 (1.28–5.02)	0.008
Age (per 5 years)	1.27 (1.14–1.40)	<0.001
Active malignant disease	2.02 (1.11–3.68)	0.021

BALF=bronchoalveolar lavage fluid; GM=galactomannan.

https://doi.org/10.1128/jcm.02298-21

PERFORMANCE OF THE EUROIMMUN *ASPERGILLUS* ANTIGEN ELISA FOR THE DIAGNOSIS OF INVASIVE PULMONARY ASPERGILLOSIS IN BRONCHOALVEOLAR LAVAGE FLUID

Journal of Clinical Microbiology, 2022 April 20; 60(4):e0021522

AUTHORS: Egger M, Penziner S, Dichtl K, Gornicec M, Kriegl L, Krause R, Khong E, Mehta S, Vargas M, Gianella S, Porrachia M, Jenks JD, Venkataraman I, Hoenigl M
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BACKGROUND & AIM: Diagnosis of invasive pulmonary aspergillosis (IPA) by testing bronchoalveolar lavage fluid (BALF) is commonly performed using galactomannan (GM) antigen enzyme-linked immunoassay (ELISA). However, this test is not always available, has lower sensitivity in patients receiving antifungal prophylaxis and may give positive results with other fungal pathogens. A novel assay that detects galactomannoprotein (GP ELISA) has been validated for use in serum samples. The current study compared GP ELISA with GM ELISA for the detection of *Aspergillus* antigen in BALF samples.

STUDY DESIGN: Laboratory study.

ENDPOINTS: Sensitivity and specificity of each test and between-test correlation indices.

METHOD: The study used 115 frozen samples of BALF from patients with suspected IPA, which had undergone testing with GM ELISA at a single US centre between 2015 and 2019. IPA was classified using EORTC/MSG criteria. These samples were re-analysed using GP ELISA by operators blinded to the original IPA classification and GM ELISA results. Receiver operating characteristic (ROC) curves were constructed for proven/probable/putative IPA versus no IPA. Between-test correlations were calculated using Spearman's rho and Cohen's kappa statistics.

RESULTS: The patients were originally classified as 43 proven/probable IPA, 15 putative IPA, 10 possible IPA and 47 no-IPA cases. Only 16 samples yielded positive *Aspergillus* cultures. After excluding possible IPA cases, the GP ELISA had a sensitivity of 74% and specificity of 96% for distinguishing proven/probable/putative IPA from no-IPA using the recommended cut-off of 25 pg/mL, compared with GM ELISA sensitivity and specificity of 90% and 96% respectively, at the recommended cut-off of ODI 1.0. However, ROC analysis showed that the greatest discriminatory power of the GP ELISA was achieved at a cut-off of 12 pg/mL. Using this revised cut-off, GP ELISA sensitivity and specificity were 90% and 96% respectively, identical to that of GM ELISA testing. Spearman's rho showed strong correlation between the two tests (ρ=0.809, p<0.0001), as did Cohen's kappa (κ=0.715, p<0.001). In 12 of the 115 patients BALF samples had been obtained during antifungal prophylaxis and in these cases the sensitivities of the GP and GM ELISA tests were 75% and 100% respectively, using the optimized cut-off value for the GP ELISA.

CONCLUSION: The performance of the GP ELISA was similar to that of GM ELISA for detecting IPA when testing BALF using a GP cut-off of 12 pg/mL.

https://doi.org/10.1128/jcm.00215-22

THE IMPACT OF THE UPDATED EORTC/MSG CRITERIA ON THE CLASSIFICATION OF HEMATOLOGICAL PATIENTS WITH SUSPECTED INVASIVE PULMONARY ASPERGILLOSIS

Clinical Microbiology and Infection, 2022 March 3; Epub ahead of print

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BACKGROUND & AIM: The EORTC/MSG criteria classify invasive pulmonary aspergillosis (IPA) as possible, probable or proven disease, based on host factors and clinical and mycological characteristics. They were revised in 2019 with the addition of new criteria, including several new host factors (haematological malignancy, solid-organ transplant, treatment with B-cell immunosuppressants, and acute graft-versus-host disease), a new clinical CT sign, and a new mycological criterium (positive *Aspergillus* polymerase chain reaction, PCR, test). The aim of this study was to assess the impact of the new EORTC criteria on the classification of patients with IPA.

STUDY DESIGN: Retrospective cohort study.

ENDPOINTS: IPA classification; 12-week all-cause mortality.

METHOD: The study included 282 patients with a haematological malignancy who underwent bronchoalveolar lavage (BAL) for suspected IPA between 2014 and 2019. Routine fungal culture was performed on samples from all participants, and galactomannan and/or *Aspergillus* PCR was performed at the discretion of the clinician. Comprehensive clinical data were retrospectively collected from all patients, who were then reclassified using the new 2019 EORTC criteria. The optimal cut-off for a positive PCR test was defined using receiver operating characteristic curve analysis, while the association between diagnostic criteria and mortality was analysed using log rank and Cox regression analyses.

RESULTS: There were 323 episodes of suspected IPA among the cohort, of which 73 (22.6%) were reclassified using the new 2019 EORTC criteria (table). The proportion of episodes classified as probable IPA increased from 19.8% (64/323) to 30.9% (100/323), and most of these changes (31/36, 86.1%) were due to the addition of a positive PCR. There was no difference in mortality between cases defined as possible and those defined as probable IPA using the 2019 criteria, but mortality was higher in probable cases that had lower versus higher PCR cycle threshold values (p=0.004). The optimal PCR cycle threshold cut-off was 36.8, with a sensitivity of 75% and specificity of 61.7% for 12-week mortality.

CONCLUSION: The new EORTC criteria led to 11.1% more episodes being classified as probable IPA, mostly due to the addition of a positive *Aspergillus* PCR.

Reclassification of 73 episodes of suspected invasive pulmonary aspergillosis (IPA) according to the 2019 EORTC/MSG criteria

	Number (%) of patients reclassified
Reclassified from possible to probable IPA	31/73 (42.5%)
Reclassified from EORTC criteria not met to probable IPA	5/73 (6.8%)
Reclassified from EORTC criteria not met to possible IPA	37/73 (50.7%)

https://doi.org/10.1016/j.cmi.2022.02.026

DEFINITION, DIAGNOSIS, AND MANAGEMENT OF COVID-19-ASSOCIATED PULMONARY MUCORMYCOSIS:

DELPHI CONSENSUS STATEMENT FROM THE FUNGAL INFECTION STUDY FORUM AND ACADEMY OF PULMONARY SCIENCES, INDIA

The Lancet Infectious Diseases, 2022 April 4; Epub ahead of print

AUTHORS: Muthu V, Agarwal R, Patel A, et al.
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BACKGROUND & AIM: COVID-19–associated pulmonary mucormycosis (CAPM) is a rare complication of COVID-19 which remains underdiagnosed and under-reported. Currently, there is no clear guidance on the diagnosis and treatment of CAPM. Therefore, an expert panel formulated a consensus statement on the diagnosis and management of CAPM using a modified Delphi method.

ARTICLE TYPE: Consensus recommendations.

FINDINGS: Twenty-six experts from various disciplines involved in the management of CAPM participated in three rounds of the Delphi process to reach a consensus of ≥70% agreement or disagreement on each draft statement. A consensus was achieved for 84 of the 89 statements.

CAPM was defined as pulmonary mucormycosis occurring within 3 months of COVID-19 diagnosis. It can be classified as proven, probable or possible. Major risk factors include uncontrolled diabetes and inappropriate or excessive glucocorticoid therapy. Although no clinical features are specific to CAPM, the presence of brownish or black sputum and haemoptysis in COVID-19 patients should trigger investigations.

Initial evaluation should include chest CT scans using intravenous contrast and conventional microbiological testing of lower respiratory tract samples. Highly suggestive imaging findings include a reversed halo sign, thick-walled cavity, bird's nest sign, mycotic aneurysm, large consolidation or necrotising pneumonia, and multiple large nodules (>1 cm). Flexible bronchoscopy is recommended to enable early diagnosis, and CT-guided transthoracic trucut core-needle biopsy can be used in patients with peripheral chest lesions.

Judicious use of glucocorticoids and other immunosuppressants for COVID-19 and maintenance of optimal glycaemic control are important steps in the prevention of CAPM. Antifungal prophylaxis is not recommended.

Surgery within 1–2 weeks of diagnosis is recommended in patients with potentially resectable lung disease, with evaluation by a multidisciplinary team beforehand. Liposomal amphotericin B 5 mg/kg/day is recommended as primary medical therapy, with the duration based on response assessment after 4–6 weeks using clinical and imaging parameters. Maintenance treatment with posaconazole or isavuconazole should be initiated on achievement of complete or partial response, although no consensus on duration of treatment was reached. Salvage therapy with posaconazole or isavuconazole for a longer duration can be considered in refractory cases.

CONCLUSION: These consensus recommendations provide guidance for defining, diagnosing and managing CAPM, although more extensive research into the disease is needed.

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TACKLING THE EMERGING THREAT OF ANTIFUNGAL RESISTANCE TO HUMAN HEALTH

Nature Reviews Microbiology, 2022 March 29; Epub ahead of print

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BACKGROUND & AIM: Resistance to antifungal drugs is a growing problem worldwide, with the emergence of resistant variants of previously susceptible organisms, and new species that are resistant to multiple drugs. Antifungal resistance can develop via genetic changes to the target binding site, overexpression of the amount of target available, or alterations in the effective drug concentration due to changes in efflux activity or inhibition of prodrug activation. This article reviews priority areas and key research needed to address antifungal resistance.

ARTICLE TYPE: Review.

FINDINGS: The Joint Programming Initiative on Antimicrobial Resistance has developed a comprehensive One Health framework covering six priority areas for addressing antifungal resistance: environment, transmission, surveillance, diagnostics, therapeutics and potential interventions.

Many opportunistic pathogenic fungi are found in the environment. The widespread use of broad-spectrum agricultural fungicides has led to resistance in crop pathogens and other environmental fungi that are potential pathogens in humans. Adaptation to fungicides in the environment may also lead to other phenotypic changes, with one potential example being azole resistance driving the adaptation of *Aspergillus fumigatus* to infection-related stress and virulence.

The identification of antifungal resistance is based on susceptibility testing, but the gold-standard methods are labour-intensive and time-consuming, and many clinicians may not have access to clinically calibrated antifungal susceptibility testing. Molecular diagnostic approaches allow the identification of genetic markers associated with antifungal resistance, but these are currently underutilized and their range needs to be expanded. Another challenge is the limitless range of potential new pathogens and variants of familiar organisms that continue to adapt when exposed to antifungals. With respect to antifungal therapy, antifungal stewardship programmes and therapeutic drug monitoring can help minimize the development of resistance.

Priorities for optimizing the surveillance of antifungal resistance include developing tools for use in low- and middle-income countries, increasing the availability of resistance screening techniques for local laboratories, appointing National Reference Laboratories, performing fundamental research on mechanisms of resistance, developing genomic antifungal resistance databases, and implementing antifungal resistance surveillance networks nationally and internationally.

CONCLUSIONS: Various factors hinder clinicians' ability to manage antifungal resistance. Global strategies are needed to control the use of existing antifungals, and to develop new therapies.

https://doi.org/10.1038/s41579-022-00720-1

SCREENING FOR OCULAR CANDIDIASIS AMONG PATIENTS WITH CANDIDEMIA:

IS IT TIME TO CHANGE PRACTICE?

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BACKGROUND & AIM: Approximately 10% of patients with candidaemia develop ocular candidiasis (OC), which can cause severe morbidity. There are conflicting recommendations regarding screening for OC, with the Infectious Diseases Society of America endorsing retinal screening for all patients with candidaemia, while the American Academy of Ophthalmology (AAO) recommends screening only those with signs or symptoms suggesting ocular infection, stating that visual outcome data supporting routine screening are lacking, endophthalmitis is now rare in candidaemia studies, and treatments carry potential complications. The authors addressed these controversies and offered opinions regarding screening candidaemia patients for OC.

ARTICLE TYPE: Review.

FINDINGS: OC encompasses chorioretinitis and endophthalmitis, with the latter potentially resulting in retinal necrosis and detachment and permanent visual impairment. Screening for OC meets the general criteria for effective routine screening for several reasons: the disease is sufficiently common and carries significant morbidity; the test is safe and accurate when performed by experienced practitioners, with an acceptable cost (typically $200–$500 per in-hospital exam); effective treatment is available; and positive screening results may change management, including treatment duration, choice of agents and need for invasive procedures.

However, there is no conclusive evidence that outcomes are improved by routine screening, there are no definitive cost–benefit data, and the AAO states that 2-week antifungal treatment for uncomplicated candidaemia is probably as effective as 4–6 weeks of therapy for resolving chorioretinitis, preventing progression to endophthalmitis, and curing established asymptomatic endophthalmitis. Complications from treatment are uncommon, with azoles being very well-tolerated and complications from intravitreal antifungal therapy and vitrectomy being unusual (1-year severe complication rates following vitrectomy are <1–5%).

Overall, in the absence of reliable prediction tools to identify candidaemia patients most likely to benefit from ophthalmological examination, it seems prudent to continue routine fundoscopic screening of all candidaemia patients. One issue that needs addressing is the difficulty in obtaining ophthalmological consultations for inpatients in many hospitals. Strategies such as bedside ocular photography and tele-ophthalmology could be used for asymptomatic candidaemic patients, with bedside ophthalmological consultations reserved for those with visual symptoms or ocular findings.

CONCLUSIONS: There is a case for continuing routine screening for OC in all candidaemia patients. Studies are needed to examine potential roles for funduscopic photography and tele-ophthalmology in asymptomatic patients.

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SINGLE-DOSE LIPOSOMAL AMPHOTERICIN B TREATMENT FOR CRYPTOCOCCAL MENINGITIS

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BACKGROUND & AIM: Cryptococcal meningitis is the primary cause of adult meningitis in regions with a high prevalence of HIV and the second most frequent cause of HIV-related death globally, with most deaths occurring in sub-Saharan Africa. Poor outcomes are achieved with conventional antifungal treatments, and standard 2-week amphotericin B deoxycholate-based regimens are associated with considerable toxicity. In a phase 2 trial, a regimen based on a single high dose of liposomal amphotericin B was effective. The aim of this study was to investigate the efficacy and safety of this regimen in a phase 3 trial.

STUDY DESIGN: Phase 3, open-label, randomized, controlled, non-inferiority clinical trial.

ENDPOINTS: All-cause mortality at 10 weeks (primary endpoint); all-cause mortality at 2, 4 and 16 weeks; fungal clearance from cerebrospinal fluid; adverse events.

METHOD: HIV-positive adults with cryptococcal meningitis from five African countries were randomized to receive either a single dose of liposomal amphotericin B 10 mg/kg on day 1 plus 14 days of flucytosine 100 mg/kg/day and fluconazole 1200 mg/day (n=407) or the current WHO-recommended regimen comprising amphotericin B deoxycholate 1 mg/kg/day plus flucytosine 100 mg/kg/day for 7 days, followed by fluconazole 1200 mg/day for 7 days (n=407). The non-inferiority margin was set at 10 percentage points.

RESULTS: At week 10, the rate of all-cause mortality was 24.8% (95% confidence interval 20.7–29.3%) in the liposomal amphotericin B group and 28.7% (95% CI 24.4–33.4%) in the control group. The absolute between-group difference was –3.9 percentage points, and the upper boundary of the one-sided 95% CI was 1.2 percentage points which was within the non-inferiority margin (p<0.001 for non-inferiority). Results for all-cause mortality at 2, 4 and 16 weeks were consistent with the primary-endpoint analysis, with upper boundaries of one-sided 95% CIs of <10 percentage points. The mean rate of fungal clearance from cerebrospinal fluid over 14 days was –0.40 and –0.42 $\log_{10}$ colony-forming units/mL/day in the liposomal amphotericin B and control groups, respectively. Grade 3/4 adverse events occurred in 50.0% and 62.3% of patients in the liposomal amphotericin B and control groups, respectively (p<0.001), and potentially life-threatening (grade 4) adverse events occurred in 21.7% and 30.1%, respectively (p=0.005).

CONCLUSIONS: In patients with HIV-associated cryptococcal meningitis, the efficacy of single-dose liposomal amphotericin B in combination with flucytosine and fluconazole was non-inferior to that of the standard WHO-recommended regimen and was associated with a lower rate of serious adverse events.

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ANTIFUNGAL PROPHYLAXIS IN ADULT LUNG TRANSPLANT RECIPIENTS:

UNCERTAINTY DESPITE 30 YEARS OF EXPERIENCE. A SYSTEMATIC REVIEW OF THE LITERATURE AND NETWORK META-ANALYSIS

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BACKGROUND & AIM: Invasive fungal infections (IFIs) such as invasive aspergillosis (IA) are an important cause of morbidity and mortality in patients who undergo lung transplantation. Universal antifungal prophylaxis is widely used following lung transplantation, but the optimal prophylaxis strategy has not yet been determined. The reported incidence of IFIs under various universal prophylaxis regimens ranges from 3.8% to 14%. The aim of this analysis was to determine which antifungal agent is most effective at preventing IA/IFI when used as universal antifungal prophylaxis in the adult lung-transplant setting.

STUDY DESIGN: Systematic literature review and exploratory network meta-analysis.

ENDPOINT: Efficacy ranking for prevention of IA/IFI after lung transplantation.

METHOD: A search of MEDLINE, Embase, Web of Science and Cochrane library databases up to September 2020 identified 13 studies that evaluated antifungal agents used for universal antifungal prophylaxis in adult lung-transplant recipients. A network meta-analysis was conducted using a frequentist framework to compare the effect of antifungal agents on the incidence of IFI/IA in the setting of universal prophylaxis or no prophylaxis following lung transplantation. Survival under the cumulative ranking curve analysis (SUCRA) was used to determine which strategy was most likely to be efficacious. The certainty of the published evidence was assessed using the GRADE framework.

RESULTS: The studies collectively included 1515 lung-transplant recipients and covered 12 different prophylaxis strategies/antifungal combinations. The greatest number of direct comparisons were between different inhaled amphotericin formulations. The top three ranked treatments were inhaled liposomal amphotericin B, inhaled amphotericin deoxycholate, and itraconazole plus inhaled amphotericin B, with SUCRA values of 74.9%, 52.1% and 24.0%, respectively, and scores of 1, 0.8 and 0.7, respectively. Isavuconazole ranked highest among azole antifungals used as single agents, while itraconazole ranked lowest. The certainty of the published evidence was very low.

CONCLUSIONS: This exploratory analysis identified inhaled liposomal amphotericin B as most likely to be effective at preventing IA/IFI after lung transplantation, while isavuconazole was the most effective oral drug. This information should inform future randomized controlled trials on this topic.

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