

# EHA Endorsement of the Global Guideline for the Diagnosis and Management of Rare Yeast Infections: An Initiative of the European Confederation of Medical Mycology in Cooperation With the International Society for Human and Animal Mycology and American Society for Microbiology

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The European Hematology Association (EHA) Guidelines Committee agreed to review the joint global guideline for the diagnosis and management of rare yeast infections of the European Confederation of Medical Mycology (ECMM) in cooperation with the International Society for Human and Animal Mycology (ISHAM) and the American Society for Microbiology (ASM).<sup>1</sup> External independent referees were nominated and revised the guideline according to a standardized reviewing process; subsequently EHA decided to endorse this guideline into its growing guideline portfolio. Earlier this year, the ECMM-ISHAM-ASM guideline on rare mold infections had already been endorsed by EHA.<sup>2</sup>

Patient numbers among populations at risk for invasive yeast infections are increasing in the clinical routine, such as patients treated on the intensive care unit, those with hematological malignancies or other immunosuppressed and seriously ill patients. Infections due to *Candida* spp. or cryptococcosis have been observed for a long time in this population. However, a growing number of infections due to other emerging yeast species have been described ultimately while to date, their epidemiology remains not well-studied, as with any orphan disease. To make matters worse, management of these diseases poses significant challenges to physicians and morbidity and mortality

remains a burden for patients and healthcare systems worldwide. Hence, the necessity to guide microbiologists and clinicians through diagnosis and management of these infections was given.

Clinical guidance on infections due to yeast species other than *Candida* spp. was limited and partially outdated. Furthermore, some pathogenic yeasts were not included at all.<sup>3,4</sup> The ECMM-ISHAM-ASM guideline was developed by medical professionals from 24 countries analyzing the available evidence body and involving personal expertise in the field. It displays a multidisciplinary, resource-overstretching approach that has been developed within the ECMM global guideline initiative for all fungal entities.<sup>5,6</sup> The considered pathogens included the genera *Geotrichum*, *Saprochaete/Magnusiomyces*, and *Trichosporon* species as well as *Kodamaea*, *Malassezia*, *Pseudozyma (Moesziomyces/Dirkmeia)*, *Rhodotorula*, *Saccharomyces*, and *Sporobolomyces* species.<sup>1</sup> Detailed recommendations to diagnose these infections including imaging, histopathology, and microbiological techniques as well as antifungal susceptibility testing were given. For treatment, the optimal antifungal therapy was discussed, but also removal of indwelling catheters and surgical approaches, for example, in the case of fungal endocarditis were included. Most of the recommendations are based on scarce evidence or are consensus statements and therefore recommended with moderate to marginal strength. Furthermore, the guideline addressed the issue of recent changes of nomenclature among yeast species, a confounding aspect for clinicians not dealing with these pathogens on an everyday basis. Differences in local epidemiology were also discussed since limited availability of diagnostic tools as well as lacking awareness may hamper the understanding of the true epidemiology of rare yeast infections.

The endorsement by the EHA Guidelines Committee underlines the particular importance of fungal infections in patients with hematological malignancies and those undergoing hematopoietic stem cell transplantation.<sup>7,8</sup> Despite low absolute patient numbers affected by systemic rare yeast infections, the hematological population is at highest risk for mortality and most often affected by severe disseminated disease. For example, geotrichosis affects mostly hematological patients leading to bloodstream or pulmonary infection with a mortality of up to

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65%.<sup>9</sup> Infections due to *Saprochaete/Magnusiomyces* spp. cause fungemia and subsequently disseminated disease.<sup>8</sup> Echinocandin monotherapy is contra-intuitively often associated with a worse outcome and treatment regimens including amphotericin b formulations in combination with flucytosine may be required. In trichosporonosis, hematology patients present most frequently with fungemia and/or metastatic skin lesions or pneumonia and hepatosplenic abscesses with voriconazole being the antifungal agent of first choice.<sup>10</sup>

Diagnosis requires first a clinical suspicion and knowledge about risk factors and epidemiology, then a full set of adequate diagnostic mycological methods and ultimately a fast and targeted treatment approach underlining the multiple challenges for treating physicians. This knowledge gap may be closed by the ECMM-ISHAM-ASM guideline on rare yeasts and subsequently improve patient prognosis.<sup>1</sup> Growing resistance due to widespread use of antifungals, for example, in agriculture and improved prophylactic regimens for invasive fungal infections in at-risk populations may lead to a selection of rare and resistant yeast strains as causative agents in the future.<sup>11</sup>

The ECMM-ISHAM-ASM guideline on rare yeast infections certainly has the intrinsic limitations that recommendations are mostly consensus-based and retrieved evidence is from retrospective data or case studies, an obvious obstacle for all orphan diseases. Due to the general low incidence and heterogeneity of emerging yeast infections, high quality evidence from prospective clinical trials is lacking. Therefore, global databases to gather larger patient cohorts are of high importance in studying rare infections.<sup>12</sup> With the present ECMM-ISHAM-ASM guideline, an unprecedented effort with a multidisciplinary approach was undertaken to assemble a valuable tool and support clinical decision making. Regional differences in availability of diagnostics or treatment are incorporated to make the recommendations also applicable in lower resource settings. Therefore, this guideline displays a major support to facilitate diagnosis and treatment of rare yeast infections for physicians all over the world with the aim to improve patient management and outcome.

The endorsement by the EHA Guidelines Committee is another step to emphasize the clinical impact of yeast infections in patients with hematological diseases and encourages an interdisciplinary, intersocietal approach for the development of future guidelines for the management of complex diseases.

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