European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Fungal Infection Study Group (EFISG) and European Confederation of Medical Mycology (ECMM) 2013 joint guidelines on diagnosis and management of rare and emerging fungal diseases


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Abstract

This guideline is the second in the line of three for fungal diseases by ESCMID and other societies. The guideline tried to follow the AGREE criteria for the development of clinical guidelines. This guideline serves as a European and potentially world-wide recommendation for the diagnosis and management of rare and emerging fungi. They include mucormycosis, hyalohyphomycosis (Fusarium, Paecilomyces, Scedosporium, etc.), phaeohyphomycosis (Alternaria, Bipolaris, Cladosporium, Rhinocladiella, etc.), and emerging yeasts (Saccharomyces, Trichosporon, Rhodotorula, etc.).

Introduction

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) wanted to tackle a challenge that no major scientific society had tried: providing a guideline on the diagnosis and management of rare and emerging fungal diseases. This guideline would obviously exclude Candida and Aspergillus diseases. Practically all invasive fungal diseases (IFD), including invasive candidiasis and aspergillosis, appear to be rare and emerging infections by definition. Although many IFD are still numerically rare, physicians treating immunosuppressed patients are increasingly confronted with a wide variety of fungal pathogens. Rarity of disease is defined by their absolute frequency in a population, and definitions range around 1 in 2000. Of course these statistics are different for populations of severely ill patients, where frequencies of IFD are much higher.

In the context of the numerically increasing patient population with immunosuppression and the expanding use of antifungal agents against common pathogens such as Candida and Aspergillus, the number of patients with IFD due to emerging and often drug-resistant pathogens is rising [1].

Still, the epidemiology of many of these rare and emerging infections is not well studied, but joint multinational efforts supported by the European Fungal Infection Study Group (EFISG) of the ESCMID, the ECMM and the International Society for Human and Animal Mycology (ISHAM) are underway [2–5].

Delayed diagnosis of IFD is a well-described problem associated with increasing mortality [5–9]. For this reason, we aim to guide physicians on the clinical characteristics, diagnostic utilities and appropriate treatment choice in an area of many unmet medical needs, where almost no well-designed randomized clinical trials have been conducted. In addition, new diagnostic utilities are being implemented and together with the growth of the antifungal armamentarium, guidelines for the correct utilization in the clinical setting are urgently needed. The implementation of a pan-European guideline may help national societies to strengthen their local guidelines in patient care of invasive fungal diseases.

Methods

Organizational structure: This guideline follows the structure and definitions of the ESCMID Guideline on Candida diseases [7,10–14]. It is in accordance with the GRADE and AGREE...
systems with minor exceptions [15,16]. To adequately address the diversity of human fungal pathogens and to facilitate using the guideline we divided the recommendations into four groups: (i) Mucormycosis, Cornely et al., (ii) Hyalohyphomycosis (Fusarium, Paecilomyces, Scedosporium) Lass-Flörl et al., (iii) Phaeohyphomycosis (Alternaria, Bipolaris, Cladosporium, Rhinocladiella) Chowdhary et al., and (iv) emerging yeasts (Saccharomyces, Trichosporon, Rhodotorula), Arendrup et al.

Members of EFISG-ESCMID and/or ECMM representing 12 European countries were invited to develop the guideline as experts. Emerging fungal diseases differ in their regional distribution patterns even more than candidiasis and aspergillosis, so we strengthened the group expertise by inviting non-European mycologists as well.

Time schedule: In January 2012 experts were contacted by the conveners (OAC, JM), and the chairs of the four subgroups agreed to coordinate efforts. Meetings were held mostly as telephone conferences with face-to-face meetings during ECCMID in London in April 2012, ISHAM in Berlin in June 2012, and stand-alone conferences in Cologne in October 2012 and Copenhagen in November 2012, and finally recommendations were presented at ECCMID in Berlin in April 2013.

Practical Working Procedure: We followed a seven-step approach tabulating published literature and expert opinion on emerging fungal diseases in a transparent fashion.

For each clinical or microbiological setting or question the adequate population was defined, followed by the intention of an intervention or diagnostic procedure. Then the procedure itself was detailed, followed by the strength of recommendation (Table 1) and the level of evidence (Table 2), and the literature supporting this recommendation. Additional explanations or comments were added if they were felt to be necessary. From this set of tables the slides for ECCMID presentations were chosen, and the manuscripts were drafted.

During the development of these guidelines we used AGREE criteria for their development [15]. As these guidelines face the task of providing guidance explicitly for rare and emerging fungi, an evidence-based evaluation remains daunting. Nevertheless, the working steps were clear and developed and communicated within the group:

1. Scope and Purpose:
   All diseases and their corresponding patient groups were predefined and appropriately covered by the guideline.

**TABLE 1. Definition of the Strength of Recommendation**

<table>
<thead>
<tr>
<th>Grad</th>
<th>ESCMID-EFISG and ECMM</th>
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<tbody>
<tr>
<td>A</td>
<td>strongly support a recommendation for use</td>
</tr>
<tr>
<td>B</td>
<td>moderately support a recommendation for use</td>
</tr>
<tr>
<td>C</td>
<td>marginally support a recommendation for use</td>
</tr>
<tr>
<td>D</td>
<td>support a recommendation against use</td>
</tr>
</tbody>
</table>

2. Stakeholder involvement:
Due to the nature of the guideline meaning that the incidence rates are low and diversity of patient groups is wide, patients’ views could not be sought. But the end-users were clearly defined by these guidelines.

These guidelines are made in collaboration between ECMM and ESCMID.

3. Rigour of development: The steps of development are similar to those used for the previous guideline of our group [14]:

   a. Defining the rare and emerging fungi.
   b. Several manuscripts of individual writing groups that were established with separate chairs and corresponding mandates composed these guidelines. The entire guideline project was then reviewed by the whole guideline group.
   c. Predefining questions that need to be answered.
   d. Providing alternative answers, all weighted by the body of evidence.
   e. Literature research was performed in PubMed with predefined search algorithms including major scientific meetings (e.g. ICAAC and ECCMID).
   f. Slide kits were prepared and circulated within the whole group for commentary.
   g. Presentation of the guidelines during ECCMID 2013.
   h. Manuscript is prepared including all valid commentary during the ECCMID and again circulated within the entire group for approval.
   i. An updated guideline will be routinely available after 4–5 years after the previous publication. An earlier update will follow if new and striking changes are found in the body of evidence.

4. Clarity of presentation:
   a. All recommendations are specific and unambiguous. The major messages are provided in tables designed to be easily read and understood.

**TABLE 2. Definition of the Quality of Evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one properly designed randomized, controlled trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-control analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees</td>
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</table>

<table>
<thead>
<tr>
<th>Index</th>
<th>Description</th>
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<tbody>
<tr>
<td>r</td>
<td>Meta-analysis or systematic review of randomized controlled trials</td>
</tr>
<tr>
<td>t</td>
<td>Transferred evidence, i.e. results from different patient cohorts, or similar immune-status situation</td>
</tr>
<tr>
<td>h</td>
<td>Comparator group is a historical control</td>
</tr>
<tr>
<td>u</td>
<td>Uncontrolled trial</td>
</tr>
<tr>
<td>a</td>
<td>Abstract published at an international meeting</td>
</tr>
</tbody>
</table>
b. Clear statements of the intention of each single recommendation and clarity regarding its intervention.

5. Applicability:

a. One of the early criteria required by AGREE was the request to consider the potential cost implication by the application of the given recommendation. This is not really feasible in a European guideline because reimbursements differ between countries and some only look at acquisition cost without considering the other outcome analyses. Therefore this criterion could not be considered for each recommendation.

b. The guidelines want to provide clear guidance to each clinician and microbiologist and recommend adaptation and individual modifications according to each hospital or country’s epidemiology and abilities, without considering itself to be the whole truth of diagnosis or treatment.

c. The guideline was peer-reviewed before its publication.

The previous definition for the strength of recommendation and quality of evidence in the ESCMID for Candida disease was again adopted for this guideline [14]. In brief, the four category grading system for the ‘strength of a recommendation’ was employed. Two extreme ends of the grading system were important: (A) ESCMID/ECMM strongly support a recommendation for use and, at the other end, (D) ESCMID/ECMM recommend against the use. This differentiation was important to clearly define treatment management for or against use of certain interventions. The two other middle graded statements (B and C) weighted in the evidence available for its recommendation and could be considered optional (Table 1). For this guideline we did adopt the strength of recommendation for the diagnostic part of the guideline.

The criteria for the quality of evidence did not differ from the previous guidelines [7,10–12,14].

Conclusions

This guideline is the second in a row of three grouped guidelines by ESCMID and others for the diagnosis and management of fungal diseases. Other groups are now adopting the ESCMID strength of recommendation and quality of evidence as well (ESCMID Study Group for Clostridium difficile [17], and ESCMID Study Group for Biofilms). This guideline serves as guidance in the clinical care of patients in Europe and potentially worldwide. Although guidelines are helpful tools for everyday decision-making, a clinical judgement call for the individual patient remains the main fundamental requirement for the physician in charge.

Transparency Declaration

OAC is supported by the German Federal Ministry of Research and Education (BMBF grant 01KN1106), has received research grants from 3M, Actelion, Astellas, Basilea, Bayer, Celgene, Cubist, F2G, Genzyme, Gilead, GSK, Merck/MSD, Miltenyi, Optimer, Pfizer, Quintiles, and Viropharma, is a consultant to 3M, Astellas, Basilea, Cubist, F2G, Gilead, GSK, Merck/MSD, Optimer, Pfizer and Sanofi Pasteur, and received lecture honoraria from Astellas, Gilead, Merck/MSD, and Pfizer.

MCE has received research grants from MSD, Astellas, Pfizer, Gilead and Ferrer, is a consultant to MSD, Astellas, Pfizer, Gilead and Ferrer, has provided expert testimony for MSD, Astellas, Pfizer, Gilead and Ferrer and received lecture honoraria from MSD, Astellas, Pfizer, Gilead and Ferrer.

JFM received grants from Astellas, Basilea and Merck. He has been a consultant to Astellas, Basilea and Merck and received speaker’s fees from Merck and Gilead. He has been supported in part by a grant from Qatar National Research Fund NPRP 5-298-3-086.

AJU has received research grants from Astellas, Gilead, Merck/Schering and Pfizer, is a consultant to Astellas, Basilea, Gilead, Merck/Schering and Pfizer, received payment for development of educational presentations from Gilead, and received lecture honoraria from Astellas, Gilead, Merck/Schering and Pfizer.

References

4. Pagano L, Cornely OA, Busca A et al. Combined antifungal approach for the treatment of invasive mucormycosis in patients with hemato-