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ESCMID Guideline for the Diagnosis and Management of Candida Diseases

GUEST EDITORS

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ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: developing European guidelines in clinical microbiology and infectious diseases

A. J. Ullmann[1†], O. A. Cornely[2†], J. P. Donnelly[3†], M. Akova[4], M. C. Arendrup[5], S. Arikan-Akdagli[6], M. Bassetti[7], J. Bille[8], T. Calandra[8], E. Castagnola[9], J. Garbino[10], A. H. Groll[11], R. Herbrecht[12], W. W. Hope[13], H. E. Jensen[14], B. J. Kullberg[3], C. Lass-Flörl[15], O. Lortholary[16,17], W. Meersseman[18], G. Petrikkos[19], M. D. Richardson[20], E. Roilides[21], P. E. Verweij[3], C. Viscoli[22] and M. Cuenca-Estrella[23†] for the ESCMID Fungal Infection Study Group (EFISG)

1) *Department of Internal Medicine II, Julius-Maximilians-University, Würzburg,* 2) *Department I of Internal Medicine, Clinical Trials Centre Cologne, ZKS Köln, BMBF 01KN1106, Center for Integrated Oncology CIO KölnBonn, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), German Centre for Infection Research, University of Cologne, Cologne, Germany,* 3) *Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands,* 4) *Department of Medicine, Hacettepe University Medical School, Ankara, Turkey,* 5) *Statens Serum Institut, Copenhagen, Denmark,* 6) *Department of Medical Microbiology, Hacettepe University School of Medicine, Ankara, Turkey,* 7) *Santa Maria Misericordia University Hospital, Udine, Italy,* 8) *Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland,* 9) *Instituto Giannina Gaslini, Children's Hospital, Genova, Italy,* 10) *University Hospitals Geneva, Geneva, Switzerland,* 11) *Center for Bone Marrow Transplantation and Department of Pediatric Hematology/Oncology, University Children's Hospital, Muenster, Germany,* 12) *Hôpital de Hautepierre, University of Strasbourg, Strasbourg, France,* 13) *Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK,* 14) *University of Copenhagen, Frederiksberg, Denmark,* 15) *Division of Hygiene & Medical Microbiology, Innsbruck Medical University, Innsbruck, Austria,* 16) *Service des Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants malades, APHP, Centre d'Infectiologie Necker-Pasteur, IHU Imagine Université Paris Descartes, Paris,* 17) *Centre National de Référence Mycologie et Antifongiques, Unité de Mycologie Moléculaire, Institut Pasteur, CNRS URA3012, Paris, France,* 18) *University Hospital Gasthuisberg, Leuven, Belgium,* 19) *4th Department of Internal Medicine, School of Medicine, National and Kapodistrian University of Athens, "ATTIKON" Hospital,* RIMINI *1 – Haidari, Athens, Greece,* 20) *Mycology Reference Centre, University Hospital of South Manchester and Manchester Academic Health Science Centre, University of Manchester, Manchester, UK,* 21) *Third Department of Pediatrics, Aristotle University School of Medicine and Hippokration Hospital, Thessaloniki, Greece,* 22) *University of Genoa, IRCCS San Martino-IST, Genoa, Italy and* 23) *Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain*

Abstract

The process to develop a guideline in a European setting remains a challenge. The ESCMID Fungal Infection Study Group (EFISG) successfully achieved this endeavour. After two face-to-face meetings, numerous telephone conferences, and email correspondence, an ESCMID task force (basically composed of members of the Society's Fungal Infection Study Group, EFISG) finalized the ESCMID diagnostic and management/therapeutic guideline for *Candida* diseases. By appreciating various patient populations at risk for *Candida* diseases, four subgroups were predefined, mainly ICU patients, paediatric, HIV/AIDS and patients with malignancies including haematopoietic stem cell transplantation. Besides treatment recommendations, the ESCMID guidelines provide guidance for diagnostic procedures. For the guidelines, questions were formulated to phrase the intention of a given recommendation, for example, outcome. The recommendation was the clinical intervention, which was graded by a score of A–D for the 'Strength of a recommendation'. The 'level of evidence' received a score of I–III. The author panel was approved by ESCMID, European Organisation for Research and Treatment of Cancer, European Group for Blood and Marrow Transplantation, European Society of Intensive Care Medicine and the European Confederation of Medical Mycology. The guidelines followed the framework of GRADE and Appraisal of Guidelines, Research, and Evaluation. The drafted guideline was presented at ECCMID 2011 and points of discussion occurring during that meeting were incorporated into the manuscripts. These ESCMID guidelines for the diagnosis and management of *Candida* diseases provide guidance for clinicians in their daily decision-making process.

Keywords: *Candida*, Europe, framework, guideline development, recommendation
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Corresponding author: A. J. Ullmann, Infectious Diseases, Department of Internal Medicine II, Julius-Maximilians-University, Oberdürrbacher Str. 6, 97080 Würzburg, Germany
E-mail: andrew.ullmann@uni-wuerzburg.de

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*European Society for Clinical Microbiology and Infectious Diseases
†Members of the subgroup committee mainly responsible for this manuscript.

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Introduction

Preparing guidelines in this day and age can be likened to the quest of the search for the Holy Grail. Numerous guidelines have been published in a variety of countries and by different scientific societies. All have the common goal of proving clinicians with best guidance for their daily working environment. Obviously, there is no single pathway to the truth in the field of medicine because science and the art of medicine are in a constant state of flux, published data might have already become obsolete and its interpretation might be biased unwittingly.

Nevertheless, it was apparent that certain guidelines for Europe are missing. Firstly, the majority of guidelines focus on treatment, usually only one host group at risk, and to a far lesser extent only a few focus on diagnostic procedures [1–10]. Moreover, North American guidelines are frequently cited in the literature, and this demonstrates their clear dominance [11–15]. Hence, recommendations for diagnostic procedures provided a clear impetus to our group of microbiologists, pathologists, haematologists and infectious diseases physicians (some with dual or more qualifications). In addition, differences in epidemiology by geography, age and local factors needed some attention. Our aim was to provide comprehensive European guidelines focusing on a single fungal disease entity caused by a single genus, namely *Candida* species to allow comprehensive coverage of diagnostics and treatment, recognizing that not all patient risk are alike. It became obvious very quickly that a matrix was needed to cover all topics of interest. This needed to be considered during the guidelines preparation. The guidelines are published as a supplement to CMI and aim to provide greater awareness and better insights into *Candida* diseases for the clinicians.

It was decided that the guidelines for the diagnosis and management of *Candida* diseases is divided into five separate parts, each of which can be used as stand-alone recommendations of the ESCMID treatment management guideline for each risk group of patients and diagnostic procedures.

Methods

Author panel recruitment and organization

The development of any guideline requires certain steps to ensure the production of an unbiased, independent and high-quality document. The executive board of EFISG decided to proceed first with a guideline for *Candida* diseases. The members of the EFISG group were first asked if they wanted to participate. Participants were chosen on the basis of their expertise in the field of medical mycology and in particular *Candida* disease, and further had experience in generating guidelines (Fig. 1). Contact was made through the ESCMID Executive Committee with four different European scientific societies. European Group for Blood and Marrow Transplantation (EBMT), European Confederation of Medical Mycology (ECMM), European Organisation for Research and Treatment of Cancer (EORTC) and European Society of Intensive Care Medicine (ESICM) approved the list of experts and made additional suggestions for experts. Some of the nominees are also members of the ESCMID and were included into the group as panel authors. Experts who were not

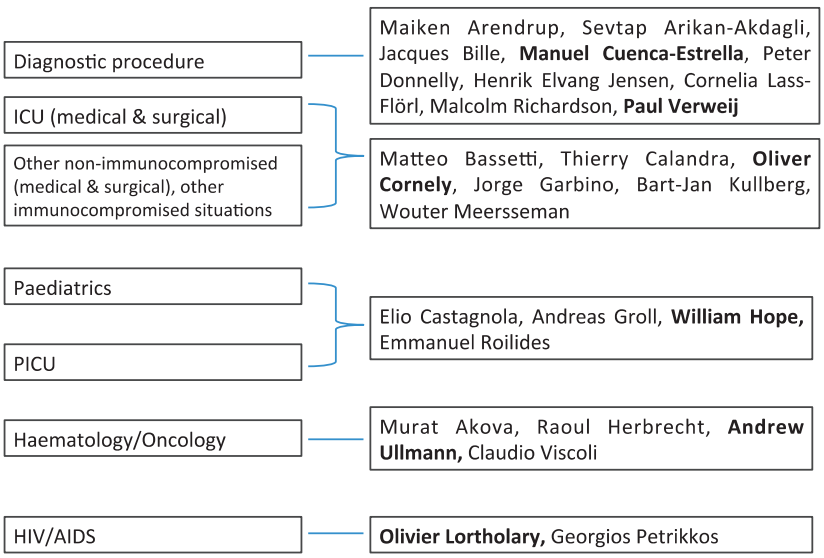

FIG. 1. Working modules and experts participating in the development of the guidelines (susceptibility testing is included for the diagnostic procedures).

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selected were asked to peer review the guideline to ensure further quality, although the final decision for the choice of peer reviewers rested with the Editor-in-Chief of CMI. These expert reviewers from the European scientific societies are acknowledged in this paper. This is a novel procedure because reviewers are usually not explicitly mentioned in terms of which papers they have reviewed.

Obviously, to achieve its aim, to provide a European guideline, the group needed to balance between different geographical regions of Europe. The list of representatives of the various European countries is provided in Table 1. For further proficiency, a group coordinator of each subgroup was nominated to provide and present the results of the discussion of this subgroup to the plenary sessions. The subgroups were set up by EFISG. They searched for relevant literature (by PubMed). This literature database was made available to the whole panel on an ftp server of ESCMID. During 2010–2012, documents and views were shared by email, teleconferences and face-to-face meetings. Once a first consensus was reached, the preliminary recommendations were presented to the whole group, that is, the other authors, and subject to wide discussion, developed further, and finalized as a group consensus. Two weekend meetings took place in 2010 and 2011 to finalize the guidelines. The finished guidelines were presented during a workshop session at the ECCMID 2011, and points of discussion occurring during that meeting were incorporated into the final publicized manuscripts. The organization plan used for the guideline is provided in Fig. 2.

TABLE 1. List of the representatives associated with the country

Country	Number (ID)	Number (CM and diagnostic experts)	Total number
Austria	0	1	1
Belgium	1	0	1
Denmark	0	1 + 1[a]	2
France	1 + 1[b]	0	2
Germany	3[c]	0	3
Greece	2	0	2
Italy	3	0	3
Netherlands	1	2	3
Spain	0	1	1
Switzerland	2	1[d]	3
Turkey	1	1[d]	2
United Kingdom	1	1	2

ID, infectious diseases specialist; CM, clinical microbiologist.
[a]Pathologist.
[b]Haematologist.
[c]Dual trained in ID and haematology.
[d]Dual trained in ID and CM.

Intention of the recommendation with defined intervention

During the preparation process, new ideas were incorporated to provide best clinical guidance. Pragmatic questions arising in everyday patient care needed to be addressed appropriately. For this reason, the 'intention' for a recommendation was defined beforehand and framed in terms of 'What does the clinician want?' and a response was tailored to address the different aspects of a given *Candida* disease. Obviously, the diagnostic and therapeutic intervention that

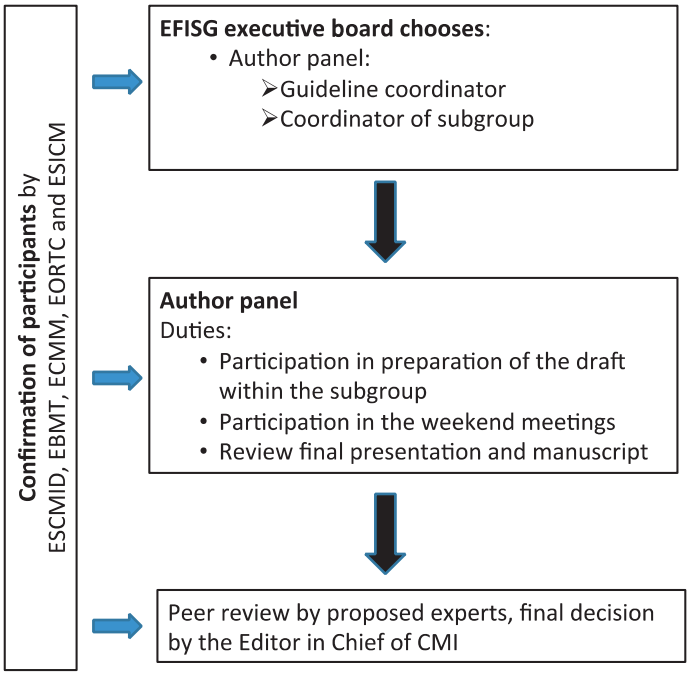

FIG. 2. Organization plan of the guidelines.

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had the greatest impact on survival of the patient was given the highest priority in terms of a recommendation.

Certain recommendations were originally controversial. Guidelines are no consensus meeting, but nevertheless, a majority vote was a necessity to formulate a recommendation if a major disagreement occurred. Only a few of the discussions were intense but only had one common goal in mind—to provide the best option for diagnosis and therapy. But whatever the decision, it was one we ensured to be the best for patients.

Every recommendation within the guidelines attempts to indicate clearly the intention (e.g. improved survival) and to describe the diagnostic or therapeutic option (intervention). Therefore, the guidelines follow the principles of the 'Grades of Recommendations, Assessment, Development, and Evaluation' (GRADE) [16]. For every recommendation, the following three questions were considered:

1. What do clinicians want (outcomes)? What is their intention?
2. Which option is better for patients? What intervention is needed to reach the desired outcome?
3. Review the chosen option whether it is truly better or not by adequate review of the literature.

These guidelines also adopted the 'Appraisal of Guidelines, Research and Evaluation' (AGREE) items for the development of guidelines as well [17,18] and basically all domains of AGREE were addressed:

1. Scope and purpose, for example, clinical questions covered by the guideline is described.
2. Stakeholder involvement, for example, the patient's view and preferences have been sought.
3. Rigours of development, for example, the health-related benefits, side effects and risks have been considered in formulating the recommendations.
4. Clarity of presentation, for example, key recommendations are easily identifiable, i.e. tables.
5. Applications, for example, the potential cost-related implications of applying the recommendations have been considered.
6. Editorial independence, for example, the guideline is editorially independent from the funding body.

Within the guideline, questions were formulated and answered according to their clinical importance. Because the guideline author panel appreciated that not all patients were alike, various risk groups were defined according to risk and handled accordingly, that is, patients with HIV/AIDS, those in the ICU, transplant recipients, haematological malignancies and cancer and paediatric populations. At all times, the patient's view and preferences were kept to the fore. One good example that caused some heated debates was the recommendation of not administrating amphotericin B deoxycholate to adults. This drug formulation with considerable toxicity, morbidity and mortality issues, but in regard to acquisition costs relatively cheap has better alternatives at least in Europe available albeit at greater costs. The responsibility to ensure good medical help needed to be considered, and the follow-up costs for the numerous side effects would make the choice of a less cheaper drug acceptable [19]. The ethical dilemma although is obvious but on balance, it was felt that given the facts, the choice of a more expensive formulation was acceptable.

Strength of recommendation

Numerous grading systems of recommendations exist, and it is imperative that they should be not too complicated to understand for the user. Hence, we utilized a similar system as previously employed by the Canadian Task Force of the Periodic Health Examination and the IDSA [12,20]. This is a four-category grading system for the 'strength of a recommendation'. Two extreme ends of the grading system were important: (A) ESCMID strongly supports a recommendation for use and on the other side: (D) ESCMID recommends against the use. This differentiation was important to clearly define treatment management for or against the use of a given interventions. The grade C is weighted with the evidence available and could be considered optional (Table 2). The grading of the 'strength of a recommendation' can be compared to traffic lights, with green indicating the recommendation for use and red the recommendation against use.

The 'strength of a recommendation' cannot easily be applied to diagnostic recommendations. Therefore, an alter-

TABLE 2. Strength of the ESCMID recommendation and quality of evidence

Strength of a recommendation	
Grade A	ESCMID strongly supports a recommendation for use
Grade B	ESCMID moderately supports a recommendation for use
Grade C	ESCMID marginally supports a recommendation for use
Grade D	ESCMID supports a recommendation against use
Quality of evidence	
Level I	Evidence from at least 1 properly designed randomized controlled trial
Level II*	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case–controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

*Added index:
$_r$: meta-analysis (or systematic review of randomized controlled trials).
$_t$:transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.
$_h$: comparator group: historical control.
$_u$: uncontrolled trials.
$_a$: published abstract (presented at an international symposium or meeting).

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TABLE 3. System used in these guidelines for grading quality of evidence about the accuracy of biomarker detection procedures in the diagnosis of candidiasis

Accuracy[a]	
Highly recommended	Technique is accurate in >70% of cases (most)
Recommended	Technique is accurate in 50–70% of cases (reasonable number)
Not recommended	Technique is accurate in <50% of cases (small number)
No recommendation	No data
Quality of evidence accepted	
Level I	Evidence from at least one properly designed prospective multicentre cross-sectional or cohort study
Level II	Evidence from (1) at least one well-designed prospective single-centre cross-sectional or cohort study or (2) a properly designed retrospective multicentre cross-sectional or cohort study or (3) from case–control studies
Level III	Opinions of respected authorities, clinical experience, descriptive case studies, or reports of expert committees

[a]Accuracy was defined as: (Numbers of true positives + true negatives) divided by (Numbers of true positives + false positives + false negatives + true negatives).

native system was adopted for biomarkers (non-cultural techniques), which included test accuracy, as this plays a pivotal role in providing an appropriate diagnosis. The GRADE system was used to grade the 'strength of a recommendation' and 'quality of evidence' [21,22]. Therefore, the system was slightly modified and is applicable for biomarkers (non-cultural techniques) only. The term accuracy of a test was introduced, and a grading system was implemented on those calculated numbers (Table 3). The grading system used a clear statement, that is, highly recommended, recommended and not recommended and did not utilize the alphabet system for treatment. If no published data were available to support any kind of recommendation, no recommendation for the test was provided. The equation for accuracy was the sum of true positive and true negative tests divided by the sum of all tests performed. The wording for the 'quality of evidence' was changed only marginally to maintain a streamlined recommendation grading system (Table 3).

Quality of evidence

The 'strength of a recommendation' was largely based on the available studies and publications. Although there were obvious exceptions, for example, drawing blood cultures for candidaemia because in this case, no literature was cited. On the other hand, various publications discussed issues surrounding the selection of appropriate literature [23,24]. This literature should support the judgement made by the panel. This guideline is not a classical systematic review of the literature. It was clearly intended to review the literature on the impact of the test and alternative management strategies on the outcome in patients [25]. The panel reviewed the available evidence and recognized its limitations but interpretation bias cannot be ruled out entirely. The panel always kept its focus on the need for an evidence-based (medicine) justification. Despite some limitations in the selection process, by which means every subgroup was internally responsible for, all retrieved literature (by PubMed) were considered. A meta-analysis was not intended and not all retrieved literature was cited. Nevertheless, we rated the evidence as the Canadian Task Force on the Periodic Health Examination and the IDSA [12,20]. One modification was added to the level II of 'Quality of Evidence'. The panel recognized that not all questions could be answered by published literature but, for example, similar immunological situations or a substantial abstract from larger international recognized scientific meetings could be used as 'evidence'. Therefore, especially for academic purposes and to increase transparency, indices were added to the level II of 'Quality of Evidence' (Table 1).

Discussion and conclusions

These ESCMID guidelines provide a European-wide guideline for clinical guidance in the diagnosis and treatment of *Candida* diseases. The guidelines offer besides diagnostic also treatment recommendations for various patients' groups and are weighted differently according to available literature. The basis of these guidelines were to follow the framework provided by GRADE and AGREE [16–18,24–26]. The panel fully acknowledges numerous published guidelines and recognized some shortcomings that the ESCMID guideline tried to overcome: Mainly providing an independent European guideline for diagnostic procedures and treatment recommendations suitable for all patients at risk for *Candida* diseases. Obviously, not all patient profiles are homogeneous, as their risk profile and response to therapy may differ. Minor changes in the view of rating systems were implemented into this guideline.

These guideline should also serve as a tool for guiding the clinical care of patients in Europe. The ESCMID guidelines consist of text but also includes tables that are easily readable. The development of the guidelines was made transparent, and the panel was also supported by other European societies as well as a broad panel of experts from various backgrounds and countries. The guidelines were (peer-) reviewed by other experts in the field of medical mycology and who were in part suggested by other European societies. Their pivotal role by peer review in the process of the guideline development cannot be underestimated and the entire panel expresses their gratitude by acknowledging their work at the end of this manuscript.

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The development of guidelines comes with a price tag, as there are inevitably costs incurred by travel and accommodation. Funding was neither sought nor granted by biomedical or pharmaceutical companies for the development of these guidelines. Additionally, biomedical or pharmaceutical companies were not involved in the development of these guidelines neither as observers or discussants. For this reason, we received a grant of 50 000€ from ESCMID to accomplish this task. Transparency declarations of the panel are provided to every guideline. This support by ESCMID guaranteed independence including editorial independence.

Challenges remain for the guidelines. Trying to assess *Candida* epidemiology in Europe remained a challenge because only a few adequate European publications were available. The guidelines want to serve as a tool for guidance as for local (hospital) guidelines, which would require individual adaptations to meet local needs [27]. Therefore, it remains important to have European guidelines that can be adapted to local use.

Costs incurred by diagnostic procedures or treatments are not considered mainly because of the differences of reimbursement systems in Europe. Cost effectiveness calculations of different treatment modalities have been assessed by others but are only applicable for the specific countries (e.g. [28]).

Obviously, more research is needed in the field of *Candida* diseases particular in epidemiology and the development of resistance. 'Strength of a recommendation' with a grading of 'C' highlights our obligation to further work in this area to arrive at a more adequate or satisfactory answer. The EFISG is actively developing guidelines in other fields of medical mycology (e.g. rare and emerging fungi and aspergillosis) and will seek cooperation with other scientific societies sharing this goal. The current *Candida* guidelines are planned to be reviewed in the next 5 years to ensure it remains up to date. If new and pivotal clinical data become available, then the planned update will take place earlier.

In summary, these ESCMID guidelines are independent of any industry funding or support or influence and were drafted as an independent recommendation by 25 European experts from 12 countries. The panel of authors hopes that these ESCMID guidelines for the diagnosis and management of *Candida* diseases will provide adequate guidance for clinicians in everyday decision-making process, which can be easily adapted to their clinical practice.

Transparency Declarations

A.J.U. has received research grants from MSD (Schering-Plough), and is/was an advisor or received lecture honorarium from Astellas, Aicuris, Basilea, Gilead, MSD, and Pfizer.

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

J.P.D. has received grant support from, Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. He has been a consultant or on an advisory board for Astellas, Gilead Sciences, Merck Sharp and Dohme, and Pfizer. He has received remuneration for giving lectures on behalf of Gilead Sciences, Merck and Pfizer.

M.A. received, during the past 5 years, research grants and honoraria for talks and consultancy from Merck, Pfizer and Gilead.

M.C.A. has received grant support from Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. She has been a consultant or at the advisory board for Gilead Sciences, Merck Sharp and Dohme, Pfizer, Pcovery, and Schering Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough.

S.A.A. has received investigator initiated research grant support from Pfizer and has been at the Advisory Board for Pfizer-Turkey. She has received speaker honoraria from Merck and Pfizer.

M.B. has received research grants from Pfizer, MSD and Astellas and is/was an advisor or received lecture honorarium from Astellas, Aventis, Bayer, Cephalon, Cubist, Gilead, MSD, Novartis, Shionogi, Pfizer, Teva and Vifor.

J.B. has nothing to declare.

T.C. is member of the Speaker bureau, and is advisor or consultant for Astellas, Baxter; bioMérieux, EISAI, Evolva, Novartis, Merck Sharp & Dohme-Chibret AG, Immunexpress, Eli Lilly Suisse, Pfizer. Grant support from Baxter, bioMérieux, Merck Sharp & Dohme-Chibret AG, Roche Diagnostic. He has also received payment from MSD, Institut Pasteur and Gilead Sciences for development of educational presentations, as well as royalties from Elsevier.

E.C. has participated as invited speaker to symposia organized by Gilead, Pfizer, Astellas, Merck, Novartis and he has been member of advisory boards for Astellas, Pfizer. He also has received payment for development of educational presentations and for lectures and consultancy.

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J.G. has nothing to declare.

A.H.G. has received research support from Gilead, Merck, and Schering. He has acted as speaker and/or consultant for Astellas, Cephalon, Gilead, Merck, Sharp & Dohme, Pfizer, Schering, and Vicuron. He has also received payment for speaking engagements from Astellas, Gilead, MSD, Pfizer, Schering-Plough and Zeneus/ Cephalon.

R.H. has been a consultant or at the advisory board for Astellas pharma, Basilea, Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer, and Schering Plough. He has been paid for talks on behalf of Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer, and Schering Plough. His travel and accommodation expenses have also been covered by Pfizer and Gilead and a research grant and investigator fees for a clinical trial from Pfizer.

W.W.H. has received grant support from National Institute of Health Research (NIHR), Medical Research Council, National Institute for the Replacement, Refinement and Reduction, of Animals in Research, Pfizer, Gilead, Schering Plough, Merck and Astellas, and has served as a consultant for Pfizer, Astellas, Gilead, F2G, Vectura, and Schering Plough. His travel costs to meetings have also been covered by ESCMID.

H.E.J. has nothing to declare.

B.J.K. has received research grants from Bio-Mérieux and Cephalon. He is a consultant to Pfizer and is a member of the Gilead, MSD and Pfizer speaker bureaus.

C.L.-F. has received grant support in the past 5 years from Astellas Pharma, Gilead Sciences, Pfizer, Schering Plough and Merck Sharp and Dohme. She has been an advisor/consultant to Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough.

O.L. is a member of the MSD board, is a consultant for Astellas and Gilead Sciences, and received grants or speaker's fees from MSD, Astellas, Gilead Sciences and Pfizer.

W.M. has received grant support from MSD and Pfizer. He had been an advisor to MSD and Pfizer. He has received honoraria for presentations on behalf of MSD/Schering Plough, and Pfizer.

G.P. has received research grants from Gilead, Astra Zeneca, Novartis, Astellas, GSK, Pfizer and MSD, has acted as paid consultant to Janssen Cilag, Gilead, Astellas, and MSD and is a member of the Gilead, Astellas and MSD speaker' s bureaus.

M.D.R. has received grants, speaker's honoraria and travel support from Pfizer, Astellas, ESCMID, MSD and Gilead Sciences. He has also received book royalties from Blackwell Publishing.

E.R. has received research support from Pfizer, Enzon, Gilead, Merck and he has made contributions in advisory boards of Gilead, Astellas, Pfizer. He has also been a consultant/speaker for Schering, Gilead, Astellas, Pfizer, Merck, Wyeth, Cephalon and Aventis.

P.E.V. has received research grants from Pfizer, Astellas, Cephalon, Gilead Sciences, Merck and Schering-Plough.

C.V. received grants as speaker/moderator in meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott, Nadirex International, BMS and received grants for participation in advisory boards by Gilead, Astellas, MSD, Pfizer. Further he obtained research grants for his institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, Novartis- He is member of the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency Member of various levels of local Infection Control, Antibiotic Stewardship, Vaccine and HIV Committees (Genoa, Liguria, Italy).

M.C.E. has received in the past 5 years grant support from Astellas Pharma, bioMerieux, Gilead Sciences, Merck Sharp and Dohme, Pfizer, Schering Plough, Soria Melguizo SA, Ferrer International, the European Union, the ALBAN program, the Spanish Agency for International Cooperation, the Spanish Ministry of Culture and Education, The Spanish Health Research Fund, The Instituto de Salud Carlos III, The Ramon Areces Foundation, The Mutua Madrileña Foundation. He has been an advisor/consultant to the Panamerican Health Organization, Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer, and Schering Plough. He has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough.

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ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: diagnostic procedures

M. Cuenca-Estrella[1†], P. E. Verweij[2†], M. C. Arendrup[3†], S. Arikan-Akdagli[4†], J. Bille[5†], J. P. Donnelly[2†], H. E. Jensen[6†], C. Lass-Flörl[7†], M. D. Richardson[8†], M. Akova[9], M. Bassetti[10], T. Calandra[11], E. Castagnola[12], O. A. Cornely[13], J. Garbino[14], A. H. Groll[15], R. Herbrecht[16], W. W. Hope[17], B. J. Kullberg[2], O. Lortholary[18,19], W. Meersseman[20], G. Petrikkos[21], E. Roilides[22], C. Viscoli[23] and A. J. Ullmann[24] for the ESCMID Fungal Infection Study Group (EFISG)

1) *Servicio de Micología, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain,* 2) *Department of Medical Microbiology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands,* 3) *Unit of Mycology, Department of Microbiological Surveillance and Research, Statens Serum Institut, Copenhagen, Denmark,* 4) *Department of Medical Microbiology, Hacettepe University School of Medicine, Ankara, Turkey,* 5) *Institute of Microbiology, University of Lausanne and University Hospital Center, Lausanne, Switzerland,* 6) *University of Copenhagen, Frederiksberg, Denmark,* 7) *Division of Hygiene and Medical Microbiology, Innsbruck Medical University, Innsbruck, Austria,* 8) *Mycology Reference Centre, University Hospital of South Manchester and Manchester Academic Health Science Centre, University of Manchester, Manchester, UK,* 9) *Department of Medicine, Hacettepe University School of Medicine, Ankara, Turkey,* 10) *Santa Maria Misericordia University Hospital, Udine, Italy,* 11) *Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland,* 12) *Instituto Giannina Gaslini, Children's Hospital, Genova, Italy,* 13) *Department I of Internal Medicine, Clinical Trials Centre Cologne, ZKS Köln, BMBF 01KN1106, Center for Integrated Oncology CIO KölnBonn, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), German Centre for Infection Research, University of Cologne, Cologne, Germany,* 14) *University Hospitals Geneva, Geneva, Switzerland,* 15) *Center for Bone Marrow Transplantation and Department of Pediatric Hematology/Oncology, University Children's Hospital, Muenster, Germany,* 16) *Hôpital de Hautepierre, University of Strasbourg, Strasbourg, France,* 17) *Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK,* 18) *Hôpital Necker-Enfants malades, Université Paris Descartes, Service des Maladies Infectieuses et Tropicales, APHP, Centre d'Infectiologie Necker-Pasteur, IHU Imagine, Paris,* 19) *Unité de Mycologie Moléculaire, Centre National de Référence Mycologie et Antifongiques, Institut Pasteur, CNRS URA3012, Paris, France,* 20) *University Hospital Gasthuisberg, Leuven, Belgium,* 21) *Fourth Department of Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece,* 22) *Third Department of Pediatrics, Aristotle University School of Medicine and Hippokration Hospital, Thessaloniki, Greece,* 23) *University of Genoa, IRCCS San Martino-IST, Genoa Italy and* 24) *Department of Internal Medicine II, Julius-Maximilians-University, Würzburg, Germany*

Abstract

As the mortality associated with invasive *Candida* infections remains high, it is important to make optimal use of available diagnostic tools to initiate antifungal therapy as early as possible and to select the most appropriate antifungal drug. A panel of experts of the European Fungal Infection Study Group (EFISG) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) undertook a data review and compiled guidelines for the clinical utility and accuracy of different diagnostic tests and procedures for detection of *Candida* infections. Recommendations about the microbiological investigation and detection of candidaemia, invasive candidiasis, chronic disseminated candidiasis, and oropharyngeal, oesophageal, and vaginal candidiasis were included. In addition, remarks about antifungal susceptibility testing and therapeutic drug monitoring were made.

Keywords: Biomarkers, *Candida*, diagnosis, guideline, noncultural

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Corresponding authors: M. Cuenca-Estrella, Servicio de Micología, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Ctra Majadahonda-Pozuelo Km 2, 28220 Majadahonda, Madrid, Spain
E-mail: mcuenca-estrella@isciii.es
and
A. J. Ullmann, Infectious Diseases, Department of Internal Medicine II, Julius-Maximilians-University, Oberdürrbacher Str. 6, 97080 Würzburg, Germany
E-mail: andrew.ullmann@uni-wuerzburg.de

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*European Society for Clinical Microbiology and Infectious Diseases.
†Members of the subgroup committee mainly responsible for this manuscript.

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Introduction

One of the main novelties of the ESCMID *Candida* Guidelines is the inclusion of recommendations about diagnostic procedures. The aim of these guidelines is to appraise the different techniques and procedures for detection and investigation of *Candida* infections. Timing of antifungal therapy has been shown to have major impact on hospital mortality. As the mortality associated with invasive *Candida* infections remains high, it is important to make optimal use of diagnostic tools to initiate antifungal therapy as early as possible with the best antifungal drug. In addition to diagnostic tools understanding of the local epidemiology, patient risk factors and resistance profiles of *Candida* species are essential. In some geographical areas, the number of patients with candidiasis is rising associated with an increase in the number of patients with immunosuppression and the expanding utilization of intensive care units. New diagnostic utilities are being implemented. Most of the new detection methods have been designed to diagnose invasive candidiasis and have been shown to be valuable techniques, which could detect infection early.

This article includes recommendations about conventional methods of microbiological diagnosis of deep-seated, oropharyngeal, oesophageal and vaginal candidiasis, antifungal susceptibility testing (AST) and alternative diagnostic procedures also known as nonculture, biomarker detection procedures. Some issues about therapeutic drug monitoring (TDM) of antifungal agents are also commented upon.

Clinicians often use diagnostic tests as a package or strategy based on evidence regarding the accuracy of procedures. Several proposals have been published for grading quality of evidence and strength of recommendations for diagnostic tests and strategies [1]. Although recommendations on diagnosis share the fundamental logic of recommendations for other interventions, they present unique aspects. Conventional diagnostic procedures such as microscopical examination, culture and identification of microorganisms are essential investigations, and their performance depends on the possibility of obtaining samples of deep tissues. Consequently, grading the quality of evidence and strength of recommendation for conventional methods of diagnosing candidiasis has not been included in this guideline.

However, strengths of recommendations about new nonculture-based techniques for biomarker detection can be assigned because many techniques are available showing different levels of accuracy. The use of tests to establish the presence or absence of the disease and their utility as early diagnostic methods can be also evaluated. Table 1 shows the system used in these guidelines for grading quality of evidence about the accuracy of biomarker detection procedures in the diagnosis of candidiasis.

TABLE 1. System used in these guidelines for grading quality of evidence about the accuracy of biomarker detection procedures in the diagnosis of candidiasis (based on reference 1)

Accuracy[a]	
Highly recommended	Technique is accurate in >70% of cases (most)
Recommended	Technique is accurate in 50–70% of cases (reasonable number)
Not Recommended	Technique is accurate in <50% of cases (small number)
No recommendation	No data
Quality of evidence accepted	
Level I	Evidence from at least one properly designed prospective multicentre cross-sectional or cohort study
Level II	Evidence from (i) at least one well-designed prospective single-centre cross-sectional or cohort study or (ii) a properly designed retrospective multicentre cross-sectional or cohort study or (iii) from case-control studies
Level III	Opinions of respected authorities, clinical experience, descriptive case studies or reports of expert committees

[a]Accuracy was defined as: (Numbers of true positives + true negatives) divided by (Numbers of true positives + false positives + false negatives + true negatives).

This document was written by a panel of experts of the European Fungal Infection Study Group (EFISG) of the ESCMID. The text is divided into seven sections, and the object of the experts was to draw up a series of practical recommendations, with the aim of answering all the questions faced by health professionals when designing diagnostic strategies for detecting *Candida* infections.

1. What are the best tests for diagnosing candidaemia?

Candidaemia can be defined as the presence of any species of the genus *Candida* in the blood. Subsequently, blood cultures (BC) are essential for diagnosing candidaemia [2]. There are a number of international guidelines including general recommendations for taking and processing of blood samples to ensure the optimal isolation of microorganisms [3–6].

The number of BC recommended in a single session is 3 (2–4), with a total volume varying according to the age of the patient, 40–60 mL for adults, 2–4 mL for children under 2 kg, 6 mL between 2 and 12 kg, and 20 mL between 12 and 36 kg. The timing for obtaining the BC is one right after the other from different sites, and venipuncture remains the technique of choice. A BC set comprises of 60 mL blood for adults obtained in a single session within a 30-min period and divided in 10-mL aliquots among three aerobic and three

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anaerobic bottles. The frequency recommended is daily when candidaemia is suspected, and the incubation period must be at least 5 days.

When these recommendations have been followed the sensitivity of BC to detect *Candida* is 50–75% although lower sensitivity rates in neutropenic patients and those undergoing antifungal treatment have been reported [7,8]. Some other remarks should be noted. Sensitivity varies depending on the species and system used. For instance, *C. glabrata* grows less optimally in the BACTEC™ medium (Becton Dickinson Diagnostic Systems) unless a mycosis bottle is included [7,8]. Identification to species level is mandatory because antifungal therapy can vary according to *Candida* species. In addition, yeasts in BC are not always *Candida* as other emerging and rare yeast pathogens have been involved in up to 5% of patients with fungemia. Lysis-centrifugation procedures showed higher efficacy when older BC systems were used as comparators. The recommendation of the panel was to use an automated validated BC system.

The performance of BC is not very high, and they cannot be considered as early diagnostic techniques. Alternative procedures based on the detection and quantification of fungal biomarkers and metabolites have been developed to improve and anticipate the detection of candidaemia. Table 2 includes the recommendations of the panel about the clinical use of these techniques.

The combined detection of mannan and anti-mannan antibodies is considered to be a method for specific detection of *Candida* spp. in serum samples [9]. There is a combination of tests available [Platelia Candida Antigen Plus (Ag Plus™) and Antibody Plus (Ab Plus™; Bio-Rad Laboratories)]. A number of studies, based on previous generations of these tests, reporting evidences from properly designed retrospective multicentre cross-sectional or cohort study and from case–control studies have proven their efficacy in the diagnosis of candidemia, with sensitivity and specificity rates around 80% and 85%, respectively, which translates into an accuracy of 50–70%. Serial determinations may be necessary. These assays can help to detect the infection early because they can be positive 6 days on average prior blood cultures. It shows also very high negative predictive value (>85%) and can be used to rule out infection. The panel considered the method as *recommended* for the diagnosis of candidaemia. It could be used as part of a diagnostic strategy to establish

TABLE 2. Summary of recommendations by *Candida* disease, specimen and test evaluated

Disease	Specimen	Test	Recommendation	Level of evidence
Candidaemia	Blood	Blood culture	Essential investigation[a]	NA
	Serum	Mannan/anti-mannan	Recommended	II
		B-D-glucan	Recommended	II
		Other antibodies	No recommendation	No data
		Septifast PCR kit	No recommendation	No data
		In-house PCR	No recommendation	No data
Invasive candidiasis	Blood	Blood culture	Essential investigation	NA
	Serum	Mannan/anti-mannan	No recommendation	No data
		B-D-glucan	Recommended	II
		Septifast PCR kit	No recommendation	No data
		In-house PCR	No recommendation	No data
	Tissue and sterile body fluids	Direct microscopy and histopathology	Essential investigation	NA
		Culture	Essential investigation	NA
		Immuno-histochemistry	No recommendation	No data
		Tissue PCR	No recommendation	No data
		In situ hybridization	No recommendation	No data
Chronic disseminated candidiasis	Blood	Blood culture	Essential investigation	NA
	Serum	Mannan/anti-mannan	Recommended	II
		B-D-glucan	Recommended	II
		Septifast PCR kit	No recommendation	No data
		In-house PCR	No recommendation	No data
	Tissue and sterile body fluids	Direct microscopy and histopathology	Essential investigation	NA
		Culture	Essential investigation	NA
		Immuno-histochemistry	No recommendation	No data
		Tissue PCR	No recommendation	No data
		In situ hybridization	No recommendation	No data
Oropharyngeal and oesophagic candidiasis	Swab	Culture	Essential investigation	NA
		In-house PCR	No recommendation	No data
	Biopsy[b]	Direct microscopy and histopathology	Essential investigation	NA
		Culture	Essential investigation	NA
		In-house PCR	No recommendation	No data
Vaginal candidiasis	Swab/vaginal secretions	Direct microscopy	Essential investigation	NA
		Culture	Essential investigation	NA
		Commercial tests	Use validated test only	NA
		In-house PCR	No recommendation	No data

NA, not applicable.
[a]Essential investigation means it must be done if possible.
[b]Oropharyngeal biopsy is not mandatory.

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the absence of the disease to reduce the unwarranted use of antifungal agents in prophylactic and empirical regimens in critical care settings (ICU).

The β-1,3-D-glucan detection (BDG) is also a technique useful for *Candida* detection. It is not specific for *Candida* because it is present in many fungal species. The BDG test is considered to be a panfungal diagnostic method and was included in the EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycosis Study Group) diagnostic criteria for invasive fungal infections in 2008, for all types of patients. There are several techniques on the market for the detection of glucan in serum. In Europe and America, the most used is Fungitell® (Associated of Cape Cod, Inc.). A number of meta-analyses have been undertaken using data from cross-sectional, cohort and case–control studies on the diagnosis of candidaemia. The sensitivity of glucan detection was >65% in most studies with a cut-off value of 80 pg/mL, with specificity rates >80%, positive likelihood ratios approximately of 4, negative likelihood ratios of 0.50 and negative predictive values >85%. The use of albumin, gauzes, immunoglobulins or haemodialysis was associated with false positives, and the test seemed of greater utility in patients who did not have haematological diseases such as surgical or medical ICU patients suffering from *Candida* infections [10]. The panel considered the BDG test (Fungitell™ only so far) as *recommended* for candidemia detection in adults being also very useful for ruling out infection. Serial determinations (twice a week) are recommended. The test has not been validated in children.

Regarding other alternative methods, the panel did not make any recommendations because no data are available to evaluate their utility for the clinical diagnosis of candidaemia. Antibody detection kits such as Serion Elisa Classic® and *Candida* germ tube antibodies are under evaluation, and there are limited data about their clinical accuracy. Molecular detection techniques largely PCR-based have also been designed, and several studies about their reliability are in progress. The Light Cycler SeptiFast® system (Roche) is a PCR-based commercial kit to detect bacteria and fungi in blood samples. Studies have reported some cases of candidaemia being detected by this kit, but the number of cases is rather limited and no recommendation can be made [11–13]. Regarding in-house PCR techniques, many reports have been published including more than 1000 patients [14–17]. Their pooled sensitivity and specificity was calculated over 85% in a meta-analysis published recently [18]. None of the PCR techniques included external validation and different material and methods were used. Third-party appraisal of results and harmonization of PCR-based techniques should be made before recommendations can be made regarding clinical utility.

2. What are the best tests for diagnosing invasive candidiasis?

Invasive candidiasis (IC) can be defined as a deep-seated disease, frequently a multiorgan infection including candidaemia although BCs are negative in as many as one-third of the cases at least in the ICU population [19]. Remarks about BC were made in the previous section. This section relates the recommendation by the panel about IC diagnosis using other specimens and procedures.

Classical diagnostic methods, such as direct microscopy, histopathology and culture, exhibit a limited sensitivity to detect IC, and their usefulness depends on the possibility of obtaining samples of deep tissues which, in many cases, cannot be taken due to the patient's condition. Therefore, these approaches must be considered as essential investigations to be performed if possible [3,5,6,20].

A number of considerations and recommendations were highlighted by the panel about the classical methods. Regarding tissue samples and body fluids from normally sterile sites, they must be obtained and collected aseptically and transported to the laboratory promptly. Small samples are prone to sampling error. Tissue for histopathology should be placed in fixative as rapidly as possible, and microscopy should include special stains such as silver stains and PAS. The use of optical brighteners is recommended for microscopical examination of un-fixed specimens. Microscopic examination requires expertise for interpretation, and morphology cannot be used for definitive identification [21–23].

Samples for culture should not be placed in histopathology fixatives and must be kept moist. They have to be processed promptly to avoid multiplication of organisms. If not possible, storage at 4–5°C is recommended. Fungal selective media must be included, and it should be observed that some species take several days (5–14 days) to grow in culture. Yeast isolation from normally sterile tissues or fluids is usually indicative of deep-seated infection. Negative culture results do not exclude *Candida* infection. Identification of the isolate to species level is mandatory [24,25].

Samples from tissues and body fluids can be also investigated using alternative procedures. Among these, immunohistochemistry [21–23], *in situ* hybridization [26] and analysis of samples by PCR-based procedures [15,27] have been positively evaluated in some studies, but they are not generally available and third-party evaluation of their accuracy has not been carried out so far. However, some general comments can be made. PCR-based procedures must use free DNA materials, and their performance may improve if they are

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carried out following laser microdissection [28]. Immunohistochemistry has shown clinical utility to confirm infection when yeasts have been seen in tissue and BCs were negative. The panel recommended genus-specific antibody commercially available only (e.g. Rabbit anti *C. albicans*, type A:Biotin®, Serotec, No. 1750-5557). It should be noted that only positive results are reliable and negative results do not exclude the disease. Regarding *in situ* hybridization and tissue and body fluid PCR, there are no clinically validated commercially available kits to detect fungal infections.

Detection of IC by quantification of fungal components in body fluids other than serum has not been evaluated. However, there are some reports including cases of IC and quantification of serum biomarkers, but significant findings were reported for the BDG test only [10]. According to these results, the BDG test can be *recommended* for IC detection similar to that recommendation made for candidaemia detection (Table 2).

3. What are the best tests for diagnosing chronic disseminated candidiasis?

The same recommendations made for BC, tissue and body fluid samples for the detection of IC (Table 2) can be considered for diagnosing chronic disseminated candidiasis (CDC). The panel remarked, however, that a tissue biopsy is highly advisable because CDC is rarely detected by BC. In addition, the detection of biomarkers can be useful. As for IC, the BDG test has shown to be strongly associated with clinical findings and the panel considered the test as *recommended* for CDC detection [10]. Chronic disseminated candidiasis can be diagnosed by mannan and anti-mannan quantification. A meta-analysis mentioned previously suggests that the technique is very useful in CDC cases [9]. The report included 21 cases of CDC and mannan and anti-mannan quantification test exhibited 86% of sensitivity rate. Positive results were seen 16 days in average prior to cultures.

4. What are the best tests for oropharyngeal candidiasis and oesophagitis?

The essential specimen for the detection of those diseases is a swab taken from the lesion. A biopsy is not mandatory (Table 2), but it might discriminate between infection and colonization. Swabs must be inoculated on selective media to avoid overgrowth by colonizing bacteria. Species identification and susceptibility testing are recommended in recurrent/complicated cases and in patients who have been exposed to azoles previously. When a biopsy is obtained, it must be processed according to recommendations stated in the IC diagnostic procedures section. PCR-based methods have been evaluated, but no recommendation can be made as results have not been validated in a clinical setting [5,29,30].

5. What are the best tests for *Candida* vaginitis?

Examination of swabs and vaginal secretions is very valuable in detecting this infection (Table 2). A swab is less useful for microscopy than secretions. Vaginal secretions spread directly onto a microscopy slide, and left to dry is recommended. The observation of pseudohyphae can help to detect the infection, but filaments can be observed in patient without infection. In addition, not all *Candida* spp. form filaments during infection (e.g. *C. glabrata*), and microscopy in such cases will show only yeast cells [31].

Culture of swabs and vaginal secretions are also essential investigations. Semi-quantitative techniques using fungal selective agar are recommended. Species identification and susceptibility testing are indicated in recurrent/complicated cases and in patients with prior azole exposure.

Commercial tests designed to detect vaginal candidiasis can be also used, but the panel recommended the use of validated tests only [32,33]. PCR-based procedures have not been validated, and no recommendations can be made [34].

6. When are AST recommended for patient management and when for epidemiological reasons?

Recommendations for AST were also made by the panel. The panel considered that AST must be recommended for patient management for all *Candida* strains isolated from blood and other deep sites. Experts advised that reference procedures [35–39] or validated commercial techniques should be used [40–43]. However, it should be noted that discrepant results may be obtained with commercial techniques (such as Etest™ and Sensititre YeastOne™) as compared to the reference methods particularly for isolates with borderline MIC values. Importantly, interpretation of AST results requires expertise and cautious evaluation. It is essential to ensure the endpoints generated for each species mirrors those of reference methods before reference breakpoints are adopted for interpretation of results by commercial techniques. Antifungal susceptibility testing can be useful particularly in some cases such as strains from patients exposed to antifungal agents, isolates from patients

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with clinical failure, strains belonging to rare and emerging species and species that are known to be resistant or less susceptible to antifungal drugs [44,45].

Regarding superficial isolates, AST can be recommended for patient management in cases who failed to respond to antifungal agents or relapsing infection. Surveillance cultures from patients exposed to antifungal agents could be also useful.

For epidemiological reasons, the panel recommended that all isolates from blood and deep sites should be tested using a reference method. Periodical epidemiological studies should be carried out including strains isolated from superficial sites to determine the susceptibility profiles and resistance rates for each individual centre [44,45].

Table 3 shows breakpoints to interpret AST results approved by both the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical Laboratory Standards Institute (CLSI) [46–53].

7. Is therapeutic drug monitoring indicated for patient management?

The panel indicated that TDM must be used for patients treated with 5-fluorocytosine. In addition, TDM is not normally required for drugs used (fluconazole, echinocandins and amphotericin B formulations) in the treatment for *Candida* infections except for patients with extra-corporeal membrane oxygenation (ECMO) treated with echinocandins as it can reduce the level of the antifungal being used [54–57].

Therapeutic drug monitoring is recommended if voriconazole or posaconazole is prescribed, and monitoring is highly recommended in unsatisfactory response to therapy, suspicion of toxicity or drug interaction(s), impaired liver or renal function and also in patients on ECMO [58–60].

TABLE 3. Interpretative breakpoints of antifungal agents approved by EUCAST and CLSI for susceptibility testing of *Candida*

		EUCAST			CLSI			
Antifungal	**Species**	**Susceptible**	**Intermediate**	**Resistant**	**Susceptible**	**S-DD**	**Intermediate**	**Resistant**
Amphotericin B	*C. albicans*	≤1	–	>1	NEY	NEY	NEY	NEY
	C. glabrata	≤1	–	>1	NEY	NEY	NEY	NEY
	C. krusei	≤1	–	>1	NEY	NEY	NEY	NEY
	C. parapsilosis	≤1	–	>1	NEY	NEY	NEY	NEY
	C. tropicalis	≤1	–	>1	NEY	NEY	NEY	NEY
Itraconazole	*C. albicans*	NEY	NEY	NEY	≤0.12	0.25–0.50	–	≥1
	C. glabrata	NEY	NEY	NEY	≤0.12	0.25–0.50	–	≥1
	C. krusei	NEY	NEY	NEY	≤0.12	0.25–0.50	–	≥1
	C. parapsilosis	NEY	NEY	NEY	≤0.12	0.25–0.50	–	≥1
	C. tropicalis	NEY	NEY	NEY	≤0.12	0.25–0.50	–	≥1
Fluconazole	*C. albicans*	≤2	4	>4	≤2	4	–	≥8
	C. glabrata	IE	IE	IE	–	≤32	–	≥64
	C. krusei	PT	PT	PT	PT	PT	PT	PT
	C. parapsilosis	≤2	4	>4	≤2	4	–	≥8
	C. tropicalis	≤2	4	>4	≤2	4	–	≥8
Voriconazole	*C. albicans*	≤0.125	–	>0.125	≤0.12	–	0.25–0.50	≥1
	C. glabrata	IE	IE	IE	IE	IE	IE	IE
	C. krusei	IE	IE	IE	≤0.50	IE	1	≥2
	C. parapsilosis	≤0.125	–	>0.125	≤0.12	–	0.25–0.50	≥1
	C. tropicalis	≤0.125	–	>0.125	≤0.12	–	0.25–0.50	≥1
Posaconazole	*C. albicans*	≤0.06	–	>0.06	NEY	NEY	NEY	NEY
	C. glabrata	IE	IE	IE	NEY	NEY	NEY	NEY
	C. krusei	IE	IE	IE	NEY	NEY	NEY	NEY
	C. parapsilosis	≤0.06	–	>0.06	NEY	NEY	NEY	NEY
	C. tropicalis	≤0.06	–	>0.06	NEY	NEY	NEY	NEY
Caspofungin	*C. albicans*	NEY	NEY	NEY	≤0.25	–	0.50	≥1
	C. glabrata	NEY	NEY	NEY	≤0.12	–	0.25	≥0.50
	C. krusei	NEY	NEY	NEY	≤0.25	–	0.50	≥1
	C. parapsilosis	NEY	NEY	NEY	≤2	–	4	≥8
	C. tropicalis	NEY	NEY	NEY	≤0.25	–	0.50	≥1
Micafungin	*C. albicans*	NEY	NEY	NEY	≤0.25	–	0.50	≥1
	C. glabrata	NEY	NEY	NEY	≤0.06	–	0.12	≥0.25
	C. krusei	NEY	NEY	NEY	≤0.25	–	0.50	≥1
	C. parapsilosis	NEY	NEY	NEY	≤2	–	4	≥8
	C. tropicalis	NEY	NEY	NEY	≤0.25	–	0.50	≥1
Anidulafungin	*C. albicans*	≤0.03	–	>0.03	≤0.25	–	0.50	≥1
	C. glabrata	≤0.06	–	>0.06	≤0.12	–	0.25	≥0.50
	C. krusei	≤0.06	–	>0.06	≤0.25	–	0.50	≥1
	C. parapsilosis	PT	PT	PT	≤2	–	4	≥8
	C. tropicalis	≤0.06	–	>0.06	≤0.25	–	0.50	≥1

NEY, breakpoints have not been established yet; IE, insufficient evidence to set breakpoints; PT, susceptibility testing not recommended as the species is a poor target for therapy with the drug; S-DD, susceptible dependant on dose.
Data in mg/L.

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Transparency Declarations

M.C.E. has received in the past 5 years grant support from Astellas Pharma, bioMerieux, Gilead Sciences, Merck Sharp and Dohme, Pfizer, Schering-Plough, Soria Melguizo SA, Ferrer International, the European Union, the ALBAN program, the Spanish Agency for International Cooperation, the Spanish Ministry of Culture and Education, The Spanish Health Research Fund, The Instituto de Salud Carlos III, The Ramon Areces Foundation, The Mutua Madrileña Foundation. He has been an advisor/consultant to the Panamerican Health Organization, Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer, and Schering-Plough. He has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering-Plough.

P.E.V. has received research grants from Pfizer, Astellas, Cephalon, Gilead Sciences, Merck and Schering-Plough. He is also a board member and consultant for Pfizer, MSD International, Astellas and Gilead. He has also been paid for development of educational presentations by Nadirex Internation.

M.C.A. has received grant support from Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering-Plough. She has been a consultant or at the advisory board for Gilead Sciences, Merck Sharp and Dohme, Pfizer, Pcovery, and Schering-Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering-Plough.

S.A.A. has received investigator initiated research grant support from Pfizer and speaker honoraria from Merck and Pfizer. She has been at the Advisory Board for Pfizer-Turkey.

J.B. has nothing to declare.

J.P.D. has received grant support from, Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering-Plough. He has been a consultant or on an advisory board for Astellas, Gilead Sciences, Merck Sharp and Dohme, and Pfizer. He has received remuneration for giving lectures on behalf of Gilead Sciences, Merck, and Pfizer.

H.E.J. has nothing to declare.

C.L.-F. has received grant support in the past 5 years from Astellas Pharma, Gilead Sciences, Pfizer, Schering-Plough and Merck Sharp and Dohme. She has been an advisor/consultant to Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering-Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma, Pfizer and Schering-Plough. Her travel and meeting expenses have also been paid by the above.

M.D.R. has received grants, speakers honoraria and travel support from Pfizer, Astellas, MSD and Gilead Sciences. He has also received book royalties from Blackwell Publishing and conference support from Astellas Pharma.

M.A. received, during the past 5 years, research grants and honoraria for talks and consultancy and is a board member for Merck, Pfizer and Gilead.

M.B. has received research grants from Pfizer, MSD and Astellas and is/was an advisor or received lecture honorarium from Astellas, Angelini Farmaceutici, Astra Zeneca, Aventis, Bayer, Cephalon, Cubist, Gilead, MSD, Novartis, Shionogi, Pfizer, Teva and Vifor. He is also a board member of Pfizer, Angelini Farmaceutici, Cubist, MSD, Astellas, Novartis, Astra Zeneca.

T.C. is member of the Speaker bureau and is advisor or consultant for Astellas, Baxter; bioMérieux, EISAI, Evolva, Eli Lilly Suisse, Novartis, Merck Sharp & Dohme-Chibret AG, Pfizer. Grant support from Baxter, bioMérieux, Merck Sharp and Dohme-Chibret AG, Roche Diagnostic. He has also received payment for educational presentations from MSD, Institut Pasteur and Gilead Sciences.

E.C. has participated as invited speaker to symposia organized by Gilead, Pfizer, Astellas, Merck, Novartis, and he has been member of advisory boards for Astellas, Pfizer.

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J.G. has nothing to declare.

A.H.G. has received research support from Gilead, Merck, and Sharp & Dohme, Schering. He has acted as speaker and/or consultant for Astellas, Cephalon, Gilead, Merck, Pfizer, Sharp & Dohme, Zeneus/Cephalon, Schering and Vicuron.

R.H. has been a consultant or at the advisory board for Astellas pharma, Basilea, Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer and Schering-Plough. He has been paid for talks on behalf of Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering-Plough. He has also received research grants and investigator fees for a clinical trial from Pfizer.

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B.J.K. has received research grants from Bio-Mérieux and Cephalon. He is a consultant to Pfizer and is a member of the Gilead, MSD and Pfizer speaker bureaus.

O.L. is a member of the MSD board, is a consultant for Astellas and Gilead Sciences and received grants or speaker's fees from MSD, Astellas, Gilead Sciences and Pfizer.

W.M. has received grant support from MSD and Pfizer. He had been an advisor to MSD and Pfizer. He has received honoraria for presentations on behalf of MSD/Schering-Plough, and Pfizer.

G.P. has received research grants from Gilead, Pfizer, Astra Zeneca, Novartis, Astellas, GSK and MSD, has acted as paid consultant to Janssen Cilag, Gilead, Astellas, and MSD and is a member of the Gilead, Astellas and MSD speaker' s bureaus. His travel costs have also been covered by ESCMID, Gilead, Astellas, Pfizer.

E.R. has received research support from Pfizer, Gilead, Enzon, Schering Merck, and he has made contributions in advisory boards of Gilead, Astellas, Pfizer. He has also received speaker's fees from Gilead, Cephalon, Pfizer, Wyeth, Schering, Merck, Aventis and Astellas. He has also consulted for Schering, Gilead, Astellas, Pfizer and Merck.

C.V. received grants as speaker/moderator in meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott, BMS and received grants for participation in advisory boards by Gilead, Astellas, MSD, Pfizer. Further, he obtained research grants for his institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, Novartis. He is member of the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency Member of various levels of local Infection Control, Antibiotic Stewardship, Vaccine and HIV Committees (Genoa, Liguria, Italy). A.J.U. has received research grants from MSD (Schering-Plough) and is/was an advisor or received lecture honorarium from Astellas, Aicuris, Basilea, Gilead, MSD and Pfizer.

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ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients

O. A. Cornely[1†], M. Bassetti[2†], T. Calandra[3†], J. Garbino[4†], B. J. Kullberg[5†], O. Lortholary[6,7†], W. Meersseman[8†], M. Akova[9], M. C. Arendrup[10], S. Arikan-Akdagli[11], J. Bille[3], E. Castagnola[12], M. Cuenca-Estrella[13], J. P. Donnelly[5], A. H. Groll[4], R. Herbrecht[15], W. W. Hope[16], H. E. Jensen[17], C. Lass-Flörl[18], G. Petrikkos[19], M. D. Richardson[20], E. Roilides[21], P. E. Verweij[5], C. Viscoli[22] and A. J. Ullmann[23]

1) *Department I of Internal Medicine, Clinical Trials Centre Cologne, ZKS Köln, BMBF 01KN1106, Center for Integrated Oncology CIO KölnBonn, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), German Centre for Infection Research, University of Cologne, Cologne, Germany,* 2) *Santa Maria Misericordia University Hospital, Udine, Italy,* 3) *Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland,* 4) *University Hospitals Geneva, Geneva, Switzerland,* 5) *Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands,* 6) *Service des Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants Malades, APHP, Centre d'Infectiologie Necker-Pasteur, IHU Imagine, Université Paris Descartes, Paris,* 7) *Institut Pasteur, Centre National de Référence Mycologie et Antifongiques, Unité de Mycologie Moléculaire, CNRS URA3012, Paris, France,* 8) *University Hospital Gasthuisberg, Leuven, Belgium,* 9) *Department of Medicine, Hacettepe University School of Medicine, Ankara, Turkey,* 10) *Statens Serum Institut, Copenhagen, Denmark,* 11) *Department of Medical Microbiology, Hacettepe University School of Medicine, Ankara, Turkey,* 12) *Instituto Giannina Gaslini, Children's Hospital, Genova, Italy,* 13) *Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain,* 14) *Center for Bone Marrow Transplantation and Department of Pediatric Hematology/Oncology, University Children's Hospital, Muenster, Germany,* 15) *Hôpital de Hautepierre, University of Strasbourg, Strasbourg, France,* 16) *Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK,* 17) *University of Copenhagen, Frederiksberg, Denmark,* 18) *Division of Hygiene & Medical Microbiology, Innsbruck Medical University, Innsbruck, Austria,* 19) *4th Department of Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece,* 20) *Mycology Reference Centre, University Hospital of South Manchester and Manchester Academic Health Science Centre, University of Manchester, Manchester, UK,* 21) *Third Department of Pediatrics, Aristotle University School of Medicine and Hippokration Hospital, Thessaloniki, Greece,* 22) *University of Genoa, IRCCS San Martino_IST, Genoa, Italy and* 23) *Department of Internal Medicine II, Julius-Maximilians-University, Würzburg, Germany*

Abstract

This part of the EFISG guidelines focuses on non-neutropenic adult patients. Only a few of the numerous recommendations can be summarized in the abstract. Prophylactic usage of fluconazole is supported in patients with recent abdominal surgery and recurrent gastrointestinal perforations or anastomotic leakages. *Candida* isolation from respiratory secretions alone should never prompt treatment. For the targeted initial treatment of candidaemia, echinocandins are strongly recommended while liposomal amphotericin B and voriconazole are supported with moderate, and fluconazole with marginal strength. Treatment duration for candidaemia should be a minimum of 14 days after the end of candidaemia, which can be determined by one blood culture per day until negativity. Switching to oral treatment after 10 days of intravenous therapy has been safe in stable patients with susceptible *Candida* species. In candidaemia, removal of indwelling catheters is strongly recommended. If catheters cannot be removed, lipid-based amphotericin B or echinocandins should be preferred over azoles. Transoesophageal echocardiography and fundoscopy should be performed to detect organ involvement. Native valve endocarditis requires surgery within a week, while in prosthetic valve endocarditis, earlier surgery may be beneficial. The antifungal regimen of choice is liposomal amphotericin B +/− flucytosine. In ocular candidiasis, liposomal amphotericin B +/− flucytosine is recommended when the susceptibility of the isolate is unknown, and in susceptible isolates, fluconazole and voriconazole are alternatives. Amphotericin B deoxycholate is not recommended for any indication due to severe side effects.

Keywords: Candidiasis, Guideline, non-neutropenic, prophylaxis, treatment

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Corresponding authors: O. A. Cornely, Department I for Internal Medicine, University of Cologne, 50924 Cologne, Germany
E-mail: oliver.cornely@ctuc.de
A. J. Ullmann, Infectious Diseases, Department of Internal Medicine II, Julius-Maximilians-University, Oberdürrbacher Str. 6, 97080 Würzburg, Germany
E-mail: andrew.ullmann@uni-wuerzburg.de

*European Society for Clinical Microbiology and Infectious Diseases.
†Members of the subgroup committee mainly responsible setting up this manuscript.

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Introduction

Invasive candidiasis remains a challenging complication, which frequently occurs in patients with one or more underlying diseases or surgical interventions. In recent point prevalence studies, a candidaemia incidence of 6.9 per 1000 ICU patients was reported, and 7.5% of ICU patients received antifungal therapy [1,2]. Candidaemia increases mortality rates in the range of 20–49% [3,4], but still there are many open management questions.

The unmet medical needs surrounding candidaemia and invasive candidiasis are defined in general from diagnosis to prophylaxis, empiric and pre-emptive strategies to treatment. So far, the scientific community has not achieved to accurately predict invasive candidiasis and thus to define populations that benefit from prophylaxis or early treatment [5]. Although it is well known that treatment is being initiated too late in the majority of patients, identification of the optimal time point to commence antifungal therapy remains challenging [6,7]. Intertwined with this problem is insufficient support of reliable mycological assays preventing timely and diagnosis-driven early treatment initiation [173].

With the diversity of various groups of patients with organ involvement beyond the bloodstream, a body of diverse evidence on the best treatments and infectious diseases management decisions, for example, treatment duration is provided.

In the light of the medical need to analyse the scientific evidence in the field of invasive *Candida* diseases, the ESCMID European Fungal Infection Study Group (EFISG) developed comprehensive practical guidance for microbiologists and clinicians to facilitate evidence-based decision making.

This guideline follows the clinical events in a chronological order. Prophylaxis in patient populations at risk for invasive *Candida* disease is followed by fever- and diagnosis-driven approaches to early therapy and finally targeted therapy. Important clinical questions on catheter management to step-down strategies are being addressed. Specific situations in deep tissue candidiasis are cherished, and for each topic, a table lists the medical/scientific evidence.

Methods

An expert group (OAC, MB, TC, JG, BJK, OL and WM) was set up by EFISG and searched the literature. Documents and views were shared by email, teleconferences, and face-to-face meetings during 2010–2012. Once a first consensus was reached, the preliminary recommendations were presented to the whole group, that is, the other authors, discussed, developed further, and finalized as a group consensus. The methods to evaluate the quality of evidence and to reach group consensus recommendations are described in this issue of *Clinical Microbiology and Infection* [172]. Definition of the strength of recommendation is given in Table 1. The quality of the published evidence is defined in Table 2. Grouping quality of evidence into three levels only may lead to diverse types of published evidence being assigned specifically a level II. To increase transparency in the evaluation of the evidence, we added an index (Table 2) to the level II recommendations, where appropriate. Of note, the strength of recommendation and the quality of evidence were assigned in two separate evaluations, thus allowing, for example, a recommendation strongly supporting a procedure even if there is a lower level of evidence.

Results

Prophylaxis

Antifungal prophylaxis has been discussed as a promising approach in ICU patients. At this moment, the optimal target population for antifungal prophylaxis remains unknown, as this question has not been sufficiently addressed in clinical trials. Some special populations though have been enrolled in randomized clinical trials, and recommendations for these can be given.

TABLE 1. Definition of the strength of recommendation

Grade	ESCMID EFISG
A	Strongly supports a recommendation for use
B	Moderately supports a recommendation for use
C	Marginally supports a recommendation for use
D	Supports a recommendation against use

TABLE 2. Definition of the quality of evidence

ESCMID EFISG
Level
I Evidence from at least one properly designed randomized, controlled trial
II Evidence from at least one well-designed clinical trial, without randomization, from cohort or case-controlled analytical studies (preferably from >1 centre); from multiple time series or from dramatic results of uncontrolled experiments
III Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies or reports of expert committees
Index (for quality of evidence II)
r Meta-analysis or systematic review of randomized controlled trials
t Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation
h Comparator group is a historical control
u Uncontrolled trial
a Published abstract (presented at an international symposium or meeting)

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Evidence. Patients who had undergone abdominal surgery recently and who had recurrent gastrointestinal perforations or anastomotic leakages were treated either with fluconazole 400 mg/day or with placebo in order to prevent intraabdominal *Candida* infection. The rate of intraabdominal candidiasis was significantly lower in the fluconazole prophylaxis group. This clinical trial exhibited high technical quality, but was performed in a very high baseline incidence population and is limited by enrolling 43 evaluable patients only [8]. In a small non-comparative trial, standard dosed caspofungin was evaluated in the same indication, but no evidence can be derived [9]. In a large prophylaxis trial, critically ill surgical patients with an expected ICU stay of ≥3 days were randomized to receive either fluconazole 400 mg/day or placebo. The primary endpoint was the time to fungal infection, which was significantly delayed in the fluconazole prophylaxis group. The trial was well designed and enrolled 260 patients. A limitation of the study is the inclusion of presumed invasive fungal infection, defined for example, by repeatedly positive urine cultures and catheter tips with ≥15 yeast colonies, into the primary endpoint [10]. In another study, patients ventilated for 48 h and expected to remain ventilated for another ≥72 h received selective digestive decontamination with polymyxin B, neomycin and vancomycin and were randomized to receive fluconazole 100 mg/day or placebo. This trial was well designed, and 204 patients were randomized. Candidaemia was more successfully prevented in fluconazole recipients, but the selective digestive decontamination regimen used in this clinical trial is not a standard in most countries [11–13]. Meta-analyses of the clinical trials above and some other studies on highly selected populations found fluconazole 400 mg/day to be superior to placebo in preventing invasive fungal infection in critically ill surgical patients [14–18]. A more recent clinical trial compared caspofungin 50 mg/day with placebo for prophylaxis in a highly selected population of ventilated patients receiving antibiotics, having a central venous catheter and fulfilling at least one of the following criteria: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids or other immunosuppressant medication. The primary endpoint of this trial was the incidence of proven and probable invasive candidiasis according to EORTC/MSG definitions [19]. The investigators found a trend only towards a reduced incidence of invasive candidiasis [5]. Other antifungals have been evaluated in prophylactic indications [20–22]. For ketoconazole 200 mg/day, evidence of prophylactic benefit is weak while adverse events and drug interactions limit its use in general [22]. The same is true for itraconazole 400 mg/day [21]. Nystatin 4 Mio IU/day has been evaluated, but concept and patient setting are basically outdated [20]. Intravenous amphotericin B and the echinocandins have not been sufficiently evaluated in this indication [23]. Antifungal prophylaxis in solid organ transplant recipients is not part of this guideline.

Of note, none of the trials proved a reduction in overall or attributable mortality. All trials were lacking power to address the potential emergence of less azole-susceptible strains during prophylaxis. Apart from historical control studies in intensive care and abdominal surgical populations, this has been shown in prophylactic settings in haematology during substantially longer azole exposure periods [24–26]. Selection of less-susceptible strains remains a caveat against broadly using antifungals in populations where substantial benefit has not been proven.

Recommendations. Fluconazole prophylaxis against invasive candidiasis is recommended in patients who recently underwent abdominal surgery and had recurrent gastrointestinal perforations or anastomotic leakages. For further recommendations, refer to Table 3.

Fever-driven approach (empiric)

We defined empiric therapy as a fever-driven approach in the clinical situation of a patient at risk for invasive candidiasis who is persistently febrile with no microbiological evidence of infection.

Evidence. The value of initiating antifungal therapy in this situation has been addressed in a number of retrospective studies. Incubation time [27] and time from first positive blood culture drawn to initiation of empiric antifungal therapy correlated with mortality increases [6,28]. Similarly, in a population-based retrospective study, empiric antifungal treatment was associated with higher survival rates, if the isolate turned out to be susceptible to the empiric regimen [29]. Another retrospective study in patients with septic shock due to any cause found empiric antifungal therapy was given infrequently, and those with invasive fungal infection not receiving empiric antifungals had a statistically significantly higher mortality [7].

Although uncontrolled, all of these studies suggest that initiating empiric therapy may be beneficial to reduce overall mortality, but none could identify reliable triggers for antifungal treatment. They analysed patients with candidaemia but not the whole population of febrile patients.

One randomized double-blind placebo-controlled clinical trial evaluated fluconazole 800 mg/day in 270 adult ICU patients with an APACHE II score >16. Rates of invasive candidiasis were not statistically different between the two groups. The primary endpoint was driven by resolution of

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TABLE 3. Recommendations on antifungal prophylaxis in ICU patients

Population	Intention	Intervention	SoR	QoE	References	Comment
Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages	To prevent intraabdominal *Candida* infection	Fluconazole 400 mg/day	B	I	[8]	Placebo *N* = 43
		Caspofungin 70/50 mg/day	C	II_u	[9]	Single arm *N* = 19
Critically ill surgical patients with an expected length of ICU stay ≥3 day	To delay the time to fungal infection	Fluconazole 400 mg/day	C	I	[10]	Placebo *N* = 260
Ventilated for 48 h and expected to be ventilated for another ≥72 h	To prevent invasive candidiasis/candidaemia	Fluconazole 100 mg/day	C	I	[162]	Placebo *N* = 204 SDD used
Ventilated, hospitalized for ≥3 day, received antibiotics, CVC, and ≥1 of: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids, immunosuppression	To prevent invasive candidiasis/candidaemia	Caspofungin 50 mg/day	C	II_a	[5]	Placebo *N* = 186 EORTC/MSG criteria used
Surgical ICU patients	To prevent invasive candidiasis/candidaemia	Ketoconazole 200 mg/day	D	I	[22]	Placebo *N* = 57
Critically ill patients with risk factors for invasive candidiasis/candidaemia	To prevent invasive candidiasis/candidaemia	Itraconazole 400 mg/day	D	I	[21]	Open *N* = 147
Surgical ICU with catabolism	To prevent invasive candidiasis/candidaemia	Nystatin 4 Mio IU/day	D	I	[20]	Placebo *N* = 46

SoR, Strength of recommendation; QoE, Quality of evidence; ICU, intensive care unit; CVC, central venous catheter; IU, international units.
The table displays the published evidence; therefore, other available antifungal agents are not mentioned here.

fever, and empirical fluconazole treatment did not improve outcome when compared with placebo [30].

Recommendations. Early treatment of presumed fungaemia is presumably associated with higher survival rates, but the optimal time point for initiating empiric antifungal treatment remains undetermined. Due to lack of data, no recommendation can be given for choosing a specific drug for fever-driven therapy. In general, such choice should be based on local epidemiology and drug–drug interactions in the individual patient and should be made among the same drugs as recommended for candidaemia. Further recommendations are given in Table 4.

Diagnosis-driven approach (pre-emptive)

We defined pre-emptive therapy as therapy triggered by microbiological evidence of candidiasis without proof of invasive fungal infection.

Evidence. Several studies have addressed diagnosis-driven therapy on grounds of detecting (1,3)-β-D-glucan in serum or plasma. In a study on 46 ICU patients without infection or with confirmed bacterial or fungal infection, glucan test results (G-test; Associates of Cape Cod, East Falmouth, MA, USA) correlated with infection, but not with fungal infection. The authors suggested using the test to rule out invasive fungal infection [31]. This was the key finding in a study using the Fungitell™

TABLE 4. Recommendations on fever-driven and diagnosis-driven therapy of candidaemia and invasive candidiasis

Population	Intention	Intervention	SoR	QoE	References
Adult ICU patients with fever despite broad-spectrum antibiotics and APACHE II >16	To resolve fever	Fluconazole 800 mg/day	D	I	[30]
ICU patients persistently febrile, but without microbiological evidence	To reduce overall mortality	Fluconazole or echinocandin	C	II_u	[28] [163] [164] [7] [27]
ICU patients with candida isolated from respiratory secretions	To cure invasive candidiasis or candidaemia early	Any antifungal	D	II_u	[42]
ICU patients with positive (1,3)-β-D-glucan test[a]	To cure invasive candidiasis or candidaemia early	Any antifungal	C	II_u	[39] [31] [37] [35] [32] [36] [34] [33]
Any patient with *Candida* isolated from a blood culture	To cure invasive candidiasis	Antifungal treatment	A	II	[46] [47] [48] [49]

APACHE, acute physiology and chronic health evaluation.
[a]The (1,3)-β-D-glucan tests have low specificity and sensitivity with false-positive results in the presence of haemodialysis, other fungal or bacterial infection, wound gauze, albumin or immunoglobulin infusion.

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(Assoc. of Cape Cod) test, too [32]. Another group of investigators found glucan (Fungitec™; Seigakaku Kogyo, Tokyo, Japan) testing useful in predicting invasive fungal infection, but in a very small population of 32 patients only [33]. During twice weekly monitoring in long-term ICU patients, glucan concentrations (Glucatell™; Cape Cod) were higher in individuals with proven fungal infection than in those without. As patients with invasive fungal infection had more bacterial infections and other intercurrent complications, the test result could still not clearly distinguish between both groups [34]. Similar results were found in a surgical ICU patient group (N = 57) and in a mixed ICU population (N = 95) where higher glucan concentrations (Fungitell™) were found in those with invasive candidiasis, but still the positive predictive value was limited [35,36]. Findings from a retrospective study on a larger number of patients (N = 871) were in favour of the test (Fungitell™), but documented generally higher glucan concentrations in patients on haemodialysis and in those receiving albumin or intravenous immunoglobulin infusions [37]. Other reasons for positive test results in the absence of invasive candidiasis have been described due to (1,3)-β-D-glucan-containing cell walls of a variety of fungi, for example, *Aspergillus* or *Histoplasma* [32,38]. Indeed, the Fungitell™ assay has been suggested useful in the diagnosis of pneumocystis pneumonia as well [39]. A discussion of glucan tests and their cut-offs to positivity can be found in the ESCMID Candida Guidelines on Diagnostic Procedures in this issue [173]. In some of the studies above, it has been stated that a negative glucan test practically rules out invasive candidiasis. Currently, the glucan tests cannot reliably confirm invasive candidiasis, although there may be a role as part of a set of diagnostic tools and patient characteristics.

Recommendations on mannan and anti-mannan antibody detection is part of the EFISG guideline on diagnosis of invasive candidiasis [173].

A controversial issue is the initiation of antifungal therapy upon *Candida* isolation from respiratory secretions. Two forms of pulmonary candidiasis have been distinguished, that is, pulmonary abscesses resulting from haematogenous spread during candidaemia, especially in febrile neutropenic patients, and direct invasion of bronchial and lung tissues. Most articles on the topic of pulmonary candidiasis were published in the 1970s and 1990s. There are hardly any data on ICU populations, but case series of patients with haematological malignancy and stem cell recipients [40,41]. While *Candida* can frequently be isolated from respiratory secretions, it appears that *Candida* invading the lung tissue is a very rare event. In a recent prospective autopsy study (N = 232) on ICU patients, a total of 58% had proven pneumonia. Regardless of whether *Candida* had been isolated pre-mortem or not, in neither case histopathological proof of *Candida* tissue invasion was found [42].

Recommendations. Candida isolation from respiratory secretions should never trigger treatment, but rather be interpreted as one site of colonization among others. (1,3)-β-D-glucan detection in serum or plasma prompting antifungal treatment is marginally supported. Detailed recommendations are given in Table 4.

Targeted treatment

Candida isolated from a single peripheral blood culture or a single central-line blood culture defines candidaemia [19,43,44]. Previous definitions may have described asymptomatic patients with a blood culture positive for *Candida*, and it has been debated whether there are patients who do not need antifungal treatment despite a positive blood culture [45]. This appears to be a very rare clinical situation, as usually blood cultures are triggered by a clinical sign, for example, fever. Each case of candidaemia, even from surveillance blood cultures in asymptomatic patients requires targeted treatment [46–49].

Evidence. A plenitude of well-designed clinical trials evaluated antifungals for the initial treatment of candidaemia and invasive candidiasis. Amphotericin B deoxycholate clearly is a very potent drug against *Candida*, but the well-documented significant toxicity justifies a recommendation against using this compound [50–55]. In the past, several approaches aimed at reducing toxicity, for example, continuous intravenous administration, but efficacy of this strategy in candidiasis remains unclear [56]. Amphotericin B lipid complex has been evaluated in candidaemia, but the single randomized trial to date has been published as abstract only. Amphotericin B lipid complex appeared to be less nephrotoxic than the deoxycholate formulation although not more effective [57], findings which were supported by a phase IV study [58]. As opposed to laboratory-confirmed adverse events, clinically defined side effects, such as infusion-related fever and chills, tend to be underestimated in uncontrolled post-marketing studies. When ABLC was compared to liposomal amphotericin B in persistently febrile neutropenic patients, infusion-related adverse events occurred very frequently [59]. Data on amphotericin B colloidal dispersion stem from a non-randomized, non-comparative study describing nephrotoxicity in the same range as found with amphotericin B lipid complex [60]. Liposomal amphotericin B and amphotericin B deoxycholate have not been compared directly in patients with candidaemia. But, liposomal amphotericin B appears at least as effective, but less toxic than the deoxycholate formulation when considering results from a large clinical trial on candidaemia and invasive candidiasis evaluating liposomal amphotericin B and micafungin [61]. Compared to micafungin,

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efficacy was similar, but renal toxicity was higher with liposomal amphotericin B [61,62]. Caspofungin when compared to amphotericin B deoxycholate was as effective, but significantly less toxic [55]. A clinical strategy became feasible, which avoided amphotericin B toxicity without losing efficacy. Two doses of micafungin (100, 150 mg/day) were compared with caspofungin in a phase III trial. All three regimens were similarly effective and safe [63]. While all echinocandin trials above proved statistical non-inferiority of the experimental study drug as compared to standard regimens, anidulafungin was found to be superior over fluconazole [64]. In particular, the outcomes for patients with *Candida albicans* were significantly better with anidulafungin (81%) than with fluconazole (62%). The latter result remained valid in a subsequent subgroup analysis of ICU patients: global response for anidulafungin 67% vs. fluconazole 47% [65].

With regard to *Candida,* all three echinocandins exhibit a broad spectrum activity; acquired resistance is rare, although there has been a first large epidemiological evaluation describing acquisition of resistance genes in *Candida glabrata* [66]. There is an ongoing debate on whether echinocandins are appropriate for treating *Candida parapsilosis*, because minimal inhibitory concentrations are found to be higher than those of other *Candida* species. Overall, that is, clinical and microbiological, response rates in *C. parapsilosis* infection were not statistically significantly different throughout the echinocandin trials: for caspofungin/amphotericin B, the success rates were 70% and 65%, for micafungin/liposomal amphotericin B 89.2% and 86.7%, for caspofungin/micafungin 100/150 rates were 64.3%, 75.9% and 71.4%, and for anidulafungin/fluconazole, they were 64% and 83% [55,61,63]. However, there were numerically higher numbers of persistent fungaemia due to *C. parapsilosis* during caspofungin as compared to amphotericin B deoxycholate treatment [55], and during standard dose caspofungin as compared to high dose, that is, 150 mg/day, caspofungin [67], and the eradication rate in *C. parapsilosis* fungaemia was lower with anidulafungin than with fluconazole [64]. It is important to note that none of these trials were powered to detect such differences.

Two further aspects we considered important when interpreting the latter trial are (i) the microbiological eradication rate as well as the overall success rate in *C. albicans* infection was higher with anidulafungin than with fluconazole and (ii) *Candida krusei* infection was excluded from the anidulafungin trial, because of fluconazole being the comparator drug [64].

In the clinical trials, all three echinocandins were well tolerated and appeared very safe. Micafungin though carries a warning label against use unless other antifungals are not appropriate by the European Medicines Agency, which reflects results of rats developing liver tumours after very long and high-dosed exposure [68]. This statement has elicited some debate in terms of its relevance to humans, but has not been withdrawn or disproved so far.

An advantage of the echinocandin class is the low potential for drug–drug interactions. For anidulafungin, no interactions have been described, and for micafungin, very few relevant interactions need to be considered [68,69]. Co-administering caspofungin with rifampin lowers caspofungin exposure, and it has been recommended to increase the dose of caspofungin in the rare cases, where both drugs need to be administered concomitantly. In addition, caspofungin dose has to be increased in patients with a high body weight [70].

For many years, fluconazole was considered the drug of choice for candidaemia [71–73]. This was based on a great number of clinical trials evaluating fluconazole in this indication [52–54,64,74–76]. As anidulafungin was superior over fluconazole in patients with candidaemia, especially those infected with *C. albicans*, we do no longer consider fluconazole as the drug of choice [64]. Fluconazole was inferior in the subgroup of patients with high APACHE scores and is known to have a limited spectrum of activity, being inactive against *C. krusei* and being considered hardly active in *C. glabrata* infection. Microbiologically, it might though be the better drug against *C. parapsilosis*, which is supported by a trend towards better outcomes in the comparative trial [64], but clinical proof is not in support of this. There have been no trials with sufficient power to assess non-inferiority of echinocandins for *C. parapsilosis*. In a large clinical trial, voriconazole was non-inferior to amphotericin B deoxycholate followed by fluconazole [43], and voriconazole offers an important additional treatment option for first-line and salvage situations [77,78]. Still there are certain limitations, that is, the multiple drug–drug interactions [79], the limit of the intravenous use to 14 days duration [79] and the variable pharmacokinetics of the drug [80]. Itraconazole yielded negative results when compared to fluconazole [76]. There are no published data on posaconazole treatment of candidaemia.

Very few clinical trials used combination treatment. Lipid-based amphotericin B was supplemented with placebo or efungumab, a monoclonal antibody targeting heat shock protein 90 (HSP-90), in 139 patients. The study design and analysis drew substantial criticism for (i) enrolling an ill-defined patient population, for example, symptomatic candiduria, (ii) enrolling patients with negative fungal cultures and (iii) excluding patients from the efficacy population who died while on treatment [81]. Furthermore, the trial allowed extensive prior antifungal treatment, used a short, 10-day, treatment time until response evaluation and did not specify

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the proportion of patients receiving which type of lipid-based amphotericin B formulation.

The combination of amphotericin B deoxycholate and fluconazole has been as effective as fluconazole monotherapy in a randomized trial, but patients had an increased risk of toxicity and no survival benefit [74]. A small study (N = 72) comparing fluconazole with amphotericin B deoxycholate and 5-flucytosine showed no difference in overall response to treatment [75].

Recommendations. Targeted treatment of candidaemia with echinocandins is strongly recommended. The recommendation for liposomal amphotericin B or voriconazole is less stringent, and fluconazole is recommended with marginal strength only, except for *C. parapsilosis*. For detailed recommendations, refer to Table 5.

Duration of targeted treatment, step-down to oral treatment and diagnostics in candidaemia

Evidence. The duration of treatment depends on the extent of organ involvement. In a population without documented organ involvement, treatment aims to clear the infection and at the same time to avoid deep-organ involvement. This can be achieved by treating for 14 days after the end of candidaemia [82]. To determine the end of candidaemia, at least one blood culture per day should be taken until culture results come back negative. Treatment can probably be simplified by stepping down to oral fluconazole after 10 days of intravenous treatment, if the patient is stable, tolerates the oral route and if the species is susceptible [55,63,64].

The diagnostic procedures to detect organ involvement comprise transoesophageal echocardiography, fundoscopy and search for a thrombus. A recent observational study found infectious endocarditis in 8.3% of patients with candidaemia; the majority of these patients had no well-established risk factors, that is, vascular prosthesis or persistent candidaemia [83].

Some prospective studies addressed ocular candidiasis as complication of candidaemia. The diagnostic approach was usually based on weekly eye examinations. Immunosuppression and repeatedly positive blood cultures are risk factors

TABLE 5. Recommendations on initial targeted treatment of candidaemia and invasive candidiasis in adult patients

Intervention	SoR	QoE	References	Comment
Anidulafungin 200/100 mg	A	I	[64]	Consider local epidemiology (*Candida parapsilosis*, *Candida krusei*), less drug–drug interactions than caspofungin
Caspofungin 70/50 mg	A	I	[67] [55] [63]	Consider local epidemiology (*C. parapsilosis*)
Micafungin 100 mg	A	I	[61] [63]	Consider local epidemiology (*C. parapsilosis*), less drug–drug interactions than caspofungin, consider EMA warning label
Amphotericin B liposomal 3 mg/kg	B	I	[61] [62]	Similar efficacy as micafungin, higher renal toxicity than micafungin
Voriconazole 6/3 mg/kg/day[a,b]	B	I	[43] [78] [77]	Limited spectrum compared to echinocandins, drug–drug interactions, limitation of IV formulation in renal impairment, consider therapeutic drug monitoring
Fluconazole 400–800 mg[a]	C	I	[165] [53] [74] [54] [64] [76] [75] [73] [72]	Limited spectrum, inferiority to anidulafungin (especially in the subgroup with high APACHE scores), may be better than echinocandins against *C. parapsilosis*
Amphotericin B lipid complex 5 mg/kg	C	II_a	[57] [58]	
Amphotericin B deoxycholate 0.7–1.0 mg/kg	D	I	[50] [51] [165] [53] [54] [55]	Substantial renal and infusion-related toxicity
Amphotericin B deoxycholate plus fluconazole	D	I	[74]	Efficacious, but increased risk of toxicity in ICU patients No survival benefit
Amphotericin B deoxycholate plus 5-fluorocytosine	D	II	[75]	
Efungumab plus lipid-associated amphotericin B	D	II	[166]	
Amphotericin B colloidal dispersion	D	II_a	[60]	
Itraconazole	D	II_a	[76]	
Posaconazole	D	III	No reference found	

EMA, European Medicines Agency.
Comparative clinical trials did not prove a survival benefit of one treatment over another. Primary intention of treating candidaemia is clearing the blood stream.
[a]Not all experts agreed, SoR results from a majority vote.
[b]The licensed maintenance dosing is 4 mg/kg/day.

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for eye involvement and should prompt fundoscopic evaluation [84,85]. Other risk factors coincided with those for candidaemia [86]. In a large clinical trial, fundoscopy revealed ocular candidiasis in 16% of patients with candidaemia, the majority had eye involvement upon diagnosis of candidaemia and additional cases were detected during treatment. Most of the patients had chorioretinitis while endophthalmitis was uncommon (1.6%) [43,87].

In patients with a central venous catheter or a peripherally inserted central catheter, the possibility of a thrombus should be taken into account.

Recommendations. For uncomplicated candidaemia, treatment duration of 14 days after the end of candidaemia is recommended. The end of candidaemia should be determined by at least one blood culture per day until negativity. Transoesophageal echocardiography and fundoscopy should be performed to detect organ involvement. Switching to oral treatment can be considered after 10 days of intravenous therapy. For detailed recommendations, refer to Table 6.

Catheter-related blood stream infection

In general, indwelling lines need to be removed early after diagnosing catheter-related candidaemia; however, removal or exchange is not always possible. As the predominant mode of device-related infections is likely biofilm formation [88], certain differences in antifungal activity on *Candida* grown in biofilms vs. planktonic cells may help decision making. Liposomal amphotericin B, amphotericin B lipid complex, caspofungin and micafungin were active against *Candida* cells in biofilms, while cells were resistant towards amphotericin B deoxycholate, fluconazole, ravuconazole and voriconazole [89]. In animal models, amphotericin B lipid complex and anidulafungin reduced candida cell numbers in biofilms, while fluconazole did not [90,91].

Evidence. Duration of candidaemia: In a prospective randomized clinical trial comparing fluconazole with amphotericin B deoxycholate for candidaemia in non-neutropenic patients [53], the exchange of catheters – not over a guidewire – within the first 24 h was associated with a shorter duration of candidaemia [92]. A *post hoc* analysis of two pooled phase III trials comparing micafungin to caspofungin or liposomal amphotericin B (N = 842) did not find an improved time to mycological eradication, if central venous catheters were removed within 24 or 48 h [61,63,93].

Impact of catheter removal on mortality: Catheter removal was identified as a protective factor in a prospective study on 272 episodes of candidaemia [94]. A population-based study analysing 345 cases of candidaemia concluded that catheter removal was associated with an improved probability of survival [95,96]. In a retrospective analysis on 92 patients with cancer, removal of non-tunnelled central venous catheters ≥72 h after diagnosis of candidaemia was associated with a significantly decreased survival rate, [97] and in a univariate analysis on 244 ICU patients with candidaemia, catheter removal within 24 h was associated with better survival [73]. Early removal of central venous catheters, that is, within 24 or 48 h, had no impact on survival at 28 or 42 days in the *post hoc* analysis of the two pooled micafungin phase III trials [93]. However, in a recent individual patient level (n = 1915) pooled analysis of seven prospective randomized controlled trials for treatment of invasive candidiasis and candidaemia, the removal of a central venous catheter was associated with decreased mortality (OR, 0.50; 95% CI, 0.35–0.72, p = 0.0001) [98].

Recommendations. In candidaemia, removal of indwelling intravascular catheters is strongly recommended. When catheter removal is not possible, lipid-based amphotericin B formulation or an echinocandin is preferable. For detailed recommendations, refer to Table 7.

TABLE 6. Recommendations on the duration of targeted treatment, step-down to oral treatment and diagnostics in candidaemia

Population	Intention	Intervention	SoR	QoE	References
Candidaemia with no organ involvement detected	To avoid organ involvement	Treat for 14 days after the end of candidaemia	B	II	[82]
		Take at least one blood culture per day until negative	B	III	No reference found
	To detect organ involvement	Transoesophageal echocardiography	B	II_a	[83]
		Fundoscopy	B	II	[87] [84] [85] [86]
		If CVC, PICC or intravascular devices, search for thrombus	B	III	No reference found
Any	To simplify treatment	*Step-down to fluconazole after 10 days of IV, if species is susceptible, patient tolerates PO, and patient is stable	B	II	[64] [55] [63]

CVC, central venous catheter; PICC, peripherally inserted central catheter.
*If *C. parapsilosis* is identified, step-down to fluconazole may occur earlier.

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Urinary tract infection

Candiduria is commonly encountered in hospitalized patients, particularly those with a urinary catheter. Candiduria is indicative for a wide spectrum of conditions which may or may not require treatment.

Evidence. Asymptomatic candiduria has been followed long term, but no adverse consequences have been described [99]. Funguria resolved without specific treatment in 76% of a large (N = 861) clinical cohort [100]. In a well-designed trial, fluconazole was superior over placebo in clearing candiduria, but at 2-week follow-up candiduria rates were similar between both groups. Removal of the urinary catheter was the most promising intervention [101]. Bladder irrigation appeared as a rarely used alternative, if treatment is judged necessary [100,102]. In symptomatic candida cystitis, fluconazole has been advocated as well as amphotericin B deoxycholate with or without 5-flucytosine, but clinical data are sparse for all these approaches [100,103]. In the rare cases of fungus balls, surgical intervention is the only promising treatment option [104,105]. Echinocandins do not achieve high urine concentrations and are thus rarely considered in urinary tract infection. Some cases though have successfully been treated with caspofungin. These were partly candidaemias with concomitant candiduria and partly infections limited to the urinary tract [106]. For candida pyelonephritis, fluconazole and amphotericin B deoxycholate each with or without flucytosine may be used, but clinical trials have not been performed.

Recommendations. Asymptomatic candiduria should not be treated, while symptomatic cystitis should be treated with fluconazole, if the isolate is susceptible. Fungus balls or casts in the pyelum or urinary bladder need surgical intervention. To cure pyelonephritis fluconazole as well as lipid-based amphotericin B are recommended either alone or in combination with flucytosine. For detailed recommendations, refer to Table 8.

Ocular candidiasis

Ocular candidiasis may cause pain or disturbed vision, but should rather be diagnosed prior to becoming clinically symptomatic [86,107]. There are two forms of ocular candidiasis. Chorioretinitis is the inflammation of the choroid and the retina, while endophthalmitis is the inflammation of the vitreous body. Fungal endophthalmitis may develop from chorioretinitis as advanced disease and is associated with poor visual outcomes [108]. Most publications in this field report on individual cases or small series, and not all clearly differentiate between the two forms of ocular involvement.

Evidence. Amphotericin B deoxycholate has been advocated for ocular candidiasis, but dosing information was not always disclosed in the early reports [107,109,110]. Amphotericin B deoxycholate followed by fluconazole has been used successfully to treat ocular involvement in the voriconazole phase III trial [43,87]. Information on amphotericin B lipid complex use in ocular candidiasis is sparse. One case of breakthrough ocular candidiasis during amphotericin B lipid complex treatment has been described [111], and another case in which amphotericin B lipid complex was successfully used with concomitant flucytosine [112]. In a rabbit model evaluating the penetration of amphotericin B deoxycholate, liposomal amphotericin B and amphotericin B lipid complex, the highest penetration into the eye was achieved with the liposomal formulation [113,114]. Intravitreal injection of amphotericin B deoxycholate 5–10 μg dissolved in 0.1 mL sterile water is part of standard approaches and frequently combined with systemic antifungals and surgery [110,115].

All three echinocandins appear to have limited penetration into the eye [116–118]. With caspofungin treatment, varying outcomes have been reported, some patients failed treatment [116,119], while only two patients have been described who responded successfully [120,121].

Successful use of fluconazole has been reported in case series, where it was used at doses varying from 100 to 400 mg

TABLE 7. Recommendations on catheter management in candidaemia

Population	Intervention	SoR	QoE	References
Central venous catheter can be removed	Remove indwelling lines (not over a guidewire)	A	II_r	[98]
Central venous catheter cannot be removed	Echinocandin, liposomal amphotericin B or amphotericin B lipid complex	B	II_r	[98] [90] [89] [91] [93] [92]
	Azole or amphotericin B deoxycholate	D	II_r	[95] [98] [73] [97] [96] [94]

Interventions are intended to clear candidaemia and to improve survival.

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TABLE 8. Recommendations on *Candida* urinary tract infections

Population	Intention	Intervention	SoR	QoE	References
Asymptomatic	To clear candiduria	None[a]	A	II_u	[100] [99]
		Fluconazole 200 mg for 14 days[b]	C	I	[100] [101]
		Removal of urinary catheter	B	I	[101]
		Amphotericin B deoxycholate bladder irrigation	C	$II_{r,u}$	[100] [102]
Cystitis	To cure	Fluconazole[b]	A	III	[100]
		Amphotericin B deoxycholate +/– flucytosine	B	III	
Fungus balls	To cure	Surgical intervention	A	III	[104] [105]
Pyelonephritis	To cure	Caspofungin 70/50 mg for 9–28 days	C	III	[106]
		Fluconazole +/– flucytosine[b]	A	III	No reference found
		Lipid-based amphotericin B +/– flucytosine	A	III	No reference found

[a]In pre-operative patients, treatment is indicated to suppress candiduria.
[b]If species is susceptible.

for at least two and up to 8 weeks. A number of these patients were treated with concomitant systemic amphotericin B deoxycholate [122–125]. Overall fluconazole 400 mg alone appeared to be effective in less-advanced disease [126].

In advanced disease, a combined strategy of surgical intervention with intraocular amphotericin B deoxycholate, and systemic fluconazole has successfully been applied [110]. Systemic antifungal treatment duration varied between 2 and 12 weeks [110,127]; an individual decision will usually take reduction of immunosuppression and the extent of ocular candidiasis into consideration.

More recently, intravitreal voriconazole has been evaluated, and in animal models, doses of 25 mg/L vitreous, that is, 100 μg absolute in an adult human eye, were found to be safe [126,128]. Published cases were frequently treated with combined approaches, so that the efficacy of voriconazole monotherapy has not yet been defined [126,129,130]. In the *post hoc* analysis of eye involvement in the voriconazole phase III trial on candidaemia, treatment was successful in most cases, but endophthalmitis was rare [87].

Recommendations. In ocular candidiasis, liposomal amphotericin B either alone or combined with flucytosine is recommended when the susceptibility of the isolate is unknown. In susceptible isolates fluconazole or voriconazole are the drugs of choice. In the case of vitreal involvement, vitrectomy and intravitreal injection of amphotericin B are recommended in addition to systemic therapy. For details, refer to Table 9.

Candida meningitis

Candida meningitis is a rare disease, and only very few reports have been published. Prognosis is generally poor [131].

Evidence. Liposomal amphotericin B has been combined with flucytosine for 10 weeks, followed by fluconazole for 5 weeks in a neonate [132]. In another neonate, a *Candida* isolate was resistant to flucytosine, and liposomal amphotericin B was combined with fluconazole for a total of 4 weeks [133]. Amphotericin B deoxycholate/flucytosine treatment had failed in the latter patient [133]. However, it is unclear to what extent these experiences can be extrapolated applied to adults. In a series of HIV-infected patients with candida meningitis, amphotericin B deoxycholate was frequently combined with flucytosine, and four of five patients were treated successfully [131]. In two other series, 27 of 34 patients survived after similar treatments [134,135]. In some cases, individualized maintenance regimens were given [131,134]. In the more recent case reports, amphotericin B deoxycholate toxicity frequently forced to replace it with the liposomal amphotericin B.

Fluconazole has been used in higher doses to treat *Candida* meningitis, when lower doses proved insufficient [136]. Published data on voriconazole use in *Candida* meningitis are sparse. In central nervous system, aspergillosis voriconazole is the drug of choice [137]. Brain tissue levels of voriconazole are satisfactory, but concentrations in cerebrospinal fluid are variable [138].

With caspofungin, a patient was cured from *Candida* meningitis refractory to amphotericin B deoxycholate and fluconazole [139], but poor penetration of echinocandins limit their use in central nervous system infection.

Recommendations. Due to lack of data, no strong recommendation can be given. Treatment should build on liposomal amphotericin B combined with flucytosine or with fluconazole if isolate is susceptible. For detailed recommendations, refer to Table 10.

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TABLE 9. Recommendations on *Candida* chorioretinitis and endophthalmitis

Population	Intervention	SoR	QoE	References
Susceptibility of isolate unknown	Liposomal amphotericin B 5 mg/kg	B	III	[113] [114] [119]
	Liposomal amphotericin B plus flucytosine	B	III	No reference found
	Amphotericin B lipid complex plus flucytosine	B	III	[112]
	Amphotericin B deoxycholate 0.7–1.0 mg/kg (for 3–7 days), followed by fluconazole 400 mg	C	II	[87]
	Amphotericin B deoxycholate 0.6–1.0 mg/kg	C	II_r	[107] [109] [110]
	Amphotericin B lipid complex 5 mg/kg	C	III	[111]
	Amphotericin B deoxycholate plus flucytosine	C	III	No reference found
	Caspofungin 50–100 mg	D	II_u	[116] [120] [121] [119] [130]
Susceptible isolate	Fluconazole 400–800 mg	A	II_u	[122] [123] [124] [126] [125]
	Voriconazole 12/6 mg/kg IV, followed by 400 mg PO	A	II_u	[129] [87] [130] [119] [126] [128]
Vitreal involvement[a]	Amphotericin B deoxycholate 5–10 μg intravitreal injection	B	II_u	[110] [167] [115] [168]
	Vitrectomy plus intravitreal amphotericin B 5–10 μg, fluconazole 400 mg for ≥2 weeks	B	II_u	[110] [127] [125]
	Voriconazole 100 μg intravitreal injection	B	III	[128] [126]

Frequent eye examinations are needed to detect disease progression.
[a]Endophthalmitis requires local and systemic treatment plus surgery.

Candida endocarditis

Candida endocarditis may manifest as native valve endocarditis, prosthetic valve endocarditis or infection in the presence of pacemaker or other implanted material prone to biofilm formation. In general, prognosis is poor with 1-year mortality >50% and substantial relapse rates [140–142].

Evidence. In native valve *Candida* endocarditis, primary intention is to decrease mortality [140]. Retrospective data suggest that patients should undergo surgery within the first week [140,141,143]. Treatment regimens published are liposomal amphotericin B or caspofungin, either one has been combined with flucytosine [140,141]. In prosthetic valve *Candida* endocarditis, valve replacement surgery needs be performed as soon as possible [142,143]. In single cases where comorbidities prevented surgery, caspofungin and liposomal amphotericin B were used successfully with or without subsequent life-long suppressive therapy with fluconazole [142,144,145]. In patients with pacemakers, implantable defibrillators or assist devices, removal of the device appears mandatory [146].

TABLE 10. Recommendations on *Candida* meningitis

Intervention	SoR	QoE	References
Liposomal amphotericin B 3 mg/kg for 10 weeks + flucytosine 150 mg/kg for 10 weeks, followed by fluconazole 3 mg/kg for 5 weeks	B	III	[132]
Liposomal amphotericin B 3 mg/kg for 4 weeks + fluconazole 6 mg/kg for 4 weeks	B	III	[133]
Voriconazole 12/6 mg/kg[a]	C	III	[137] [138] [43]
Fluconazole 800 mg	C	III	[136] [169]
Amphotericin B deoxycholate 0.5–1.0 mg/kg for >2 weeks +/– flucytosine 30–120 mg/kg for >2 weeks	D	II_u	[131] [134] [133] [135]
Caspofungin 70/50 mg for 4 weeks, followed by fluconazole 400 mg for 2 weeks	D	III	[139] [170]

Interventions are intended to cure *Candida* meningitis.
[a]Therapeutic drug monitoring recommended.

Recommendations. In native valve *Candida* endocarditis, surgery within a week is recommended, and in prosthetic valve *Candida* endocarditis, even earlier surgery may be beneficial. The antifungal regimen of choice is liposomal amphotericin B, which can be combined with flucytosine. For detailed recommendations, refer to Table 11.

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Bone and joint candidiasis

Candida infections of bones and joints are grouped into osteomyelitis/spondylodiscitis, arthritis and prosthetic joint infection. No randomized clinical trials have been conducted, so that evidence for the best therapeutic approach is somewhat limited.

Evidence. Typical indications for surgical debridement in osteomyelitis or spondylodiscitis are instability or large abscesses. Usually, cases of *Candida* osteomyelitis are diagnosed by biopsy. Over the years, most experience has been gathered with amphotericin B formulations, sometimes combined with flucytosine, sometimes followed by fluconazole [147]. Today, in patients with osteomyelitis as well as spondylodiscitis due to a susceptible isolate, treatment can commence with liposomal or lipid complex amphotericin B to be followed by fluconazole [147], or – if isolate is susceptible – fluconazole monotherapy may be used from the beginning [147–149]. Posaconazole has been successfully used in a single case as add-on during unsuccessful caspofungin treatment [150]. Voriconazole treatment has been reported in three patients with *Candida* osteomyelitis [78]. In addition, in *Aspergillus* osteomyelitis, voriconazole was used either as the only antifungal or as maintenance following liposomal amphotericin B [151]. Use of echinocandins has not been reported, with the exception of four patients with osteomyelitis and/or septic arthritis successfully treated with caspofungin [120].

A case of *Candida* shoulder arthritis was cured with a 3-week course of caspofungin [152], and a knee arthritis was treated with 7 weeks of caspofungin added on to a failing fluconazole therapy [153]. The most prevalent joint prone to *Candida* infection is the knee. Standard treatment of knee arthritis due to *Candida* was an amphotericin B–based approach, which may have been supplemented with flucytosine [154]. More recently, fluconazole and voriconazole were used with success [78,155,156].

Joint prosthesis is an important risk factor for *Candida* arthritis, and prosthesis is mandatory [154,157,158]. If the prosthesis must be retained, life-long suppressive treatment should be tried. In some patients, surgery was considered not possible, and knee or hip prosthetic joint arthritis was cured with use of fluconazole alone [157,159–161]. Bias towards publishing the unusual and successful cases can be assumed, so that the standard approach remains prosthesis removal and an intensive course of systemic antifungals.

Recommendations. Treating osteomyelitis, spondylodiscitis or arthritis with fluconazole is strongly recommended if species is susceptible. Fluconazole may be preceded by an induction phase with lipid-based amphotericin B. If joint prosthesis cannot be removed, lifelong fluconazole suppressive therapy is indicated. For details, refer to Table 12.

Transparency Declarations

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M.B. has received research grants from Pfizer, MSD and Astellas and is/was an advisor or received lecture honorarium from Astellas, Astra Zeneca, Angelini Farmaceutici, Aventis, Bayer, Cephalon, Cubist, Gilead, MSD, Novartis, Shionogi, Pfizer, Teva and Vifor. He is also a board member for Pfizer, Angelini Farmaceutici, Cubist, MSD, Astellas, Novartis and Astra Zeneca.

TABLE 11. Recommendations on *Candida* endocarditis

Population	Intention	Intervention	SoR	QoE	References
Native valve	To cure	Surgery within 1 week	A	II	[140] [143] [171]
		Liposomal ampho B +/– flucytosine for 6–8 weeks, followed by fluconazole	B	II	[171]
		Caspofungin +/– flucytosine	C	II	[171]
Prosthetic valve	To cure	Surgery within days	A	III	[142] [143]
Prosthetic valve, if surgery not possible	To cure	Liposomal amphotericin B 5 mg/kg	B	III	[142]
		Caspofungin 70/50 mg	B	III	[142]
	To suppress infection	Fluconazole 400–800 mg, life long	C	III	[142] [145]
Pacemaker, ICD, VAD	To cure	Removal	A	II	[146] [144]

ICD, implantable cardioverter defibrillator; VAD, ventricular assist device.
Surgery – even if restricted to removal of hardware – always needs to be combined with systemic antifungal treatment.

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TABLE 12. Recommendations on bone and joint candidiasis

Population	Intention	Intervention	SoR	QoE	References
Osteomyelitis/spondylodiscitis	To cure	Surgical debridement[a,b]	C	III	[147]
		Fluconazole 400 mg for 6–12 months[c]	A	II_u	[149] [148] [147]
		Liposomal amphotericin B 3 mg/kg or amphotericin B lipid complex 5 mg/kg for 2–6 weeks followed by fluconazole 400 mg for 5–11 months[c]	A	II_u	[149] [147]
		Posaconazole 800 mg for ≥6 weeks[c]	C	III	[150]
		Voriconazole 12/6 mg/kg for 6–12 weeks[c]	B	II_t	[78]
		Caspofungin 100 mg for 3 weeks, followed by fluconazole 400 mg for ≥4 weeks[c]	B	II	[120]
Arthritis	To cure	Liposomal Ampho B 3 mg/kg/ABLC 5 mg/kg 2 weeks, followed by fluconazole 400 mg for ≥4 weeks[c]	A	II_u	[154]
		Fluconazole 400 mg for ≥6 weeks[c]	A	II_u	[155]
		Voriconazole 12/6 mg/kg for ≥6 weeks[c]	B	III	[156]
		Caspofungin 70/50 mg for 6 weeks	C	II	[120] [152] [153]
Prosthetic joint infection	To cure	Prosthesis removal[b]	A	III	[154] [158] [157]
Prosthetic joint infection with prosthesis retention	To suppress infection	Fluconazole 400 mg, life long	A	III	[160] [161] [159] [157]

[a]Indications for surgery are, for example, instability or large abscess.
[b]Surgery needs to be combined with antifungal treatment.
[c]Treat longer if erythrocyte sedimentation rate or C-reactive protein not returned to normal.

T.C. is member of the Speaker bureau and is advisor or consultant for Astellas, Baxter, bioMérieux, EISAI, Evolva, Novartis, Merck Sharp and Dohme-Chibret AG, Immunexpress, Eli Lilly Suisse and Pfizer and received grant support from Baxter, bioMérieux, Merck Sharp and Dohme-Chibret AG and Roche Diagnostic. He has also received speaker's fees from MSD, Institut Pasteur and Gilead Sciences, travel support from Astellas, Pfizer and MSD.

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B.J.K. has received research grants from Bio-Mérieux and Cephalon. He is a consultant to Pfizer and is a member of the Gilead, MSD and Pfizer speaker's bureaus.

O.L. is a member of the MSD board, is a consultant for Astellas and Gilead Sciences and received grants or speaker's fees from MSD, Astellas, Gilead Sciences and Pfizer.

WM has received grant support from MSD and Pfizer. He had been an advisor to MSD and Pfizer. He has received honoraria for presentations on behalf of MSD/Schering Plough and Pfizer.

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E.C. has participated as invited speaker to symposia organized by Gilead, Pfizer, Astellas, Merck ans Novartis, and he has been member of advisory boards for Astellas and Pfizer.

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A.H.G. has received research support from Gilead, Merck and Schering. He has acted as speaker and/or consultant for Astellas, Cephalon, Gilead, Merck, Pfizer,Schering and Vicuron.

R.H. has been a consultant or at the advisory board for Astellas pharma, Basilea, Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer and Schering Plough. He has been paid for talks on behalf of Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. He has received research support from and been paid investigator fees for a clinical trial by Pfizer.

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G.P. has received research grants from Gilead, Pfizer, Astra Zeneca, Novartis, GSK, Astellas and MSD, has acted as paid consultant to Janssen Cilag, Gilead, Astellas and MSD and is a member of the Gilead, Astellas and MSD speaker' s bureaus. He has also received travel support from ESCMID, Gilead, Astellas and Pfizer.

M.D.R. has received grants, speaker's honoraria and travel support from ESCMID, Pfizer, Astellas, MSD and Gilead Sciences. He has also received book royalties from Blackwell Publishing and conference support from Astellas Pharma, as well as consulted for Gilead Sciences and MSD.

E.R. has received research support from Pfizer, Gilead and Merck, and he has made contributions in advisory boards of Gilead, Astellas and Pfizer. He has also been paid for talks on behalf of Gilead, Cephalon, Pfizer, Wyeth, Schering, Merck, Aventis and Astellas.

P.E.V. has received research grants from Pfizer, Astellas, Cephalon, Gilead Sciences, Merck and Schering-Plough. He has also received travel support from Gilead Sciences.

C.V. received grants as speaker/moderator in meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott and BMS and received grants for participation in advisory boards by Gilead, Astellas, MSD and Pfizer. Further, he obtained research grants for his institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, and Novartis. He is a member of the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency Member of various levels of local Infection Control, Antibiotic Stewardship, Vaccine and HIV Committees (Genoa, Liguria, Italy). He has also received payment for educational presentations from Nadirex International (Pavia, Italy).

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ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: prevention and management of invasive infections in neonates and children caused by *Candida* spp.

W. W. Hope[1†], E. Castagnola[2†], A. H. Groll[3†], E. Roilides[4†], M. Akova[5], M. C. Arendrup[6], S. Arikan-Akdagli[7], M. Bassetti[8], J. Bille[9], O. A. Cornely[10], M. Cuenca-Estrella[11], J. P. Donnelly[12], J. Garbino[13], R. Herbrecht[14], H. E. Jensen[15], B. J. Kullberg[12], C. Lass-Flörl[16], O. Lortholary[17,18], W. Meersseman[19], G. Petrikkos[20], M. D. Richardson[21], P. E. Verweij[12], C. Viscoli[22] and A. J. Ullmann[23] for the ESCMID Fungal Infection Study Group (EFISG)

1) *Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool L69 3GE, United Kingdom,* 2) *Instituto Giannina Gaslini, Children's Hospital, Genova, Italy,* 3) *Department of Pediatric Hematology/Oncology, Center for Bone Marrow Transplantation, University Children's Hospital, Muenster, Germany,* 4) *Third Department of Pediatrics, Aristotle University School of Medicine, Hippokration Hospital, Thessaloniki, Greece,* 5) *Department of Medicine, Hacettepe University School of Medicine, Ankara, Turkey,* 6) *Statens Serum Institut, Copenhagen, Denmark,* 7) *Department of Medical Microbiology, Hacettepe University School of Medicine, Ankara, Turkey,* 8) *Santa Maria Misericordia University Hospital, Udine, Italy,* 9) *Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland,* 10) *Department I of Internal Medicine, Clinical Trials Centre Cologne, ZKS Köln, BMBF 01KN1106, Center for Integrated Oncology CIO KölnBonn, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), German Centre for Infection Research, University of Cologne, Cologne, Germany,* 11) *Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain,* 12) *Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands,* 13) *University Hospitals Geneva, Geneva, Switzerland,* 14) *Hôpital de Hautepierre, University of Strasbourg, Strasbourg, France,* 15) *University of Copenhagen, Frederiksberg, Denmark,* 16) *Division of Hygiene & Medical Microbiology, Innsbruck Medical University, Innsbruck, Austria,* 17) *Service des Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants malades, APHP, Centre d'Infectiologie Necker-Pasteur, Université Paris Descartes, IHU Imagine, Paris,* 18) *Institut Pasteur, Centre National de Référence Mycologie et Antifongiques, Unité de Mycologie Moléculaire, CNRS URA3012, Paris, France,* 19) *University Hospital Gasthuisberg, Leuven, Belgium,* 20) *Fourth Department of Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece,* 21) *Mycology Reference Centre, University Hospital of South Manchester and Manchester Academic Health Science Centre, University of Manchester, Manchester, UK,* 22) *IRCCS San Martino-IST, University of Genoa, Genoa, Italy and* 23) *Department of Internal Medicine II, Julius-Maximilians-Universität, Würzburg, Germany*

Abstract

Invasive candidiasis (IC) is a relatively common syndrome in neonates and children and is associated with significant morbidity and mortality. These guidelines provide recommendations for the prevention and treatment of IC in neonates and children. Appropriate agents for the prevention of IC in neonates at high risk include fluconazole (A-I), nystatin (B-II) or lactoferrin ± *Lactobacillus* (B-II). The treatment of IC in neonates is complicated by the high likelihood of disseminated disease, including the possibility of infection within the central nervous system. Amphotericin B deoxycholate (B-II), liposomal amphotericin B (B-II), amphotericin B lipid complex (ABLC) (C-II), fluconazole (B-II), micafungin (B-II) and caspofungin (C-II) can all be potentially used. Recommendations for the prevention of IC in children are largely extrapolated from studies performed in adults with concomitant pharmacokinetic data and models in children. For allogeneic HSCT recipients, fluconazole (A-I), voriconazole (A-I), micafungin (A-I), itraconazole (B-II) and posaconazole (B-II) can all be used. Similar recommendations are made for the prevention of IC in children in other risk groups. With several exceptions, recommendations for the treatment of IC in children are extrapolated from adult studies, with concomitant pharmacokinetic studies. Amphotericin B deoxycholate (C-I), liposomal amphotericin B (A-I), ABLC (B-II), micafungin (A-I), caspofungin (A-I), anidulafungin (B-II), fluconazole (B-I) and voriconazole (B-I) can all be used.

Keywords: Antifungal agents, candida disease, children, Europe, neonates

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Corresponding authors: W. W. Hope, BMBS, FRACP, FRCPA, PhD, Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, 1.09 Sherrington Building, Liverpool L69 3GE, United Kingdom
E-mail: william.hope@liverpool.ac.uk
A. J. Ullmann, MD, Infectious Diseases, Department of Internal Medicine II, Julius-Maximilians-University, Oberdürrbacher Str. 6, 97080 Würzburg, Germany
E-mail: andrew.ullmann@uni-wuerzburg.de

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*European Society for Clinical Microbiology and Infectious Diseases.
†Members of the subgroup committee mainly responsible for this manuscript.

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Introduction

The process of defining therapeutic recommendations in this document is consistent with paediatric development regulations and guidelines from the European Medicines Agency (EMA) [1,2]. The EMA has a relatively pragmatic approach to the licensure of pharmaceutical agents for neonates and children. The EMA accepts the requirement for extrapolation of evidence for efficacy from studies in adults to paediatric patients, or from older to younger paediatric patients when the following criteria are met: (i) a medicinal product is to be used for the same indication(s); (ii) the disease process or target sensitivity is similar; and (iii) the outcome of therapy is likely to be comparable [1,2].

Pharmacokinetic studies performed in all the age ranges of paediatric patients likely to receive a compound, together with safety studies, may provide adequate information for use by allowing selection of paediatric doses that will produce drug exposure similar to those observed in adults. In situations where the comparability of the disease course or outcome of therapy is expected to be similar, but the relevant drug exposure in adults is not known, a pharmacokinetics/pharmacodynamics approach combined with safety and other relevant studies may avoid the need for clinical efficacy studies [1]. More complex disease–drug combinations may require specific studies.

The grading scheme used in this manuscript is consistent with guidelines developed for adults [141]. However, there are some subtle differences for paediatric patients. The Expert Group considered three components for grading of each drug–syndrome combination: (i) evidence for efficacy, which was frequently, but not invariably, obtained from studies in adults; (ii) the quality of the pharmacokinetic data and models performed in either neonates or children that enable an informed decision about an appropriate regimen for the specific population; and (iii) specific safety data obtained in neonates or children that support the use of a given compound in that specific population. These guidelines are intended to facilitate optimal antifungal therapy for neonates and children with invasive candidiasis. They are not necessarily exhaustive. Contraindications, drug–drug interactions and specific warnings for each compound should be considered by treating physicians. Furthermore, these guidelines should be coupled with diagnostic and therapeutic algorithms tailored to the specific case mix and local fungal epidemiology of each institution. The incorporation of these therapeutic guidelines with a risk stratification strategy is also recommended, especially for prophylaxis and empirical antifungal therapy.

Overview of syndromes and pathogenesis of invasive candidiasis in paediatrics

Neonates

Invasive candidiasis (IC) is a common and serious infection in premature neonates [3]. Invasive candidiasis may present as candidaemia, urinary tract infection and involvement of essentially any other tissue or structure. A syndrome that is particularly unique to premature infants is haematogenous *Candida* meningoencephalitis (HCME), where there is invasion of the central nervous system (CNS) by *Candida*. This syndrome occurs in 15–20% of cases of IC and may contribute to the increased mortality and long-term neurodevelopmental abnormalities [3,4].

The risk factors for development of IC in the neonatal intensive care unit (NICU) include prematurity, central vascular catheterization, abdominal surgery, necrotising enterocolitis (NEC), exposure to broad-spectrum antibacterial agents (e.g. third-generation cephalosporins and carbapenems), parenteral nutrition, antacids and endotracheal intubation. Infants with a smaller gestational age have a higher incidence of IC (e.g. neonates with gestational age of 23–24, 25–27 and ≥28 weeks have an incidence of 10–20%, 5–10% and <5%, respectively [5]). Similarly, smaller infants have a higher incidence of IC (e.g. neonates with birth weight <750 g, 750–1000 g and >1000 g have an incidence of IC of >10%, 5–10% and <5%, respectively).

Candida albicans is the most frequent *Candida* species causing IC in neonates [6,7]. *Candida parapsilosis, Candida tropicalis* and other *Candida* species are seen less commonly. Unlike adults, *Candida glabrata* and *Candida krusei* are infrequent causes of IC in the NICU.

Older children

The invasive *Candida* syndromes in older children closely resemble those seen in adults. *Candida* spp. are important causes of healthcare–associated infections in children and adolescents with indwelling central venous catheters, in paediatric cancer patients receiving treatment for haematological malignancies and in paediatric haematopoitic stem cell transplant (HSCT) recipients. Severe sepsis and/or septic shock occurs in approximately 30% [8,9]; mortality rates range between 10 and 25% in most series [9] and are close to 50% in patients admitted to the ICU [8,10,11]. IC is also an important syndrome in solid organ transplant recipients. The incidence in this setting remains relatively poorly defined, but is *c.* 5–10% in liver, small bowel and pancreas transplantation [12]. In the individual reports that are available, the incidence of IC for paediatric heart, lung and liver transplant recipients is 3.9%, 5% and 19%, respectively [10,13,14].

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Prevention of IC in neonates (see Table 1)

General principles

Antifungal prophylaxis may be an appropriate strategy, especially for the most vulnerable patients (e.g. extremely low-birth-weight [ELBW] neonates [i.e. <1000 g]). Avoidance of horizontal transmission in the NICU is paramount and requires rigorous infection control measures [15]. Treatment of maternal vaginal candidiasis prior to delivery may prevent subsequent neonatal colonization [15]. Rational use of broad-spectrum antibacterial agents (especially third-generation cephalosporins and carbapenems) and central venous catheters is probably important, although there is no specific evidence to support these interventions. The Expert Group has evaluated three prophylactic strategies for IC in premature neonates: (i) oral nonabsorbable antifungal agents; (ii) oral administration of *Lactobacillus* and lactoferrin; and (iii) i.v. and oral administration of fluconazole.

Nonabsorbable antifungal agents

Nonabsorbable antifungal agents are used to decrease the burden of *Candida* in the gut and therefore the probability of translocation into the bloodstream. Currently available agents include nystatin (1 mL suspension, 100 000 U/mL, every 8 h, during high-risk period) and miconazole oral gel 15 mg Q8 h.

There is a reasonable amount of data that support the use of nystatin for neonates <1500 g (B-II). This recommendation is based on randomized controlled trials that have compared the utility of oral nystatin versus no medication for the prevention of IC [16,17]. A subsequent Cochrane review and meta-analysis suggest that oral nystatin results in a significant reduction in IC, but has no impact on mortality [18]. Two further studies have compared nystatin with fluconazole [19,20]. While the impact of nystatin on IC is variable (some studies [16,17,19] suggest that the use of nonabsorbable agents results in a reduction in colonization and IC [e.g. from *c.* 44 to 12% and *c.* 4–32 to 1.8–6%, respectively, while others do not [20]]), there is no impact on mortality, and longer-term outcomes have not been assessed. A potential problem with the use of nonabsorbable agents is inadvertent damage of the very fragile gut epithelium of premature infants and the subsequent development of necrotizing enterocolitis (NEC). A grading of B-II reflects the potential concern for the development of NEC, the absence of an overall effect on mortality and methodological weaknesses in these studies.

Miconazole is an alternative nonabsorbable agent for the prevention of IC in neonates. The only trial that has examined the utility of miconazole for this indication in neonates suggests that there is a reduction in rectal colonization by *Candida*, but no impact upon IC [21]. Given the potential for the development of triazole resistance that may preclude the subsequent use of fluconazole, the Expert Group suggests a grading of D-II.

Administration of *Lactobacillus* and lactoferrin

The administration of *Lactobacillus casei* subsp. *rhamnosus* is intended to prevent the establishment of a microbiological niche for *Candida* spp. in the gut. Studies of oral probiotic administered (10^6 colony-forming units per day) from the third day of life until either the end of the sixth week of life or until discharge from the NICU suggest that this approach prevents enteric colonization by *Candida* species, but has no impact on the overall incidence of IC [22]. Lactoferrin is an alternative agent that may be effective via the abrogation of the invasive potential of *Candida* spp. The administration of bovine lactoferrin (100 mg/day), alone or in combination with *Lactobacillus rhamnosus* GG, significantly reduces the incidence of late-onset sepsis in very low-birth-weight (VLBW, <1500 g) neonates, including those episodes attributable to *Candida* [23]. Bovine lactoferrin does not affect the incidence of *Candida* colonization but reduces the incidence of IC in VLBW neonates [24]. The Expert Group considers that lactoferrin alone or in combination with *Lactobacillus* is equally reasonable (B-II).

Fluconazole prophylaxis

The use of fluconazole (i.v. or oral) is supported by robust data that attest to both the efficacy and safety of this agent. Five RCTs [19,25–28], eight historical control studies [29–36] and one meta-analysis [37] have examined the utility of fluconazole for the prevention of IC in neonates. Collectively, all these studies suggest that prophylactic administration of fluconazole 3–6 mg/kg/dose (i.v. or oral) twice weekly results in a reduction in *Candida* colonization and a 91% decrease of IC in neonates <1000 g. While there is a reduction in mortality, this is not statistically significant (RR 0.74 [CI 0.51–1.09]) [37,38]. Potential theoretical concerns with the routine use of fluconazole include neurodevelopmental toxicity and emergence of drug resistance. Reassuringly, a recent study suggests no toxicity after 8–10 years, nor the emergence of less susceptible or inherently resistant *Candida* species in the NICU [39]. Of note, studies examining fluconazole prophylaxis were conducted in NICUs with relatively high incidence of IC (e.g. >12%). Most NICUs have an incidence of IC of <5% for neonates <1000 g, and some <2% [40]. The potential benefits of fluconazole prophylaxis may be less with a low incidence of IC.

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The Expert Group recommends that the use of fluconazole is combined with a risk stratification strategy. Thus, fluconazole 3–6 mg/kg/dose twice weekly i.v. or orally is appropriate for all neonates <1000 g in NICUs with relatively high frequency of IC (A-I). For NICUs with a lower incidence of IC (i.e. <2%), the decision to use the same fluconazole prophylaxis regimen should be made on a case-by-case basis and embedded in a risk stratification strategy (e.g. <1000 g, additional risk factors for IC such as central venous catheterization, receipt of third-generation cephalosporins or carbapenems) (B-II).

Treatment of IC in neonates (See Table 2)

General principles

Because cultures from deep sites are frequently negative, a definitive diagnosis of IC in neonates may be problematic [3]. Information on local epidemiology may help guide initial therapy [6]. Any premature infant with microbiological or clinical evidence of invasive candidiasis should be assumed to have disseminated disease, and this should prompt a thorough clinical examination and relevant investigations. In particular, the possibility of HCME should be considered, and if deemed probable, antifungal therapy should be designed to treat the CNS [41]. This important pharmacodynamic difference between neonates and adults means that the strategy of combining efficacy data from adults with well-designed PK studies in neonates may not be appropriate. In this regard, the Expert Group notes that evidence to support various compounds in neonatal settings is accrued either from: (i) case series describing the outcome of drug therapy in neonates or (ii) *in vivo* to clinical bridging studies. The latter has been recently applied to the echinocandins.

Amphotericin B formulations

Amphotericin B deoxycholate 1 mg/kg/day can be used for the treatment of IC in neonates (B-II). This recommendation is supported by relatively limited clinical data for IC [42] and HCME [43]. The recommendation is also supported by limited pharmacokinetic data [44]. There is no specific clinical information for optimal regimen for the treatment of HCME, although amphotericin B deoxycholate is effective in a preclinical model of HCME [45]. Liposomal amphotericin B 2.5–7 mg/kg/day can be used for IC in neonates [46–48] (B-II) and is safe [49]. While there is no specific clinical information for the optimal regimen for HCME, liposomal amphotericin B penetrates the CNS in a preclinical model of HCME and has antifungal activity in the brain [45]. ABLC 2.5–5 mg/kg/day i.v. is an alternative agent to both LAmB and DAmB (C-II). Evidence for efficacy and the population pharmacokinetics of ABLC have been described in neonates [50]. Furthermore, preclinical data suggest ABLC is effective for HCME [45]. The lower grading compared with other amphotericin B formulations reflects continuing uncertainty regarding the use of this agent for IC in general (for both children and adults) and the relative paucity of clinical data compared with other formulations.

Triazoles

There are relatively few studies that have specifically examined the efficacy of fluconazole for neonates. Fluconazole (12 mg/kg with consideration given to a loading dose of 25 mg/kg although further safety studies are required) can be used to treat IC in neonates who have not previously received this agent (B-II). This recommendation is based on data for efficacy and safety in neonates [51–53]. Recent population pharmacokinetic studies have been used to define an appropriate regimen [54,55]. There are no preclinical or clinical data that are available to guide definitive regimens for HCME. Potential limitations of fluconazole include a relatively narrow spectrum of antifungal activity compared with other antifungal agents, and a fungistatic (as opposed to fungicidal) antifungal effect.

Echinocandins

The echinocandins are increasingly used for treatment of IC in the NICU. The recommendation for micafungin 4–10 mg/kg/day (B-II) is based on a PK–PD bridging study and detailed PK studies [56–58]. Micafungin 4 mg/kg approximates drug exposures achieved in adults. If HCME is thought to be likely, a higher dosage (e.g. 10 mg/kg) should be used because of the dose-dependent penetration of micafungin into the CNS [57]. The Expert Group notes the 'black box' warning for micafungin issued by the EMA indicating micafungin should only be used if other agents are not appropriate. This warning is based upon an increased incidence of hepatic tumours in rats receiving prolonged dosing of micafungin. To date, there is no corresponding clinical signal, despite extensive clinical use of micafungin throughout the world. Furthermore, similar studies have not been performed for the other echinocandins, raising uncertainty as to whether this preclinical finding is a class effect. Preclinical data and PK–PD bridging studies suggest that an elevated dosage of anidulafungin may be required to treat HCME [59]. While limited PK is available [60], further clinical PK studies are required, and until results from these studies are available, the Expert Group has not graded anidulafungin for use in this setting. The currently recommended infant dosage of caspofungin (25 mg/m^2/day) is based on achieving comparable AUCs to those seen in adults [61]. While clinical efficacy has been

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demonstrated in a small number of case reports and case series [62–64], there is no evidence that this dosage is necessarily adequate to treat infants with HCME. Moreover, the use of body surface area as a metric of size may be inaccurate in neonates. For these reasons, and until further data are available, the Expert Group suggests a grading of C-II is appropriate.

Prevention and treatment of invasive candidiasis in children (See Table 3 and 4)

General principles

Primary prophylaxis is a widely accepted strategy for patients at high risk of developing IC. The underlying incidence of IC is the most important factor for determining whether prophylaxis is a reasonable strategy, with 10% frequently being used as a value where the risk–benefit analysis is favourable. The incidence for patients with acute myeloid leukaemia, recurrent leukaemia and following allogeneic HSCT is 5–15% [65–68]. For patients with acute lymphoblastic leukaemia and solid tumours who are receiving dose-intense chemotherapy with or without autologous stem cell rescue, the reported incidence rates are <5% [68,69]. Apart from these general considerations, the institutional epidemiology is the most important consideration for designing an appropriate prophylactic regimen.

Prevention of invasive candidiasis in allogeneic HSCT recipients

Fluconazole (8–12 mg/kg QD i.v. or orally; studied from day 0 to day +75) may be used in allogeneic HSCT recipients (A-I). This recommendation is based on randomized clinical trials performed in adults who have demonstrated a reduction in invasive *Candida* infections [70,71], a persistent survival benefit in one study [71,72], the existence of paediatric PK and safety data [73–75], and a paediatric label from the EMA. Fluconazole should only be used when the risk of invasive mould infections is suitably low or in combination with a screening programme for these pathogens.

Itraconazole suspension (2.5 mg/kg Q12h; started after completion of the conditioning regimen; not approved by the EMA in patients <18 years of age), which has additional activity against *Aspergillus* spp., may also be used for children ≥2 years of age (B-II). The evidence for the use of this agent for HSCT recipients is derived from randomized clinical trials in adults [76,77] and relatively small paediatric pharmacokinetic studies [78–80]; the latter is the reason for the designation of level II evidence. TDM should be performed to verify absorption, compliance and the attainment of effective and nontoxic concentrations. A trough concentration target of 0.5 mg/L when estimated using HPLC is reasonable [81,82]. A further option for children aged ≥2 years is voriconazole (day 1: 9mg/kg Q12 h, then 8 mg/kg Q12h i.v): 9 mg/kg Q12 h PO (max. 350 mg Q12 h) for 2–12 years and 12–14 years with <50 kg; adult dose for patients 12–14 years >50 kg and for patients >14 years; studied from day 0 until at least day +100) (A-I). The basis for this recommendation includes a randomized clinical trial performed in adults that demonstrates comparable prophylactic efficacy to fluconazole [83] and adequate PK and safety data [84–89]. An additional consideration is activity against *Aspergillus* spp. Prophylactic use of voriconazole should be coupled with therapeutic drug monitoring; a trough concentration of ≥1 mg/L is probably a reasonable target [89–91]. For adults with GVHD and augmented immunosuppression, posaconazole (200 mg Q8 h) has been shown to prevent invasive fungal infections, although there was no effect on overall mortality [92]. Limited data in children 13–17 years of age suggest minimal differences in pharmacokinetics compared with adults [93]. Therefore, posaconazole may be appropriate for children who are receiving immunosuppression for GVHD (B-II). The Expert Group suggests a lower recommendation than adults because of relatively rudimentary pharmacokinetic studies in paediatric patients. If posaconazole is used, therapeutic drug monitoring should be considered, and a trough concentration of 0.7 mg/L after 1-week therapy is a reasonable therapeutic target [94,95].

Micafungin (1 mg/kg/day i.v. administered from the beginning of the preparative regimen to day +30) may be used (A-I). This recommendation is based upon robust paediatric PK [96,97], safety [98], regulatory approval for this indication and a large randomized clinical trial with inclusion of paediatric patients [99].

Prevention of invasive candidiasis in children with AML and recurrent leukaemia

The recommendations for patients with AML and/or recurrent leukaemia are similar to the allogeneic HSCT setting; the risk of developing invasive mould disease may be significant and should be considered [69]. Fluconazole (8–12 mg/kg/day i.v./orally (max. 400 mg) after the last dose of chemotherapy and until neutrophil recovery) [100] (A-I) should only be used when the risk of invasive mould infections is suitably low or in combination with a screening programme for these pathogens. Micafungin (1 mg/kg/day i.v.) is approved for prophylaxis of invasive *Candida* infections in patients with profound and prolonged neutropaenia [ANC <500 for ≥10 days]) [99](A-II). The Expert Group

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TABLE 1. Prevention of invasive candidiasis in neonates

Recommendation and grading	Comments	References
Oral nystatin, 1 mL 100 000 IU Q8 h (B-II)	Reduction in fungal infection, but no change in mortality, potential gut damage & NEC	[18–20]
Miconazole oral gel 15 mg Q8 h (D-II)	Concerns regarding generation of triazole resistance	[21]
Lactoferrin 100 mg/day alone or in combination with *Lactobacillus* 10^6 colony-forming units per day from the third day of life until either the end of the sixth week of life or until discharge from the NICU (B-II)	Reduction in fungal infection by *Lactobacillus* and lactoferrin	[22–24]
Fluconazole 3 or 6 mg/kg 2 times per week iv or orally in ALL neonates <1000 g in NICUs with high frequency of IC (A-I)	Reduction in *Candida* colonization, fungal infection, but no change in overall mortality. Concerns for neurodevelopmental toxicity, emergence of resistant species	[19,25–37,39]
Fluconazole 3 or 6 mg/kg 2 times per week iv or orally in NICUs with a lower incidence of IC (i.e. <2%) for neonates: (a) with birth weight <1000 g, (b) who have risk factors (i.e. central venous catheters, third-generation cephalosporins and carbapenems) for the development of IC (B-II)	Decision for prophylaxis is on an individual basis	References as immediately above

TABLE 2. Therapeutic options for infants with invasive candidiasis and/or HCME

Recommendation and Grading	Comments	References
Amphotericin B deoxycholate 1 mg/kg/day (B-II)	PK in neonates relatively poorly defined, leading to some uncertainty regarding optimal dosage for HCME	Clinical trials in adults [123,124] Pharmacokinetics in neonates [44] Evidence for efficacy and toxicity [43,135]
Liposomal amphotericin B 2.5–7 mg/kg/day (B-II)	PK in neonates remains undefined, leading to some uncertainty regarding optimal dosage for neonates The optimal dosage for HCME is not known	Pharmacokinetics in neonates: nil Evidence for efficacy in neonates [46–48]
Fluconazole 12 mg/kg/day, with consideration given to a loading dose of 25 mg/kg (B-II)	Relatively limited data for the treatment of IC	Evidence for efficacy [51–53] Pharmacokinetics in neonates: [54,55]
Micafungin 4–10 mg/kg/day i.v. (B-II)	The EMA has issued a 'black box' warning on the basis of an elevated incidence of hepatic tumours in rats receiving prolonged dosing and drug exposures higher than typically seen in clinical contexts. These studies have not been performed for other echinocandins The currently licensed dosage is 2–4 mg/kg/day. If HCME is present, preclinical models and PK-PD bridging studies suggest a higher dosage is required for effective therapy	Evidence for efficacy derived from preclinical models [57] Pharmacokinetics in neonates: [56,58]
Caspofungin 25 mg/m^2/day (C-II)	Relatively limited PK and dosing designed to approximate drug exposure in adults, rather than HCME	Evidence for efficacy [62–64] Pharmacokinetics in neonates: [61]
ABLC 2.5–5 mg/kg/day (C-II)	The Expert Group rated ABLC 'C' because of the relative paucity of clinical data The optimal regimen for the treatment of HCME is not known	Pharmacokinetics in neonates [50] Preclinical data suggests that ABLC is an effective agent for the treatment of HCME [45]

suggests level II evidence is appropriate because of the absence of specific studies in this patient population. Posaconazole prevents invasive fungal infections and provides a survival advantage for patients with AML/MDS compared with patients receiving fluconazole or itraconazole [101]. Based on limited PK and safety data [93,102], posaconazole (200 mg Q8 h following completion of chemotherapy until neutrophil recovery; plus TDM) (B-II) is an option for adolescents >12 years of age.

Further alternatives include the following: (i) itraconazole (2.5 mg/kg Q12h following chemotherapy with concomitant TDM; not approved by the EMA for patients <18 years of age) [103] (B-II); (ii) liposomal amphotericin B (1 mg/kg/every other day) (B-I) based on studies in adult patients with leukaemia [104] and concomitant paediatric pharmacokinetic and safety data [105,106]; and (iii) voriconazole (day 1: 9 mg/kg Q12 h, then 8 mg/kg BID i.v.); 9 mg/kg Q12 h PO (max.: 350 mg Q12 h) for 2–14 years; adult dose for patients >14 years; plus TDM) [83,107] (A-II). Of note, both micafungin and liposomal amphotericin B may be useful for patients with acute lymphoblastic leukaemia (ALL) who are receiving repeat treatments with vincristine and in whom antifungal triazoles are contraindicated [108].

Prevention of invasive candidiasis in autologous HSCT recipients and in children with ALL

Patients who have received high-dose chemotherapy with autologous stem cell rescue (autologous HSCT), who also have profound and prolonged neutropaenia (ANC <500 for ≥10 days) despite hematopoietic growth factors and/or severe mucositis, may benefit from primary antifungal prophylaxis [100]. Because the risk of developing invasive mould

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TABLE 3. Primary prophylaxis of invasive candidiasis in children

Clinical Context	Recommendation and Grading	Comments	References
Allogeneic HSCT	Fluconazole 8–12 mg/kg QD i.v. or orally; studied from day 0 until day +75 post transplant (A-I)	Fluconazole should only be used if the institutional incidence of invasive mould infections is low, or if there are active diagnostic and therapeutic algorithms for mould infections	Clinical trials in adults [70–72] PK studies in children [73] Safety and efficacy in children [74,75]
Allogeneic HSCT	Micafungin 1 mg/kg QD i.v.; studied from the start of the preparative regimen until day +30 (A-I)	Spectrum of antifungal activity also extends to *Aspergillus* spp.	Clinical trials in adults with inclusion of paediatric patients [99] PK studies in children: [96,97] Safety and efficacy in children [98]
Allogeneic HSCT	Voriconazole 8 mg/kg BID (day 1: 9 mg/kg BID) for i.v., and 9 mg/kg BID for oral administration (max.: 350 mg BID) for the ages of 2–14 years and the approved adult dose for patients 15 years and older and 12-14 year olds weighing >50 kg; studied from day 0 until at least day +100 (A-I)	Spectrum extends to *Aspergillus* spp. and other medically important opportunistic moulds TDM should be performed; dosing target/ trough concentration of ≥1 mg/L	Clinical trials in adults [83] PK studies in children: [84–88] TDM dosing target: [89–91] Safety/efficacy in children: [84–89,136–138]
Allogeneic HSCT	Itraconazole suspension 2.5 mg/kg Q12 h for patients ≥2 years of age; to be started after completion of the conditioning regimen; studied until at least day +100 (B-II)	Spectrum extends to *Aspergillus* spp. and other medically important opportunistic moulds Not approved in patients <18 years TDM is suggested; dosing target: trough concentration of ≥0.5 mg/L	Clinical trials in adults: [76,77] PK studies in children [78–80] TDM dosing target [81,82] Safety/efficacy in children [79]
Allogeneic HSCT	Posaconazole suspension 200 mg Q8 h orally for patients with ≥ grade II GVHD and ≥13 years of age (B-II)	Spectrum extends to *Aspergillus* spp. and other medically important opportunistic moulds Not approved in patients <18 years TDM is suggested; dosing target: trough concentration of ≥0.7 mg/L	Clinical trials in adults: [92] PK studies in children: [93] TDM dosing target [94] Safety/efficacy in children: nil
AML and recurrent leukaemia	Fluconazole 8–12 mg/kg i.v. or orally after last dose of chemotherapy until neutrophil recovery (A-I)	Fluconazole should only be used if the institutional incidence of invasive mould infections is low, or with an active diagnostic and therapeutic algorithms for clinical signs and symptoms suggestive of these infections	Clinical trials in adults [100] PK studies in children [73] Safety/efficacy in children: [74,75]
AML and recurrent leukaemia	Micafungin 1 mg/kg QD i.v.; after last dose of chemotherapy until neutrophil recovery (A-II)	Prophylactic efficacy inferred from study in HSCT patients Alternative for patients with leukaemia receiving vincristine	As above
AML and recurrent leukaemia	Itraconazole suspension 2.5 mg/kg Q12 h for patients ≥2 years of age; after last dose of chemotherapy until neutrophil recovery (B-II)	Spectrum extends to *Aspergillus* spp. and other medically important opportunistic moulds Not approved in patients <18 years TDM is suggested; dosing target: trough concentration of ≥ 0.5 mg/L	Clinical trials in adults [103] PK studies in children: [78–80] TDM dosing target: [81,82] Safety/efficacy in children [79]
AML and recurrent leukaemia	Liposomal amphotericin B 1 mg/kg QOD i.v. (B-I)	Spectrum extends to *Aspergillus* spp. and other medically important opportunistic moulds Alternative antifungal agent for patients with leukaemia receiving vincristine	Clinical trials in adults [104] PK studies in children [105] Safety/efficacy in children [106]
AML and recurrent leukaemia	Voriconazole 8 mg/kg BID (day 1: 9 mg/kg BID) for i.v., and 9 mg/kg BID for oral administration (max.: 350 mg BID) for the ages of 2–14 years and the approved adult dose for patients 15 years and older and 12-14 year olds weighing >50 kg; after last dose of chemotherapy until neutrophil recovery (B-I)	As above	As above
AML and recurrent leukaemia	Posaconazole 200 mg TID orally for patients ≥13 years of age; after last dose of chemotherapy until neutrophil recovery (B-II)	As above	As above
Autologous HSCT	Fluconazole 8–12 mg/kg i.v. or orally after last dose of chemotherapy until neutrophil recovery (A-I)	Patients with expected profound and prolonged neutropaenia (ANC <500 ≥ 10 days) despite use of growth factors and/or severe mucositis may benefit from antifungal prophylaxis	References as above
Autologous HSCT	Micafungin 1 mg/kg QD i.v.; after last dose of chemotherapy until neutrophil recovery (A-I)	As above	References as above
Autologous HSCT	Itraconazole suspension 2.5 mg/kg Q12 h for patients ≥2 years of age; after last dose of chemotherapy until neutrophil recovery (B-II)	As above	References as above
Autologous HSCT	Liposomal amphotericin B 1 mg/kg QOD i.v. (B-I)	As above	References as above

HSCT, haematopoietic stem cell transplantation; PK, pharmacokinetics; TDM, therapeutic drug monitoring.
Note that individual ALL patients exhibiting prolonged and profound neutropaenia (ANC <500 for ≥10 days) and receiving high doses of glucocorticosteroids may benefit from antifungal prophylaxis [68]. As these risk factors are shared by opportunistic moulds, a mould active agent is preferred (CIII).

infections is <5% [108], primary options include micafungin (1 mg/kg QD; studied from the start of high-dose chemotherapy until engraftment) [99] (A-I) and fluconazole (8–12 mg/kg/day i.v./orally (max. 400 mg) (A-I) [100]. Alternative options include itraconazole (2.5 mg/kg Q12h with TDM; not approved in subjects <18 years of age) [103] (B-II) and liposomal amphotericin B 1 mg/kg/every other day i.v. (B-I) based on data derived from adult patients leukaemia [104].

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TABLE 4. Treatment of invasive candidiasis in children

Recommendation and Grading	Comments	References
Amphotericin B deoxycholate 0.6–1 mg/kg/day (C-I)	Lipid preparations of amphotericin B have a more favourable toxicity profile Issues related to supply in some European countries	Clinical trials in adults [123,124] PK studies in children [132] Evidence for safety and efficacy in children with invasive candidiasis: Nil
Liposomal amphotericin B 3 mg/kg/day (A-I)		Clinical trials in adults and children [48,127] PK studies in children [105] Safety in children [48]
Fluconazole 8–12 mg/kg/day (B-I)	Fungistatic antifungal activity	Evidence for efficacy in adults [123,139] PK studies in children [73] Evidence for safety and efficacy in children [75]
Voriconazole (day 1: 9 mg/kg Q12h, then 8 mg/kg BID i.v.); and 9 mg/kg BID for oral administration (max.: 350 mg BID) for the ages of 2–14 years and the approved adult dose for patients 15 years and older and 12–14 year olds weighing >50 kg; after last dose of chemotherapy until neutrophil recovery (B-I)	Fungistatic antifungal activity Spectrum extends to *Candida glabrata* and *Candida krusei* TDM should be considered	Evidence for efficacy in adults [134] PK studies in children: [84–88] TDM dosing target: [89–91]
Micafungin <40 kg 2–4 mg/kg (A-I)	Well conducted PK trials to define dosages that lead to comparable drug exposures in children The EMA has issued a 'black box' warning on the basis of an elevated incidence of hepatic tumours in rats receiving prolonged dosing and drug exposures higher than typically seen in clinical contexts.	Efficacy established in clinical trials in children and adults [48,127] PK studies in children: [96,97] Safety/efficacy in children [98]
Anidulafungin 3 mg/kg as a single loading dose followed by 1.5 mg/kg/day (B-II)	Some uncertainty about optimal paediatric regimen because of relatively limited PK data No data for efficacy and safety in children	Evidence for efficacy in adults [128] PK studies in children [129]
Caspofungin Loading dose 70 mg/m^2/day, followed by 50 mg/m^2/day. Option to increase to 70 mg/m^2/day if clinically indicated, maximum absolute dose of 70 mg/day (A-I)		Evidence for efficacy in adults [124] PK studies in children [125] Evidence for safety in children [126]
Amphotericin B Lipid Complex (B-II)	Relatively limited clinical data for efficacy and safety No PK data for children	Evidence for efficacy and safety [131,140] PK in children: nil

While no general recommendation can be made for de novo acute lymphoblastic leukaemia, individual patients exhibiting prolonged and profound neutropaenia (ANC <500 for ≥10 days) and receiving high doses of corticosteroids may benefit from antifungal prophylaxis [68]; because these risk factors are shared by opportunistic moulds, a mould active agent is preferred (CIII).

Prevention of invasive candidiasis in solid organ transplant recipients and critically Ill nonneutropaenic children

Because robust data on epidemiology and risk factors are absent, firm recommendations for the prevention of IC are somewhat difficult. The most appropriate agent depends on the underlying incidence of invasive aspergillosis, which in turn is a function of the transplant type and institutional incidence of mould infections. If the incidence of invasive aspergillosis is suitably low, then fluconazole 8–12 mg/kg/day i.v. or orally is reasonable in the majority of cases (recommendation not rated).

Similar uncertainties exist for critically ill nonneutropaenic children in the paediatric intensive care unit (PICU). While no evidence-based recommendations can be made, fluconazole 8–12 mg/kg/day i.v. or orally is a reasonable option for the prevention of invasive candidiasis in critically ill nonneutropaenic children in the intensive care unit, especially in cases of extensive abdominal surgery (recommendation not rated).

Secondary Prophylaxis

Secondary chemoprophylaxis, as a term, is ill-defined for invasive candidiasis and may overlap with continued treatment or maintenance treatment in chronic disseminated candidiasis with an agent that has proven efficacy against *Candida* spp. [109]. Similar to adults, secondary chemoprophylaxis is not indicated in case of prior uncomplicated candidaemia without any sign of deep seated infection – including situations in which the patient is exposed to a new immunosuppressive condition such as prolonged neutropaenia induced by chemotherapy, autologous or allogeneic HSCT (CIII).

Empirical and pre-emptive antifungal therapy

Empirical antifungal therapy is considered by many experts a standard of care in haemato-oncological patients with prolonged neutropaenia (ANC <500 for ≥10 days) and refractory or new fever, despite broad-spectrum empirical antibacterial therapy. It may provide targeted prevention in a high-risk situation and early treatment of yet occult infections. Based on large randomized clinical trials with inclusion and separate analysis of paediatric patients [110–113], adequate paediatric PK and safety data, recommended options in paediatric patients of all age groups include liposomal amphotericin B (1–3 mg/kg QD) (A-I) and caspofungin (loading dose 70 mg/m^2/day, followed by 50 mg/m^2/day. Option

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to increase to 70 mg/m^2/day if clinically indicated with a maximum dose of 70 mg/day) (A-I). Of note, incidence and extent of nephrotoxicity of liposomal amphotericin B in children appears to be lower than in adults, hence the higher rating compared with adults. Fluconazole may be used if the incidence of invasive aspergillosis is low or if a mould-specific diagnostic algorithm is being used (B-II) [114]. Amphotericin B deoxycholate 0.7–0.8 mg/kg/day may be reasonable if this compound is available, and the higher toxicity is tolerable from a clinical perspective (B-II).

Empirical therapy in adult ICU patients has been shown to be of no benefit when using a fever criterion [115], but no data exist for nonneonatal paediatric patients. While several studies in adult ICU patients show potential utility of scoring systems as the basis for pre-emptive treatment of invasive candidiasis (see for example [116–120]), no data exist in other populations and in paediatric patients, and therefore, no recommendations are made.

Treatment of invasive candidiasis and candidaemia in children

General principles

Many of the general principles pertinent to the management of invasive candidiasis in children are derived from adults, and these are as follows: (i) antifungal therapy should be administered as quickly as possible (extrapolated from [121,122]); (ii) the optimal duration of therapy is 14 days after blood cultures are sterile, provided there is no unresolved deep infection or a severe persistent underlying immunological deficit (extrapolated from [123]); (iii) the appropriate choice of an anti-*Candida* agent may be influenced by local epidemiology because of the reduced susceptibility or resistance of some species to certain antifungal classes/agents; (iv) clinical evaluation for deep sites of infection, including an ophthalmological examination is required in all cases of candidaemia; (v) consideration should be given to removing or at least replacing intravenous catheters and/or other implanted prosthetic devices in a timely manner; and (vi) there is no firm recommendation regarding combination antifungal chemotherapy, but this may be considered in some situations (e.g. severe life-threatening infection, compromised drug penetration (e.g. cases of CNS infection, osteomyelitis, complicated urinary tract infections and complicated intra-abdominal infections).

Echinocandins

The echinocandins are first-line agents for the treatment of IC in children. The Expert Group does not consider that there are significant microbiological nor pharmacological differences between caspofungin, micafungin and anidulafungin. Differences in recommendations reflect the different stages in the development of these compounds for paediatric patients. Caspofungin (70 mg/m^2 loading dose followed by 50 mg/m^2/day i.v.) can be used for the treatment of IC (A-I). This recommendation is based on established efficacy in adults, a well-designed PK study [124,125], documented safety [126] and the existence of a paediatric label from the EMA. Similarly, micafungin (2–4 mg/kg/day i.v.) can also be used (A-I); this recommendation is based on a randomized control trial in adults and children [48,127], extensive pharmacokinetics [96,97], safety data [98] and the existence of a paediatric label. Anidulafungin (3 mg/kg loading dose, followed by 1.5 mg/day) is an alternative agent (B-II). While there is a RCT in adults [128] and some paediatric PK data [129], the Expert Group suggests a lower level recommendation for children because of uncertainty regarding the optimal paediatric dosage and relatively limited paediatric safety data. The Expert Group anticipates an 'upgrading' of anidulafungin with further clinical and PK studies and future regulatory approval for use in paediatric patients.

Amphotericin B formulations

Liposomal amphotericin B 3 mg/kg/day is an alternative first-line agent (A-I). This is based on a RCT in adults and children, concomitant pharmacokinetic studies [48,105,106,127] and safety data in children [48]. A higher rating compared with adults (i.e. B-I) is based on the lower incidence of toxicity in children [48,106]. ABLC is an alternative agent for IC, and there is some clinical experience in children [130,131]. Because of an absence of pharmacokinetic studies, and some uncertainty regarding the optimal regimen for invasive candidiasis, the Expert Group rated this agent B-II. Amphotericin B deoxycholate 0.6–1 mg/kg can be used for IC (C-I). This recommendation is supported by clinical data from adults [123,124] and concomitant PK data for children [132,133]. Amphotericin B deoxycholate is graded lower than lipid preparations principally because of a less favourable toxicity profile. Nevertheless, the Expert Group recognizes the use of amphotericin B deoxycholate for treatment of IC may be appropriate if other amphotericin B formulations are not available and also recognize a different grading compared with adults.

Triazoles

The triazoles have been widely used for treatment of invasive candidiasis in children. The use of fluconazole 8–12 mg/kg/day i.v. [B-I] is based on extensive RCT data in adults and paediatric PK studies [73,123,124,128] and extensive safety data [75]. The lower rating than suggested for prophylaxis reflects a fungistatic mode of activity. Nevertheless, fluconaz-

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ole may be a reasonable initial choice for children with IC who are haemodynamically stable and if there is a low institutional incidence of less susceptible or frankly resistant *Candida* species. There is some uncertainty regarding the use of fluconazole for *Candida glabrata* infections because this organism tends to exhibit higher MICs. *Candida krusei* is intrinsically resistant to fluconazole, and this agent should not be used in this context. Voriconazole (day 1: 9 mg/kg Q12 h, then 8 mg/kg BID i.v.); 9 mg/kg Q12 h PO (max. 350 mg Q12 h) for 2–12 years and 12–14 years with <50 kg; adult dose for patients 12–14 years >50 kg and patients >14 years) can be used for IC. A recommendation of B-I is based on a RCT in adults coupled with several well-designed PK studies in children [84–89,134]. Therapeutic drug monitoring should be performed. The 'B' rating reflects the fungistatic pattern of killing that appears common to the triazoles. Voriconazole is more potent *in vitro* against *Candida glabrata* than fluconazole and has activity against *Candida krusei* and may be a reasonable choice for these infections.

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W.W.H. has received grant support from National Institute of Health Research (NIHR), Medical Research Council, National Institute for the Replacement, Refinement and Reduction, of Animals in Research, Pfizer, Gilead, Schering-Plough, Merck and Astellas, and has served as a consultant for Pfizer, Astellas, Gilead, F2G, Vectura and Schering-Plough. He receives travel support from ESCMID.

E.C. has participated as invited speaker to symposia organized by Gilead, Pfizer, Astellas, Merck, Novartis and he has been member of advisory boards for Astellas and Pfizer.

A.H.G. has received research support from Enzon, Schering, Gilead, Merck and Schering. He has acted as speaker and/or consultant for Astellas, Cephalon, Gilead, Merck, Pfizer, Schering and Vicuron.

E.R. has received research support from Pfizer, Enzon, Schering, Gilead and Merck and he has made contributions in advisory boards of Gilead, Astellas and Pfizer. He has also received payment for talks on behalf of Gilead, Cephalon, Pfizer, Wyeth, Schering, Merck, Aventis and Astellas.

M.A. received, during the past 5 years, research grants and honoraria for talks and consultancy from Merck, Pfizer and Gilead.

M.C.A. has received grant support from Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering-Plough. She has been a consultant or at the advisory board for Gilead Sciences, Merck Sharp and Dohme, Pfizer, Pcovery and Schering-Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering-Plough.

S.A.A. has received investigator-initiated research grant support from Pfizer and has been at the Advisory Board for Pfizer-Turkey. She has received speaker honoraria from Merck and Pfizer.

M.B. has received research grants from Pfizer, MSD and Astellas and is/was an advisor or received lecture honorarium from Astellas, Angelini Farmaceutici, Astra Zeneca, Aventis, Bayer, Cephalon, Cubist, Gilead, MSD, Novartis, Shionogi, Pfizer, Teva and Vifor. He is also a board member of Pfizer, Angelini Farmaceutici, Cubist, MSD, Astellas, Novartis and Astra Zeneca.

J.B. has nothing to declare.

T.C. is member of the Speaker bureau and is advisor or consultant for Astellas, Baxter; bioMérieux, EISAI, Evolva, Immunexpress, Eli Lilly Suisse, Novartis, Merck Sharp & Dohme-Chibret AG and Pfizer. Grant support from Baxter, bioMérieux, Merck Sharp & Dohme-Chibret AG and Roche Diagnostic. He also received Royalties from Elsevier, payment for educational presentations from MSD, Institut Pasteur and Gilead Sciences, and travel support from Astellas, Pfizer and MSD.

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J.P.D. has received grant support from Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering-Plough. He has been a consultant or on an advisory board for Astellas, Gilead Sciences, Merck Sharp and Dohme, and Pfizer. He has received remuneration for giving lectures on behalf of Gilead Sciences, Merck and Pfizer.

J.G. has nothing to declare.

R.H. has been a consultant or at the advisory board for Astellas pharma, Basilea, Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer and Schering-Plough. He has been paid for talks on behalf of Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering-Plough. He has also received travel support from Pfizer and Gilead, research grants and invesigator fees from Pfizer.

H.E.J. has nothing to declare.

B.J.K. has received research grants from Bio-Mérieux and Cephalon. He is a consultant to Pfizer and is a member of the Gilead, MSD and Pfizer speaker bureaus.

C.L.-F. has received grant support in the past 5 years from Astellas Pharma, Gilead Sciences, Pfizer, Schering-Plough, and Merck Sharp and Dohme. She has been an advisor/consultant to Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering-Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering-Plough. She has had travel support from Astellas Pharma, Pfizer, Gilead Sciences and Schering Plough.

O.L. is a member of the MSD board, is a consultant for Astellas and Gilead Sciences and received grants or speaker's fees from MSD, Astellas, Gilead Sciences and Pfizer.

W.M. has received grant support from MSD and Pfizer. He had been an advisor to MSD and Pfizer. He has received honoraria for presentations on behalf of MSD/Schering-Plough and Pfizer.

G.P. has received research grants from Gilead, Pfizer, Astra Zeneca, Novartis, Astellas, GSK and MSD, has acted as paid consultant to Janssen Cilag, Gilead, Astellas and MSD, has received travel support from ESCMID, and is a member of the Gilead, Astellas and MSD speaker' s bureaus.

M.D.R. has received grants, speaker's honoraria and travel support from ESCMID, Pfizer, Astellas, MSD and Gilead Sciences. He has also received royalties from Blackwell Publishing, conference support from Astellas Pharma.

P.E.V. has received research grants from ESCMID, Pfizer, Astellas, Cephalon, Gilead Sciences, Merck and Schering-Plough.

C.V. received grants as speaker/moderator in meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott and BMS and received grants for participation in advisory boards by Gilead, Astellas, MSD, Nadirex Internation (Pavia, Italy) and Pfizer. Further, he obtained research grants for his institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS and Novartis. He is member of the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency Member of various levels of local Infection Control, Antibiotic Stewardship, Vaccine and HIV Committees (Genoa, Liguria, Italy).

A.J.U. has received research grants from MSD (Schering-Plough) and is/was an advisor or received lecture honorarium from Astellas, Aicuris, Basilea, Gilead, MSD and Pfizer.

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ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT)‡

A. J. Ullmann[1], M. Akova[2], R. Herbrecht[3], C. Viscoli[4], M. C. Arendrup[5], S. Arikan-Akdagli[6], M. Bassetti[7], J. Bille[8], T. Calandra[8], E. Castagnola[9], O. A. Cornely[10], J. P. Donnelly[11], J. Garbino[12], A. H. Groll[13], W. W. Hope[14], H. E. Jensen[15], B. J. Kullberg[11], C. Lass-Flörl[16], O. Lortholary[17,18], W. Meersseman[19], G. Petrikkos[20], M. D. Richardson[21], E. Roilides[22], P. E. Verweij[11] and M. Cuenca-Estrella[23] for the ESCMID Fungal Infection Study Group (EFISG)

1) *Department of Internal Medicine II, Julius-Maximilians-University, Würzburg, Germany,* 2) *Department of Medicine, Hacettepe University School of Medicine, Ankara, Turkey,* 3) *Hôpital de Hautepierre, University of Strasbourg, Strasbourg, France,* 4) *University of Genoa, IRCCS San Martino-IST, Genoa, Italy,* 5) *Statens Serum Institut, Copenhagen, Denmark,* 6) *Department of Medical Microbiology, Hacettepe University School of Medicine, Ankara, Turkey,* 7) *Santa Maria Misericordia University Hospital, Udine, Italy,* 8) *Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland,* 9) *Instituto Giannina Gaslini, Children's Hospital, Genova, Italy,* 10) *Department I of Internal Medicine, Clinical Trials Centre Cologne, ZKS Köln, Center for Integrated Oncology CIO KölnBonn, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), German Centre for Infection Research, University of Cologne, Cologne, Germany,* 11) *Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands,* 12) *University Hospitals Geneva, Geneva, Switzerland,* 13) *Department of Pediatric Hematology and Oncology, Center for Bone Marrow Transplantation, University Children's Hospital, Muenster, Germany,* 14) *Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK,* 15) *University of Copenhagen, Frederiksberg, Denmark,* 16) *Division of Hygiene & Medical Microbiology, Innsbruck Medical University, Innsbruck, Austria,* 17) *Université Paris Descartes, Service des Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants malades, APHP, Centre d'Infectiologie Necker-Pasteur, IHU Imagine, Paris, France,* 18) *Institut Pasteur, Centre National de Référence Mycologie et Antifongiques. Unité de Mycologie Moléculaire, CNRS URA3012, Paris, France,* 19) *University Hospital Gasthuisberg, Leuven, Belgium,* 20) *4th Department of Internal Medicine, School of Medicine, National and Kapodistrian University of Athens, 'ATTIKON Hospital,* RIMINI *1 – Haidari, Athens, Greece,* 21) *Mycology Reference Centre, University Hospital of South Manchester and Manchester Academic Health Science Centre, University of Manchester, Manchester, UK,* 22) *Third Department of Pediatrics, Aristotle University School of Medicine and Hippokration Hospital, Thessaloniki, Greece, and* 23) *Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain*

Abstract

Fungal diseases still play a major role in morbidity and mortality in patients with haematological malignancies, including those undergoing haematopoietic stem cell transplantation. Although *Aspergillus* and other filamentous fungal diseases remain a major concern, *Candida* infections are still a major cause of mortality. This part of the ESCMID guidelines focuses on this patient population and reviews pertaining to prophylaxis, empirical/pre-emptive and targeted therapy of *Candida* diseases. Anti-*Candida* prophylaxis is only recommended for patients receiving allogeneic stem cell transplantation. The authors recognize that the recommendations would have most likely been different if the purpose would have been prevention of all fungal infections (e.g. aspergillosis). In targeted treatment of candidaemia, recommendations for treatment are available for all echinocandins, that is anidulafungin (AI), caspofungin (AI) and micafungin (AI), although a warning for resistance is expressed. Liposomal amphotericin B received a BI recommendation due to higher number of reported adverse events in the trials. Amphotericin B deoxycholate should not be used (DII); and fluconazole was rated CI because of a change in epidemiology in some areas in Europe. Removal of central venous catheters is recommended during candidaemia but if catheter retention is a clinical necessity, treatment with an echinocandin is an option (CII_c). In chronic disseminated candidiasis therapy, recommendations are liposomal amphotericin B for 8 weeks (AIII), fluconazole for >3 months or other azoles (BIII). Granulocyte transfusions are only an option in desperate cases of patients with *Candida* disease and neutropenia (CIII).

Keywords: Candida, European, guideline, haematopoietic stem cell transplantation, malignancies

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Corresponding author: A. J. Ullmann, Infectious Diseases, Department of Internal Medicine II, Julius-Maximilians-University, Oberdürrbacher Str. 6, 97080 Würzburg, Germany
E-mail: andrew.ullmann@uni-wuerzburg.de

*European Society for Clinical Microbiology and Infectious Diseases.
†Members of the subgroup committee mainly responsible for this manuscript.
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Introduction

Infectious complications remain a major obstacle in the successful treatment of patients with malignant diseases. This part of the ESCMID guidelines focuses on the special need of this patient population with malignancies that had received chemotherapy or radiotherapy. *Candida* diseases played a pivotal role in the past in patients with malignancies [1–3]. In an Italian study, patients with AML and ALL developed candidaemia at incidence rates of 2–3% and 4–5%, respectively [4]. In one German hospital, candidaemia remains a disease with a high fatality rate [5]. Studies report an overall mortality risk as high as 38% with an attributable mortality of 19% [2]. Risk factors such as previous triazole exposure, age, high APACHEII scores, renal failure and neutropenia contribute to these high mortality rates [2,6]. A change in the *Candida* species epidemiology also needs special attention since fluconazole sensitive *C. albicans* is not the sole cause of disease [2,7]. Therefore, *Candida* diseases deserve special attention in this high-risk population. We included recommendations for haematopoietic stem cell transplant recipients, which is an integral part of the guideline. This guideline is divided into four parts: prophylaxis, pre-emptive/empirical therapy strategies, targeted treatment and specific situations in patients with malignancies.

Numerous guidelines have been published to date and have usually included all fungal diseases [8–11]. Here, we focus on Candida diseases with diagnostic procedures and recommendations for treatment. This guideline was originally edited as described previously by the first 4 authors and later reviewed and edited by the entire EFISG (ESCMID Fungal Infection Study Group) guideline group [155].

Other fungal diseases, for example aspergillosis in this patient population will also need special attention. The authors recognize that other filamentous fungal infections besides aspergillosis play a more pivotal role in the morbidity and mortality in this patient population (e.g. agents of mucormycosis) [12–16]. Therefore, the recommendations for prophylaxis and empirical/pre-emptive therapy would possibly direct our guideline recommendation in a different direction because this guideline focuses solely on *Candida* diseases.

The same grading system for the strength of recommendation and its documented quality of evidence are used throughout of this guideline as in the majority of the EFISG guidelines. The explanations and abbreviations used in this document are given in Table 1.

TABLE 1. Strength of the EFISG Recommendation and Quality of Evidence. Two parts: Strength of a Recommendation (SoR) and Quality of Evidence (QoE)

Strength of a recommendation	
Grade A	ESCMID strongly supports a recommendation for use
Grade B	ESCMID moderately supports a recommendation for use
Grade C	ESCMID marginally supports a recommendation for use
Grade D	ESCMID supports a recommendation against use
Quality of Evidence	
Level I	Evidence from at least one properly designed randomized, controlled trial
Level II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

*Added index:
$_r$: Meta-analysis or systematic review of randomised controlled trials.
$_t$: Transferred evidence that is results from different patients' cohorts, or similar immune-status situation.
$_h$: Comparator group is a historical control.
$_u$: Uncontrolled trial.
$_a$: Published abstract (presented at an international symposium or meeting).

Anti-Candida prophylaxis in allogeneic haematopoietic stem cell transplantation

The intention of the EFISG recommendations for prophylaxis in allogeneic haematopoietic stem cell transplantation is to look at the possibility of reducing morbidity and mortality due to *Candida* diseases. Obviously, the authors recognize that the recommendations would have been significantly different if the purpose would have been prevention of all fungal infections (e.g. aspergillosis). The prescribing physician should be aware of these interpretations. Different immune deficient situations, often referred to as the 'net state of immunosuppression', need to be appreciated during the course of allogeneic haematopoietic stem cell transplantation [17]. During the early post-transplantation phase, neutropenia is a major finding in these patients. Criteria for selecting prophylaxis throughout the various phases after transplantation should be a low toxicity profile and good efficacy. For the purpose of reducing morbidity, various antifungal agents have similar outcomes as fluconazole and have therefore received a similarly strong recommendation. But the strength of recommendation by the EFISG when including all possible fungal infections (i.e. aspergillosis) would be most likely different.

For prevention during the early neutropenic phase after transplantation, almost all available azoles are scored as highly recommended. Indeed, several publications demonstrated a reduction in morbidity for *Candida* diseases [18–23]. Later studies utilized voriconazole in comparison with itraconazole or fluconazole as comparators [24,25]. Despite

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the absence of noninferiority testing in the recent voriconazole trials, an equal outcome compared with fluconazole is assumed and therefore voriconazole received an AI recommendation for the prevention of *Candida* disease. Posaconazole was not tested in a trial during the early phase of allogeneic haematopoietic stem cell transplantation but the duration and severity of neutropenia is very similar to that observed during induction chemotherapy for AML therapy [26]. Because of this implied evidence, posaconazole received an AII_t recommendation. Micafungin and caspofungin were the only echinocandins so far assessed in prophylaxis and demonstrated similar efficacy to fluconazole in transplant recipients [27]. Chou *et al.* used caspofungin in allogeneic stem cell recipients. In this retrospective study, 7.3% of the 123 patients developed a fungal disease. Two of the nine cases with fungal disease were *Candida tropicalis* and *Candida glabrata* infections [28].

In addition to the early neutropenic phase, another time period plays historically an important role after allogeneic haematopoietic stem cell transplantation, that is, the first 100 days after transplantation. During this period, patients are also prone to fungal diseases but not all antifungal agents (e.g. micafungin and posaconazole) have been tested during this period [27]. Historically, a few azoles were able to reduce morbidity and mortality, especially fungal-attributable mortality, during this phase [18,19]. However, other trials examined the value of prophylaxis beyond the neutropenic phase to include this first 100 days period. As for the voriconazole prophylaxis trial that was performed during the first 100 days after transplantation, it had a similar outcome to fluconazole [24]. Therefore, the AI recommendation with the intention to reduce morbidity in invasive candidiasis is ascribed to voriconazole and fluconazole. In the well-known trials by Goodman *et al.* [18] and Slavin *et al.* [19], survival advantage was driven by reduced mortality to *Candida* disease. In the trial performed by Marr *et al.* [22], itraconazole demonstrated superiority to fluconazole but no mortality difference was noted. Itraconazole was associated with significantly more toxicity and this explains a weaker strength of recommendation for itraconazole than fluconazole. It remains unclear whether patients without GVHD and recovered neutrophils need anti-*Candida* prophylaxis during the first 100 days after transplantation.

Another important intention for the outcome of patient care is the survival advantage when using antifungal agents as prophylaxis. Again, during the early phase of neutropenia, all azoles except fluconazole received a lower recommendation (C). During the first 100 days after transplantation, only fluconazole compared with placebo was able to demonstrate a survival advantage in *Candida* diseases [18,19]. Both voriconazole trials did not demonstrate any mortality difference [24,25]. The overall death rate in the Cornely *et al.* [26] trial was significantly lower in patients with posaconazole, and therefore, posaconazole received a slightly stronger grade of recommendation. Finally, during moderate to severe graft-versus-host disease, posaconazole received a weaker BI recommendation. In the Ullmann *et al.* [29] trial, posaconazole had an identical outcome regarding *Candida* infection compared with fluconazole, but the rate of fungal-related death was lower with posaconazole and consequently posaconazole received a slightly higher recommendation, although the *Candida*-associated death rate was not clear. The association between intention and the dosage of the intervention, including strength of recommendation, are noted in Table 2.

Another important scenario of immunosuppression plays a significant role in the outcome in the transplant recipient. Due to increased immunosuppressive therapy during the latter phase (beyond 100 days) in patients with graft-versus-host disease, slow T-cell recovery and increased risk of fungal infections is obvious. The trial by Ullmann *et al.* [29] demonstrated that posaconazole and fluconazole were equally efficacious in preventing candida infections. Other drugs were rated weaker (Table 2). Itraconazole and amphotericin B deoxycholate received a weaker recommendation because of a weaker safety profile [22,30–32].

Anti-*Candida* prophylaxis in autologous haematopoietic stem cell transplantation and in severe and prolonged neutropenia

In the autologous transplant setting, only the neutropenic phase can be considered a possible risk situation for *Candida* diseases. But with the improvement of autologous transplantation procedures over time, antifungal prophylaxis is not recommended for autologous transplantation recipients [33]. Nevertheless, in centres with a high incidence of *Candida* disease, prophylaxis could remain an option, but based on recent data only a weak C recommendation is provided for itraconazole and posaconazole (C) [26,34]. The group was not able to provide a recommendation when antibody treatment is co-administered (e.g. rituximab) due to the lack of data, and obviously, there seems to be no increased risk of fungal infections. There is indirect evidence for a survival advantage in prophylaxis for invasive candida disease, which is only available from the Cornely *et al.* [26] trial for patients with severe and prolonged neutropenia. None were studied with other drugs for *Candida* disease in autologous stem cell recipients. In general, autologous haematopoietic stem cell transplantation is not considered a high-risk situation for patients.

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TABLE 2. Anti-*Candida* prophylaxis for allogeneic haematopoietic stem cell recipients

	Intention: Morbidity reduction		Intention: Survival improvement		
	SoR	QoE	SoR	QoE	References
Intervention (anti-Candidal prophylaxis) during the neutropenic phase					
Fluconazole 400 mg qd if no prophylaxis is considered	A	I	A	I	[18–20,22,23]
Itraconazole* 2.5 mg/kg oral solution tid	B	I	C	I	[22,23]
Posaconazole* 200 mg tid	A	II_t	B	II_t	[26,29]
Voriconazole* 200 mg bid	A	I	C	I	[24]
Caspofungin* 70/50 mg qd	C	II_u	C	III	[28]
Micafungin* 50 mg qd	A	I	C	I	[27]
Anidulafungin	NR	ND	NR	ND	
Liposomal amphotericin B 50 mg every other day iv, 100 mg/weekly	B	II	C	III	[38,39]
Intervention (anti-Candidal prophylaxis) during the first 100 days without GVHD and neutrophil recovery					
Fluconazole 400 mg qd	A	I	A	I	[18–20,22,23]
Itraconazole* 2.5 mg/kg oral solution tid	B	I	C	I	[22,23]
Posaconazole* 200 mg tid	C	III	C	III	[26,29]
Voriconazole* 200 mg bid	A	I	C	I	[24]
Caspofungin* 70/50 mg qd	C	II_u	C	II_u	[28]
Micafungin* 50 mg	C	III	C	III	[27]
Anidulafungin	NR	ND	NR	ND	
Liposomal amphotericin B 50 mg every other day iv, 100 mg/weekly	C	III	C	III	[38,39]
Intervention (anti-Candidal prophylaxis) in GVHD					
Fluconazole 400 mg qd	A	I	C	I	[18–20,22,23]
Itraconazole* 2.5 mg/kg oral solution tid	C	I	C	I	[22,23]
Posaconazole* 200 mg tid	A	I	B	I	[29], equal outcome regarding *Candida* disease
Voriconazole* 200 mg bid	B	I	C	I	[24] equal outcome regarding *Candida* disease
others	NR	ND	NR	ND	ND

NR, no recommendation; ND, no data available.
*Decision was based on comparative trials with fluconazole.

TABLE 3. Anti-Candida prophylaxis outside of allogeneic haematopoietic stem cell transplantation (e.g. autologous haematopoietic stem cell transplantation or chemotherapy induced neutropenia)

		Autologous HCT		Severe and prolonged neutropenia		
Intention	Situation	Intervention	SoR/QoE	Intervention	SoR/QoE	References
Reduce morbidity and mortality (during and after high dose chemotherapy)		Any prophylaxis	DIII	Any prophylaxis	DIII	[33]
Additional antibody treatment (e.g. retuximab)		Any prophylaxis	DIII	Any prophylaxis	DIII	
Morbidity reduction or survival advantage*	Neutropenia*	Fluconazole	ND	Fluconazole	CI	For autologous HCT: [26, 34]
		Itraconazole	CII	Itraconazole	CI	
		Posaconazole	CIIt	Posaconazole	CIIt	For neutropenia: [26, 32, 35-38, 40–43]
		Voriconazole	ND	Voriconazole	ND	
		Anidulafungin	ND	Anidulafungin	ND	
		Caspofungin	ND	Caspofungin	CI	
		Micafungin	ND	Micafungin	ND	
		Nystatin	DIIt	Nystatin	DII	
		Any amphotericin B formulation	ND	Any amphotericin B formulation	DI	

*If an institution wishes prophylaxis, weak recommendations for selected antifungal agents are provided.
ND, no data.

The treatment of numerous other malignant diseases causes neutropenia in varying degrees of severity and duration. Prophylaxis in this patient population is usually administered only if the patient develops profound and prolonged neutropenia. Again, our group does not support prophylaxis for the prevention of *Candida* diseases in this setting (prophylaxis: DII).

In nontransplantat settings, all recommendations are very similar to those for autologous transplantation. There is only very weak evidence for the use of azole prophylaxis against *Candida* diseases for the group of azoles. The study by Glasmacher *et al.* [32] saw no difference between fluconazole and itraconazole. Another randomized placebo-controlled study demonstrated the superiority of itraconazole for

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TABLE 4. Empiric therapy to treat possible *Candida* disease: All situations causing severe and prolonged neutropenia

Intention	Intervention	Allogeneic HCT included	SoR	QoE	References
Morbidity reduction	Liposomal amphotericin B (3 mg/kg/day)	Yes	A	I	[44,45,47,55]
	Caspofungin (70 mg on day 1 then 50 mg)	Yes	A	I	[46,47]
	Amphotericin B colloidal dispersion (4 mg/kg/day)	Yes	C	I	[54]
	Amphotericin B lipid complex (5 mg/kg/day)	Yes	B	I	[55]
	Itraconazole (200 mg iv q12h on day 1 & 2 then 200 mg iv/day)	ND	B	I	[56,57]
	Voriconazole (2 × 6 mg/kg on day 1 then 2 × 3 mg/kg/day)§	Yes	B	I	[48]
	Fluconazole (400 mg/day)	ND	C*	I*	[52,53]
	Amphotericin B deoxycholate (0.5–1.0 mg/kg/day)	Yes	D	II_t	[44,54,56,57]
	Micafungin (100 mg)	Yes	B	II	[49,50]
	Anidulafungin	ND	NR		No data

*Limited use since fluconazole has no mould activity. Application requires appropriate work-up to rule out mould disease.
NR, no recommendation; ND, no data available, §, dosis according to trial [48].

preventing superficial fungal infection in patients with haematological malignancies and neutropenia [35]. Only one study by Menichetti *et al.* [36] demonstrated a significant lower incidence of fungaemia due to *Candida* species in 0.5% of itraconazole recipients and in 4% of placebo recipients, a difference of 3.5 percentage points (95% CI, 0.5–6%; p <0.01). Obviously, no overall survival advantage in *Candida*-associated mortality was noted.[36,37] In the trial by Penack *et al.* [38], low dose of liposomal amphotericin B did not significantly prevent *Candida* infections. In a similar but smaller trial by Cordonnier *et al.* [39], only one of twenty-nine patients developed probable *Candida* disease. Other trials utilized various comparators (e.g. amphotericin B/nystatin or fluconazole vs. itraconazole), but none demonstrated superiority [40,41]. Nystatin, an oral polyene, cannot be recommended as prophylaxis [42]. Only one retrospective trial where micafungin was assessed as prophylaxis led to a significant decrease in the occurrence of IFI (from 12.3% to 1.5%, p 0.001) [43] (Table 3).

Secondary prophylaxis is not indicated in cases of prior candidaemia without any sign of deep-seated infection when patients are exposed to a new immunosuppressive therapy or where prolonged neutropenia is induced by chemotherapy, autologous or allogeneic HCT. The strength of recommendation for secondary prophylaxis in patients with a history of deep-seated invasive *Candida* disease (not candidaemia alone) was rated C III.

Empiric or pre-emptive (diagnostic driven) antifungal therapy

In patients expected to suffer prolonged duration of neutropenia [>10 days] (induction and consolidation chemotherapy of AML/MDS and autologous, or allogeneic transplantation) fever occurs frequently and is usually treated primarily with broad-spectrum antibacterial agents. If the patient does not defervesce after at least 3–4 days of antibacterial treatment, the presence of an undetected fungal infection is assumed and antifungal therapy is usually added with the intention of preventing further morbidity or death (AII) [44]. Extensive diagnostic workup is required to exclude a clinically or mycological documented infection which might require specific therapy.

Again, similar to the prophylactic indication, a challenge in providing recommendations was the fact that empirical treatment is not only given for the intention of treating as early as possible an undetected *Candida* disease, but also any kind of fungal infection (e.g. filamentous fungal infections). With regards to a reduction in morbidity, liposomal amphotericin B and caspofungin received an AI recommendation [44–47] (Table 4). Voriconazole failed to demonstrate noninferiority when compared to liposomal amphotericin B but in a subset analysis of high-risk patients no differences were noted [48]. In a prospective but one-armed trial with micafungin, not a single patient receiving empiric treatment developed a breakthrough fungal infection [49]. In a retrospective trial comparing micafungin and caspofungin, breakthrough *Candida* diseases were detected at a rate of 0.7% and 2.8%, respectively [50]. Amphotericin B deoxycholate and fluconazole were not recommended for empirical treatment despite the existence of adequate studies in the past, because of toxicity in the first case, and narrow spectrum of action in the second case [51–53]. The differences in the grading of amphotericin B formulations lie solely in the different toxicity profiles [54–56]. Amphotericin B colloidal dispersion causes infusion-related events similar in frequency and intensity to amphotericin B deoxycholate and in a direct double-blind comparison trial amphotericin B lipid complex was more toxic than liposomal amphotericin B [54,55]. The use of itraconazole provided some promising results in a noncomparator trial and in a recent published trial compared with amphotericin B [56,57]. In the latter trial, itraconazole had a better outcome. The major limitation for fluconazole was

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the lack of antimould activity. Therefore, if fluconazole is used, it remains essential to rule out a mould infection by the *Aspergillus* galactomannan index (GMI) ELISA and chest and sinus CT scan.

A consensus criteria defining pre-emptive (sometimes also called 'diagnostic driven') treatment of fungal infections in cancer patients does not exist. The term 'pre-emptive treatment' is associated more with filamentous fungi infections than with *Candida*-associated diseases. This approach is not driven by persistent fever or neutropenia but rather by galactomannan antigen detection in serum and/or BAL fluid or high-resolution CT scan in high-risk patients [58]. The role 1,3-ß-D-glucan and PCR testing for aspergillosis/candidiasis remains controversial [59,60]. Whether or not any kind of infiltrate in the presence of *Aspergillus* galactomannan should trigger antifungal therapy is still debatable, although few experts would not add an antifungal agent in all of these situations. Some experts wait for *Aspergillus* associated typical radiographic signs [halo, wedge shaped, air crescent or cavity] before starting treatment [58]. Other authors are more flexible [61,62]. Basically, no recommendation can be given at this point on the choice between the empirical and pre-emptive approach.

No clinical trial has been performed to compare antifungal drugs for this indication, and therefore, no recommendation can be made. The main studies which tested the pre-emptive approach used liposomal or deoxycholate formulation of amphotericin B or voriconazole [61–63]. As treating pre-emptively should mean treating at an early phase of disease, drugs approved for the treatment of fungal diseases might be effective or at least should be evaluated.

In summary, no data exist regarding whether or not *Candida* diseases can be managed by pre-emptive anti-Candida therapy. If *Candida* disease is the main concern and the patient is not on azole prophylaxis, then fluconazole might be a good choice. However, in contrast to the ICU setting, no trial has prospectively assessed the role of *Candida* spp. colonization or 1,3-ß-D-glucan in these patients [64]. 1,3-ß-D-glucan was assessed previously in a meta-analysis by Lamoth *et al.* [65] The group concluded that two consecutive positive antigen tests in patients with haemato-oncological patients demonstrate a high specificity, positive predictive value but a low sensitivity. Therefore, the test needs to be combined with clinical and radiological assessments and microbiological findings [65].

Mucosal oropharyngeal or oesophageal candidiasis

Mucosal candidiasis does not play a significant role for morbidity or mortality in haematological malignancies. The occurrence of oropharyngeal or oesophageal candidiasis is more inconvenient than threatening for the patient and usually easy to treat. For a rapid response, oral azoles, for example fluconazole, are recommended (AI) [66]. Physicians should keep in mind that azole-resistant *Candida* species can be selected during therapy even without prolonged treatment periods [67,68]. Other azoles can then be used [69–74]. Topical polyenes treatment is recommended for mild forms as in nonimmunocompromised patients [66,75–78].

Oral candidiasis with dysphagia and thoracic pain when swallowing is suggestive of oesophageal involvement. In this situation, topical treatment is not recommended (topical polyene treatment for oesophagitis: DIII). Cases refractory to fluconazole can be treated with any other azole if MIC tests suggest susceptibility [70,71,79–82]. In the event of severe or refractory disease, intravenous antifungals such as an echinocandin or liposomal amphotericin B might be indicated [83–90] (Table 5). It is essential to identify the species causing candidiasis to ensure susceptibility to the chosen agent [91]. This is a minimum requirement in immune-compromised patients, because resistance might have developed and a mixed aetiology might be possible.

Targeted treatment of invasive candidiasis/candidaemia

Treatment of invasive candidiasis or candidaemia should always focus on the success of treatment with improved survival. Once the diagnosis of candidaemia is established, blood cultures should be drawn on a daily basis until negativity for at least two consecutive samples (B I). Treatment should at least continue for 14 days after the last positive blood culture [92]. Individuals who have negative blood cultures for more than 14 days but remain neutropenic at approximately day 28 (or are not expected to recover from neutropenia) should be evaluated for the resolution of clinical signs and symptoms including exclusion of endocarditis and endophthalmitis by appropriate examination. But defining an exact and appropriate duration of therapy is still an issue of debate.

It is recommended that for patients who are on prophylaxis that the class of drugs for antifungal treatment be changed (C III). In prospective trials, only a few neutropenic patients were enrolled [93–97]. This consideration reduces the level of our recommendation in comparison with intensive care patients. Caspofungin and micafungin trials included approximately 10% neutropenic patients [94–96]. The outcome of these patients was also favourable, and therefore, both agents received an AII_t recommendation. Anidulafungin

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TABLE 5. Treatment of mucosal oropharyngeal or oesophageal candidiasis. Identification of *Candida* species would be desirable

Diseases	Intension	Intervention	SoR/QoE	References
Oropharyngeal	Eradication	Nystatin suspension (non-neutropenic, mild presentation)	CII_t	[76,77]
		Miconazole buccal	BII_t	[78]
		Fluconazole	AI	[66,75]
		Itraconazole solution	BII_t	[72–74]
		Posaconazole	AII_t	[69,70]
		Voriconazole	BIII	[71]
		Echinocandins (anidulafungin, caspofungin) only in very severe and refractory cases	BIII	[84,149,150]
		Liposomal amphotericin B as an option only in very severe and refractory cases	CIII	
Oesophageal	Eradication	Fluconazole	AII_t	[81,82,151–153]
		Itraconazole	BII_t	[72,80,82]
		Posaconazole	AII_t	[70]
		Voriconazole	AIII	[71]
		Topical treatment	DIII	
		Echinocandins (anidulafungin, caspofungin and micafugnin) or liposomal amphotericin B only in very severe and refractory cases	BII_t	[84–90]

on the other hand received a marginally weaker recommendation (BII_t) because there were <3% neutropenic patients in this trial [97]. The extensive usage of echinocandins could trigger resistance against this class of antifungal agents in the future because some areas in the world have demonstrated an increase in *C. parapsilosis* which usually has higher MICs compared with other *Candida* species [98,99]. Despite good sensitivity results, first reports demonstrate caution on the usage of echinocandins [100,101]. These are some of the reasons for species discrimination and susceptibility testing which are highly recommended in these settings.

Fluconazole, once considered gold standard in the treatment of candidaemia received a weaker recommendation despite positive outcomes in a number of trials [92,102]. These trials are considered out-dated, especially when considering the risk of the development of resistance. In recent publications, previous fluconazole or triazole exposure and gastrointestinal tract surgery are risk factors for fluconazole-resistant candidaemia. In addition to invasive ventilation, renal impairment, age >65 years and steroids and triazole exposure are considered risk factors for death [6,103]. Therefore, fluconazole should only be considered as a step-down treatment option in neutropenia when the *Candida* species isolates demonstrate susceptibility to fluconazole. Other azoles had only limited data and because of this, itraconazole and posaconazole in particular, cannot be recommended for treatment [104]. On the other hand, more data exist for voriconazole and it may be considered as an option [105,106]. Despite equal outcome when compared to micafungin, liposomal amphotericin B received only a BII recommendation due to its higher nephrotoxicity profile [96,107]. Due to different toxicity profiles and weak data of other lipid formulations of amphotericin B, a C grading for the recommendation for treating invasive candidiasis or candidaemia is given [108–112]. Extensive nephrotoxicity, consecutive higher mortality and other unacceptable toxicity are factors that make amphotericin B deoxycholate not recommendable for treatment (DII) [30,31] (Table 6).

If patients were receiving fluconazole or liposomal amphotericin B, a switch to an echinocandin might be desirable (BII_t). Basically, there is no adequately powered randomized trial for this situation neither for neutropenic patients nor for stem cell transplant recipients but the identification of the *Candida* species and susceptibility testing could be helpful for making a decision (e.g. *Candida krusei*)(BIII).

In vitro and animal data of antifungal combinations seem to improve the efficacy of antifungal treatment. In humans, especially neutropenic patients this outcome is not so clear-cut.

TABLE 6. Targeted treatment of invasive candidiasis/candidaemia in patients with malignancies, usually with neutropenia

Intention	Intervention	SoR	QoE	Comment	References
Morbidity reduction and survival improvement	Fluconazole	C	II_t	Caution regarding resistance. Fluconazole should rather be considered as a step-down treatment option	[92,93,102]
	Itraconazole	D	III	Only abstract in non-neutropenics	[154]
	Posaconazole	D	III	One case report in a non-neutropenic	[104]
	Voriconazole	C	II_t	Alternative agent due to better susceptibility data in comparison with fluconazole but limited clinical data	[105,106]
	Amphotericin B colloid dispersion	C	III	Considerable nephrotoxicity	[111,112]
	Amphotericin B deoxycholate	D	II_t	Unacceptable toxicity	[30,31,44,93,94]
	Amphotericin B lipid complex	C	II_a	Considerable nephrotoxicity	[108,110]
	Anidulafungin	B	II_t	<3% of the participants were neutropenic	[97]
	Caspofungin	A	II_t	~10% of the participants were neutropenic	[94,95]
	Liposomal amphotericin B	B	II_t		[96,107]
	Micafungin	A	II_t	~10% of the participants were neutropenic consider EMA warning	[95,96]

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Only a few combinations have been studied without any improved outcome. Combination of amphotericin B deoxycholate and 5-flucytosine is not recommended due to its toxicity and erratic pharmacokinetics [113–115]. Efungumab and a lipid formulation amphotericin B are also not recommended because flaws in the design of the study hampered outcome [116]. Efungumab is not an approved or marketed drug. The combination of amphotericin B deoxycholate and fluconazole was studied as a sequential therapy and did not demonstrate any improvement to the comparators [105]. There was even more toxicity in the amphotericin B group despite a median of only 3 days of amphotericin B deoxycholate exposure. Another trial assessed whether this combination was antagonistic [117]. Due to its similar outcome, this combination can be considered an option (CII_t). Other combinations were not studied but the expert opinion is that antifungal combinations might be useful in severe deep-seated infections (e.g. abdominal infection, CNS and endocarditis, CIII).

Chronic disseminated candidiasis

Chronic disseminated candidiasis or hepato-splenic candidiasis is a very specific syndrome in patients with malignant diseases. The disease usually occurs after the recovery of neutrophils due to previous chemotherapy. The diagnosis of chronic candidiasis is challenging when prior candidaemia has not been documented. Imaging by ultrasound examination demonstrates a weaker sensitivity in comparison with CT or MRI [118–121]. Only one study could show a higher sensitivity utilizing MRI in comparison with CT [118]. But despite adequate imaging techniques, the confirmation of the diagnosis by biopsy remains troublesome. Histology with culture positivity is seldom. No comparator trials in regard to morbidity improvement or survival advantage have been performed or published. Antigen detection [e.g. mannan/anti-mannan or 1,3-ß-D-glucan) are probably helpful, but data in this situation are scarce [122]. Histology requires the use of special staining (Gomori) and immunohistochemistry and molecular-genetic workup is highly recommended.

In terms of treatment, only a few case series have been published [96,123–126]. The experience of treatment is currently only anecdotal. Lipid formulations of amphotericin B might be a good choice because of potential accumulation in the reticulo-endothelial system [127]. Frequently, sequential approaches are employed empirically, for example liposomal amphotericin B followed by prolonged treatment of fluconazole. The disease has been recently considered to be an inflammatory immune reconstitution syndrome [128]. There are interesting publications that suggest the co-administration of steroids at the beginning of treatment [129,130]. The duration of antifungal treatment appears to be at least 8 weeks. Again the use of amphotericin B deoxycholate is not encouraged (Table 7).

Biofilms and central venous catheters

Central venous catheters (CVC) play a major role in the care of this patient population. Once inserted, the removal or replacement might threaten the life of the patient because of frequently experienced thrombocytopenia. Upon review of the published data, a negative outcome during therapy by not removing the central venous catheter early appears only to occur in the situation where echinocandins were not used [6,94–97,131,132]. In the recently published trials, where the central venous catheter was retained, the outcome was similar but the numbers noted in those trials were low [94,95,97]. Additionally, these trials demonstrated an equal outcome in *C. parapsilosis* disease despite other publications indicating higher MICs [133,134]. As *C. parapsilosis* is associated with catheter infections, removal would be desirable.

On the other hand, if catheter retention is clinical necessary, treatment with an echinocandin remains an option. Nevertheless, persistence of positive blood cultures for yeast should prompt removal of a central venous catheter. Velasco and Bigni [135] saw in their study by multivariate analysis that comorbidities and neutropenia were independently associated with mortality in adults and not CVC removal. In a trial by Liu *et al.*, early catheter removal is associated with better survival. In this trial, the retention of the catheter, high APACHE II score or thrombocytopenia was associated with a higher mortality rate [131]. Nucci *et al.* [136] looked especially on the outcome in terms of CVC removal and reported no differences between the groups being given caspofungin, micafungin or liposomal amphotericin B. But

TABLE 7. Treatment of chronic disseminated candidiasis

Intention	Intervention	Duration	SoR/QoE	Comments	Reference
Eradication	Fluconazole	Reported duration minimum 3 months	BIII	[125,126]	[125,126]
	Other azoles (if susceptibility is expected)		BIII	Lacking data	ND
	Amphotericin B deoxycholate		DIII	Toxicity issues	[30,31]
	Lipid formulations of amphotericin B	8 weeks	AIII	Better exposure	[96,124]
Defervesce	Steroid therapy	Until defervesce	CIII		[129,130]

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TABLE 8. Treatment of *Candida* Biofilm and catheter-related candidaemia

Intention	Intervention	SoR/QoE	Comment	Reference
Survival advantage	Early catheter removal	AII_u	Retention and high APACHE II and thrombocytopenia also associated with higher mortality.	[131,132,137]
Morbidity reduction	Catheter retention	CII_t	Patients in trials treated with echinocandins and CVC retention had equal outcome (low numbers)	[94–97]
	If catheter retention use echinocandins or liposomal amphotericin B, not azoles or amphotericin B deoxycholate	CII_t	Worse outcome in non echinocandins trials	[94–97,137]
	Other implanted hardware (pace-maker, port-a-cath)	CIII	Keep unless proven associated with candidaemia. No published data available	ND

another work by Andes *et al.* [137] saw in review of seven clinical trials that improved survival and greater clinical success is associated with the use of an echinocandin and removal of the CVC. A few in vitro studies indicate that echinocandins penetrate *Candida* biofilm better than other antifungal agents [138,139]. A more clinically challenging question is how to handle other implanted hardware, for example pacemaker, port-a-cath. Unless an association could be provided, in cases with implanted hardware and with candidaemia, retention of the hardware is appropriate but no published data are available. Unfortunately, no reliable symptom or sign associated with hardware is available (Table 8).

Cytokines, colony-stimulating factors and granulocyte infusions for the treatment of invasive candidiasis or candidaemia

The question regarding the use of colony-stimulating factors or cytokines in the treatment of invasive candidiasis or candidaemia remains unanswered. No controlled trials are available and only anecdotal data from small numbers of patients exist. As persistent neutropenia is related to treatment failure, recovery from neutropenia substantiates the efficacy of antifungal agents [140–142]. Therefore, the use of colony-stimulating factors appears to be an option (C III). A recent Cochrane review indicates no mortality differences for all infections in patients suffering from neutropenia [143]. There is only a weak recommendation for granulocyte infusions, but the data are basically from children (CIII) [144–148]. This treatment might be considered an option in desperate cases.

Transparency Declarations

A.J.U. has received research grants from MSD (Schering Plough) and is/was an advisor or received lecture honorarium from Astellas, Aicuris, Basilea, Gilead, MSD and Pfizer.

M.A. received, during the past 5 years, research grants and honoraria for talks and consultancy from Merck, Pfizer and Gilead.

R.H. has been a consultant or at the advisory board for Astellas pharma, Basilea, Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer and Schering Plough. He has been paid for talks on behalf of Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. He has received research support from Pfizer, travel support from Pfizer and Gilead, and investigator fees for a clinical trial from Pfizer.

C.V. received grants as speaker/moderator in meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott, BMS and received grants for participation in advisory boards by Gilead, Astellas, MSD, Pfizer. Further, he obtained research grants for his institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, Novartis. He is member of the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency Member of various levels of local Infection Control, Antibiotic Stewardship, Vaccine and HIV Committees (Genoa, Liguria, Italy), Nadirex International (Pavia, Italy).

M.C.A. has received grant support from Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. She has been a consultant or at the advisory board for Gilead Sciences, Merck Sharp and Dohme, Pfizer, Pcovery and Schering Plough. She has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough.

S.A.A. has received investigator initiated research grant support from Pfizer and has been at the Advisory Board for Pfizer-Turkey. She has received speaker honoraria from Merck and Pfizer.

M.B. has received research grants from Pfizer, MSD and Astellas and is/was an advisor or received lecture honorarium from Astellas, Angelini Farmaceutici, Astra Zeneca, Cubist, Aventis, Bayer, Cephalon, Cubist, Gilead, MSD, Novartis, Shionogi, Pfizer, Teva and Vifor.

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J.B., J.G., H.E.J. has nothing to declare. T.C. is member of the Speaker bureau and is advisor or consultant for Astellas, Baxter; bioMérieux, EISAI, Evolva, Novartis, Merck Sharp and Dohme-Chibret AG, Pfizer. Grant support from Baxter, bioMérieux, Merck Sharp and Dohme-Chibret AG, Roche Diagnostic.

E.C. has participated as invited speaker to symposia organized by Gilead, Pfizer, Astellas, Merck, Novartis and he has been member of advisory boards for Astellas, Pfizer.

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A.H.G. has received research support from Gilead, Merck and Schering. He has acted as speaker and/or consultant for Astellas, Cephalon, Gilead, Merck, Pfizer, Schering and Vicuron.

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B.J.K. has received research grants from Bio-Mérieux and Cephalon. He is a consultant to Pfizer and is a member of the Gilead, MSD and Pfizer speaker bureaus.

C.L.-F. has received grant support in the past 5 years from Astellas Pharma, Gilead Sciences, Pfizer, Schering Plough and Merck Sharp and Dohme. She has been an advisor/consultant to Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough. She has received travel support and has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough.

O.L. is a member of the MSD board, is a consultant for Astellas and Gilead Sciences and received grants or speaker's fees from MSD, Astellas, Gilead Sciences and Pfizer.

W.M. has received grant support from MSD and Pfizer. He had been an advisor to MSD and Pfizer. He has received honoraria for presentations on behalf of MSD/Schering Plough and Pfizer.

G.P. has received research grants from Gilead, Astra Zeneca, Novartis, Astellas, GSK, Pfizer and MSD, has acted as paid consultant to Janssen Cilag, Gilead, Astellas, and MSD and is a member of the Gilead, Astellas and MSD speaker' s bureaus. He has also speaker's honoraria and received travel support from ESCMID, Pfizer, Astellas, MSD and Gilead Sciences.

M.D.R. has received grants, speaker's honoraria and travel support from ESCMID, Pfizer, Astellas, MSD and Gilead Sciences. He has also received book royalties from Blackwell Publishing and travel support from Astellas Pharma.

E.R. has received research support from Pfizer, Gilead, Merck, Enzon, Schering and he has made contributions in advisory boards of Gilead, Astellas, Pfizer, Merck, Schering. He has also been paid for talks on behalf of Gilead, Cephalon, Pfizer, Wyeth, Schering, Merck, Aventis and Astellas.

P.E.V. has received research grants and/or travel support and/or travel support from Pfizer, Astellas, Cephalon, Gilead Sciences, Merck and Schering Plough.

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ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: patients with HIV infection or AIDS

O. Lortholary[1,2†], G. Petrikkos[3†], M. Akova[4], M. C. Arendrup[5], S. Arikan-Akdagli[6], M. Bassetti[7], J. Bille[8], T. Calandra[9], E. Castagnola[10], O. A. Cornely[11], M. Cuenca-Estrella[12], J. P. Donnelly[13], J. Garbino[14], A. H. Groll[15], R. Herbrecht[16], W. W. Hope[17], H. E. Jensen[18], B. J. Kullberg[13], C. Lass-Flörl[19], W. Meersseman[20], M. D. Richardson[21], E. Roilides[22], P. E. Verweij[13], C. Viscoli[23] and A. J. Ullmann[24†] for the ESCMID Fungal Infection Study Group (EFISG)

1) *Université Paris Descartes, Service des Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants malades, APHP, Centre d'Infectiologie Necker-Pasteur, IHU Imagine,* 2) *Institut Pasteur, Centre National de Référence Mycoses Invasives et Antifongiques, Unité de Mycologie Mole'culaire, CNRS URA3012, Paris, France,* 3) *4th Department of Internal Medicine, School of Medicine, National and Kapodistrian University of Athens, "ATTIKON" Hospital, RIMINI 1 - Haidari, Athens, Greece,* 4) *Department of Medicine, Hacettepe University School of Medicine, Ankara, Turkey,* 5) *Statens Serum Institut, Copenhagen, Denmark,* 6) *Department of Medical Microbiology, Hacettepe University School of Medicine, Ankara, Turkey,* 7) *Santa Maria Misericordia University Hospital, Udine, Italy,* 8) *Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland,* 9) *Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland,* 10) *Instituto Giannina Gaslini, Children's Hospital, Genova, Italy,* 11) *Department I of Internal Medicine, Clinical Trials Centre Cologne, ZKS Köln, BMBF 01KN1106, Center for Integrated Oncology CIO KölnBonn, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), German Centre for Infection Research, University of Cologne, Cologne, Germany,* 12) *Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain,* 13) *Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands,* 14) *University Hospitals Geneva, Geneva, Switzerland,* 15) *Department of Pediatric Hematology/Oncology, Center for Bone Marrow Transplantation, University Children's Hospital, Muenster, Germany,* 16) *Hôpital de Hautepierre, University of Strasbourg, Strasbourg, France,* 17) *Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK,* 18) *University of Copenhagen, Frederiksberg, Denmark,* 19) *Division of Hygiene & Medical Microbiology, Innsbruck Medical University, Innsbruck, Austria,* 20) *University Hospital Gasthuisberg, Leuven, Belgium,* 21) *Mycology Reference Centre, University Hospital of South Manchester and Manchester Academic Health Science Centre, University of Manchester, Manchester, UK,* 22) *Third Department of Pediatrics, Aristotle University School of Medicine and Hippokration Hospital, Thessaloniki, Greece,* 23) *University of Genoa, IRCCS San Martino-IST, Genoa, Italy and* 24) *Department of Internal Medicine II, Julius-Maximilians-University, Würzburg, Germany*

Abstract

Mucosal candidiasis is frequent in immunocompromised HIV-infected highly active antiretroviral (HAART) naive patients or those who have failed therapy. Mucosal candidiasis is a marker of progressive immune deficiency. Because of the frequently marked and prompt immune reconstitution induced by HAART, there is no recommendation for primary antifungal prophylaxis of mucosal candidiasis in the HIV setting in Europe, although it has been evidenced as effective in the pre-HAART era. Fluconazole remains the first line of therapy for both oropharyngeal candidiasis and oesophageal candidiasis and should be preferred to itraconazole oral solution (or capsules when not available) due to fewer side effects. For patients who still present with fluconazole-refractory mucosal candidiasis, oral treatment with any other azole should be preferred based on precise *Candida* species identification and susceptibility testing results in addition to the optimization of HAART when feasible. For vaginal candidiasis, topical therapy is preferred.

Keywords: Candidiasis, Europe, guideline, HIV AIDS
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Corresponding authors: O. Lortholary, Université Paris Descartes, Hôpital Necker-Enfants malades, Centre d'Infectiologie Necker-Pasteur 149, rue de Sèvres, 75743 Paris Cedex 15, France
E-mail: olivier.lortholary@nck.aphp.fr
and
A. J. Ullmann, Infectious Diseases, Department of Internal Medicine II, Julius-Maximilians-University, Oberdürrbacher Str. 6, 97080 Würzburg, Germany
E-mail: andrew.ullmann@uni-wuerzburg.de

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*European Society for Clinical Microbiology and Infectious Diseases.
†Members of the subgroup committee mainly responsible for this manuscript.

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Introduction

Oropharyngeal (OPC) and oesophageal (OEC) candidiasis are by far the most common fungal infections among patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) [1]. This guideline focuses on patients with HIV infection or AIDS with *Candida* diseases. The same grading system for the strength of recommendation and its documented quality of evidence are used throughout of this guideline as in the majority of the ESCMID *Candida* guidelines. The explanations and abbreviations used in this document are given in Table 1 [85].

Before the era of highly active antiretroviral therapy (HAART), OPC occurred in as many as 90% of patients, at some point during the course of HIV infection [1]. Although the incidence of mucosal *Candida* colonization and infection has been dramatically reduced with the introduction of HAART, it remains a common opportunistic infection in those HIV-infected patients without access to HAART or those in whom antiviral therapy is started late.

Oesophageal candidiasis was the leading opportunistic infection before the HAART era [2] and remains the second AIDS-defining illness in Europe [3]. In addition, mucosal candidiasis is still problematic in patients with poor adherence to treatment and/or multiple virological–immunological failures. The occurrence of OPC and OEC are indicators of profound immune suppression, and these syndromes are most often observed in patients with CD4+ counts <200 cells/μL with OEC being found in a more advanced stage of AIDS than OPC [1]. OPC and OEC are more difficult infections to treat in the context of HIV infection compared with other immunocompromised patients [4].

TABLE 1. Strength of the ESCMID recommendation and quality of evidence

Strength of a recommendation	
Grade A	ESCMID strongly supports a recommendation for use
Grade B	ESCMID moderately supports a recommendation for use
Grade C	ESCMID marginally supports a recommendation for use
Grade D	ESCMID supports a recommendation against use
Quality of evidence	
Level I	Evidence from at least one properly designed randomized, controlled trial
Level II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

*: Added index:
$_r$: meta-analysis (or systematic review of randomized control trials).
$_e$: transferred evidence , that is, results from different patients' cohorts, or similar immune-status situation.
$_h$: comparator group: historical control.
$_u$: uncontrolled trials.
$_a$: published abstract (presented at an international symposium or meeting).

Candida albicans is the most prominent pathogen. This organism can be found in the oral cavity of up to two-thirds of healthy individuals [5]. No particular strains have a preponderance to cause mucosal candidiasis. Acquired fluconazole (or pan triazole) resistance is related to previous exposure to fluconazole (or other triazoles), particularly if repeated and prolonged exposure in the context of profound immunosuppression [6–8]. Fluconazole resistance is associated with the cumulative exposure to fluconazole; patients failing fluconazole have received larger cumulative dosages of fluconazole (mean value, 8.7 g) [9]. The transmission of isolates (including those resistant to fluconazole) has been documented between HIV-infected partners [10]. Therefore, examination of partners is recommended.

In this setting, *C. albicans* resistance has also been accompanied by an emergence of non-*albicans Candida* species with intrinsic reduced azole susceptibility in the oral cavity (particularly *C. krusei* and *C. glabrata* [11]) and in the vagina [12]. *C. glabrata* may cause refractory mucosal candidiasis, particularly in patients with advanced immunosuppression [13].

Candida dubliniensis was first associated with OPC in HIV-infected patients [14]. The introduction of HAART with immunological reconstitution has led to a dramatic decline in the incidence of refractory disease and of infections caused by resistant *Candida* isolates. Barchiesi *et al.* [11] found that 93% of *Candida* collected from oral cavities among 102 HAART-treated patients remained susceptible to fluconazole, despite many of these patients receiving repeated courses of triazoles.

Clinical manifestations

Three clinical patterns of OPC have been described: erythematous, pseudo-membranous and angular cheilitis. OPC can occur at any stage of HIV infection (primary infection, chronic asymptomatic phase and AIDS), but erythematous (erythematous patches without white plaques visible on the anterior or posterior upper palate or diffusely on the tongue) and pseudomembranous (creamy white, plaque-like lesions of the buccal or oropharyngeal mucosa or tongue surface) forms are predictive of progressive immunodeficiency [15].

Oesophageal symptoms include retrosternal burning pain, altered taste and odynophagia. Endoscopic examination reveals whitish plaques similar to those observed with OPC that might progress to superficial ulceration of the OEC mucosa, with central or surface whitish exudates.

As relapse of OPC and OEC is common, it is often associated with recurrence of intense pain that contributes to weight loss because of poor nutrition.

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In contrast, vulvovaginal candidiasis is common among healthy adult women and is often unrelated to HIV status. Consequently, recurrent vulvovaginal candidiasis alone cannot be ascribed to advanced HIV disease.

Candida vulvovaginitis may be mild to moderate in severity and sporadic (similar to normal hosts). This syndrome is characterized by a white adherent vaginal discharge that is associated with burning and itching. In patients with advanced immunosuppression, episodes may be more severe and more frequently recurrent. Compared with OPC, vaginal candidiasis is frequently more responsive to triazole therapy.

Diagnosis of oropharyngeal candidiasis and oesophagitis

A diagnosis of OPC is usually made on clinical grounds. Lesions can be readily scraped with a tongue depressor or other instrument to obtain samples for a microbiological diagnosis. Fungal selective media should be used to avoid overgrowth by colonizing bacteria [16]. Identification to species level and susceptibility testing are recommended in recurrent cases of OPC and for patients repeatedly exposed to fluconazole (and/or other triazoles). If an upper endoscopy is performed, a biopsy may enable infection to be distinguished from colonization or other mucosal diseases [16].

The diagnosis of OEC requires endoscopic visualization of lesions with histopathologic demonstration of characteristic *Candida* yeast forms in tissue and culture confirmation of the presence of *Candida* species.

The diagnosis of vulvovaginal candidiasis is made with a combination of characteristic clinical appearances combined with standard microbiological investigations. The detection of serum biomarkers such as mannan/antimannan or ß-D-glucan is not required to confirm a diagnosis of mucosal candidiasis.

Primary prophylaxis of mucosal candidiasis

Despite the demonstrated efficacy of fluconazole, primary antifungal prophylaxis for the prevention of OPC and OEC is not recommended in Europe (DI). Fluconazole (200 mg/day) is superior to clotrimazole troches in a large randomized multicentric unblinded trial for the prevention of both OEC and OPC with a greatest benefit in patients with less than 50 CD4/mm^3 [17]. In addition, in a double-blind trial, Havlir *et al.* [18] observed double the rate of OPC among patients receiving 400 mg fluconazole weekly compared with those treated with 200 mg daily. Fluconazole 200 mg/week in a randomized double-blind placebo-controlled trial involving HIV-infected women prevented OPC and vaginal candidiasis but not OEC [19]. In a retrospective study, Manfredi *et al.* [20] demonstrated that fluconazole 100 mg/day every 3 weeks prevented the occurrence of OEC vs. no therapy. Finally, other triazoles such as itraconazole are more effective than placebo in the prevention of superficial *Candida* sp. infections [21] (Table 2).

While OPC may be associated with significant morbidity, the disadvantages of primary prophylaxis include the potential for drug–drug interactions between triazoles and HAART, the development of fluconazole resistance and/or cross-resistance to azoles, the availability of effective antifungal therapy for OPC and the cost and potential toxicity of triazole antifungal agents. Thus, the best prophylaxis of both OPC and OEC is the appropriate compliance to HAART (AII).

Treatment of first OPC episodes due to triazole susceptible isolates

More than 20 years after its introduction, fluconazole remains the leading antifungal drug that is used for OPC. Fluconazole is fungistatic against *Candida* spp. with an oral bioavailability of over 80%, which is not influenced by concomitant food intake or gastric pH. Penetration into saliva is excellent. Tablets, oral solution and intravenous formulation can all be used to treat OPC. Because of hepatic metabolism via the CYP450 enzyme complex, many drug interactions with fluconazole have been described. Fluconazole is well tolerated within the recommended range of doses for mucosal candidiasis. Side effects increasingly occur with doses in excess of 400 mg per day, which are not usually necessary for treatment of mucosal candidiasis [22]. Finally, EUCAST and CLSI susceptibility breakpoints have been defined for fluconazole and *C. albicans, C. parapsilosis* and *C. tropicalis:* susceptible, MIC ≤2 mg/L; and resistant, MIC >4 mg/L according to both EUCAST and CLSI (http://www.eucast.org).

Fluconazole at a dosage of 100 mg/day for 7–14 days is recommended for the first-line agent for the treatment of OPC for adults [23–28] and children (AI) [29,30] (Table 2). The majority of patients with OPC that is caused by fluconazole-susceptible isolates will respond to therapy within 72 h. Approximately 80% of patients are cured, and a further 10% experience significant improvement in their symptoms [31]. OPC is a mandatory indication of HAART's initiation (AII). No long-term suppressive triazole therapy should be used (DIII).

Potential alternatives to fluconazole include (i) miconazole as a mucoadhesive tablet 10 or 50 mg once daily for 7–14 days (approved in Europe since 2008 in its 50 mg for-

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TABLE 2. Recommendations made for patients with HIV infection or AIDS and Candida disease

Intention	Intervention	SoR	QoE	Reference/Commentary
Primary prophylaxis of mucosal candidiasis (OPC/OEC)	Primary antifungal prophylaxis of OPC/OEC	D	I	[17][19][18][20][21] although effective [interactions/ acute therapy effective/induction of resistance/no mortality related to OPC/cost)
	Best prophylaxis is appropriate compliance to HAART	A	II	[80][81][82][83][84]
Treatment of first episodes of oropharyngeal candidiasis (OPC) due to azole susceptible isolates	HAART should be initiated	A	II	[80][81][82][83][84]
	Fluconazole (100 mg/day in adults, at least 7 days)	A	I	[23][11][26,27][25][28][29][30]
	Miconazole mucoadhesive tablet	B	I	[32][33]
	Itraconazole oral solution	B	I	[35][36]
	Posaconazole (100 mg/day)	C	I	[4]
	Voriconazole	–	–	No published data
	Topical agents	D	I	[27][29]
	Ketoconazole	D	I	[23][11][45][42]
	Itraconazole capsules	D	III	Because of poor absorption [39]
	Echinocandins and any amphotericin B formulation	D	III	No published data
	Chronic suppressive therapy	D	III	No published data
Treatment of oesophageal candidiasis	Start treatment without endoscopy	A	III	In case of oesophageal symptoms and OPC, endoscopy is not indicated.
	Oral fluconazole (200 mg/day for 14–21 days) (or i.v. for those who cannot swallow)	A	I	[23][48][46][47]
	Itraconazole solution	B	I	[49][46][47]
	Echinocandins can be used in patients who cannot swallow but not better than Fluconazole	C	I	[55][56][57][53][54] Higher relapse rate with caspofungin and anidulafungin vs fluconazole
	Ketoconazole	D	I	[48][42]
	Any i.v. amphotericin B formulation	D	III	No role for the management of OEC due to azole susceptible isolates
	Local treatments	D	III	Less effective than fluconazole
Treatment of refractory OPC/OEC	Itraconazole oral solution (≥200 mg/day)	A	II	[64][63][65]
	Posaconazole (400 mg twice daily)	A	II	[66][67]
	Voriconazole (200 mg twice daily)	C	II	[68]
	Any echinocandin	A	II	[70][71][72] All echinocandins may be considered equivalent here
	Any amphotericin B formulation	C	II	No published data
Suppressive therapy	Fluconazole 100–200 mg 3×/week	A	I	[75][76][77][78][19][18][9][79]

HAART, highly active antiretroviral; OEC, oesophageal.

mulation) (BI). Miconazole was studied in a randomized trial vs. ketoconazole (similar efficacy but reportedly had more episodes of vomiting in patients on ketoconazole) and in a large phase III double-blind double dummy trial vs. clotrimazole (similar efficacy and acceptable tolerability), but not to the reference drug fluconazole [32–34]; (ii) itraconazole oral solution. Itraconazole solution for 7–14 days (100 or 200 mg/day) is equivalent to fluconazole for 14 days [35,36] (BI). Itraconazole solution may be beneficial even without the attainment of detectable serum levels because of its direct effect if swished in mouth for few seconds before swallowing [37]. Itraconazole solution is associated with a 30% increase in itraconazole absorption in comparison with the capsule formulation [38] and with a comparable rate of side effects compared with fluconazole [35,36] for OPC. Itraconazole has a higher incidence of erratic oral bioavailability and drug–drug interactions compared with fluconazole. The use of itraconazole may be complicated by cross-resistance to fluconazole. Indeed, in one study, 30% of fluconazole-resistant isolates were cross-resistant to itraconazole, and itraconazole solution has been shown effective during OPC in this context against itraconazole susceptible isolates [39]; (iii) voriconazole has not been studied for fluconazole-susceptible OPC; (iv) posaconazole (200 mg on day 1 then 100 mg daily) is also an alternative to fluconazole [40]. Posaconazole is better tolerated and has fewer interactions compared with both itraconazole and voriconazole, but has a broad spectrum of activity for treating initial episodes of OPC and is considered an option for therapy in cases with fluconazole-resistant *Candida* sp. (CI).

Topical agents (e.g. amphotericin B lozenges or nystatin) should not be used for the treatment of OPC because of suboptimal tolerability (bitter taste, gastro-intestinal side effects, frequent dosing) and lower efficacy [27] (DI). Furthermore, a recommendation for clotrimazole was not considered because this agent is not available in Europe. While clotrimazole is effective, it is less efficacious and associated with a higher rate of relapses in comparison with fluconazole at least in some studies [25,26,28]. Finally, acquired resistance to clotrimazole has been documented in *Candida* isolates in OPC [41].

Ketoconazole is efficacious in comparison with fluconazole and itraconazole but its use is limited by hepatotoxicity, drug–drug interactions, limited oral bioavailability in the set-

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ting of hypochlorhydria and appears to select for triazole cross-resistance [11,23,42–45]. Ketoconazole is thus not recommended for the management of OPC (DI).

Echinocandins should not be considered for OPC episodes caused by isolates that are susceptible to triazoles due to their parenteral availability and cost in comparison with fluconazole (DIII). Finally, any intravenous formulation of amphotericin B is also not recommended for the management of OPC due to numerous adverse events and associated nephrotoxicity (DIII).

Treatment of oesophageal candidiasis due to triazole susceptible isolates

Antifungal therapy for OEC should be initiated without endoscopy, especially if patients have signs and symptoms of OEC and oropharyngeal lesions are suggestive of mucosal candidiasis (AIII). Topical agents are not effective enough and should be avoided (DIII). Oral fluconazole (200 mg/day for 14–21 days) is the treatment of choice [46–48] (AI). Intravenous formulation can be used in case of severe oesophagitis (Table 2).

Itraconazole (oral solution) is an alternative agent that has been shown to be as effective clinically and mycologically as fluconazole, but endoscopic cure was found less frequently especially during short-term therapy in the itraconazole arm [46,47,49] (BI). Itraconazole capsules are not recommended because of limited oral bioavailability (DII) The addition of flucytosine to itraconazole is not superior to fluconazole and is not recommended [50] (DI).

Voriconazole 200 mg twice daily for 14–21 day is equally as efficacious as fluconazole, but associated with a higher incidence of adverse events [51] and more potential drug–drug interactions, visual abnormalities and phototoxicity in ambulatory patients (BI).

Oral flucytosine alone was tested against fluconazole but was proven less effective [52], in addition to potential side effects (DI). Oral ketoconazole was tested against fluconazole in a large double-blind trial, and endoscopic and clinical cure rates were inferior in the ketoconazole arm [48].

Ketoconazole was also tested in a small trial against itraconazole with a higher efficacy than itraconazole [42] (DI). Finally among azoles, posaconazole has not been specifically studied in the context of primary treatment of oesophagitis in azole susceptible isolates and should be reserved for refractory or resistant disease.

The echinocandins have been evaluated for the treatment of AIDS-associated OEC mostly in comparison with fluconazole. However, these antifungals are only available parenterally and are much less convenient to use than oral azoles (CI). Caspofungin is associated with similar response rates and tolerability compared with fluconazole although higher relapse rates were observed with caspofungin [53]. Caspofungin has been shown superior (74–91% efficacy) to amphotericin B (63%) in one study [54]. Micafungin (50–150 mg/day) produces a dose-dependent response rate in OEC [55]. The use of 150 mg/day regimen was comparable both in terms of efficacy, relapse rate and tolerance compared with fluconazole (200 mg/day) in a large double-blind study [56]. The currently licensed dosage is 150 mg/day. Similarly, anidulafungin [100 mg/day after loading dose] produces comparable response rates to fluconazole, but the rate of relapse 2 weeks after cessation of therapy was higher [57].

Intravenous formulations of amphotericin play no role for the management of OEC due to azole susceptible *Candida* isolates (DII).

Management of refractory OPC and or OEC

Refractory OPC or OEC is defined by symptoms that persist after more than 14 days of fluconazole ≥200 mg/day. This syndrome is reported in approximately 5% of HIV-infected patients and typically in those with CD4+ counts <50 cells/μL who have received multiple and prolonged courses of antifungals/triazole agents for a high number of OPC episodes [6–8]. The clinical impact of refractory mucosal candidiasis has been well documented [58]. In this situation, careful identification to species level and *in vitro* susceptibility testing to fluconazole and other triazoles are mandatory. Detection of resistance based on *in vitro* established breakpoints is indeed of major importance as mucosal candidiasis is one of the clinical settings where the correlation between *in vitro* results and *in vivo* outcome has been established [59,60].

Any use of a topical antifungal agent such as amphotericin B [61] should be avoided because of low efficacy rates (DIII). The use of fluconazole at a higher daily dosage may be beneficial at least transiently, particularly with the suspension, which provides increased salivary concentrations [62] (BIII). Itraconazole solution (up to 600 mg/day) is an alternative and is associated with a 55–75% response rate, but relapses occur subsequently [63–65] (AII).

Posaconazole oral suspension [400 mg twice daily (i.e. a higher dosage than that used for nonrefractory mucosal infections) for 28–90 days] can also be used and is efficacious in up to 86% of patients with fluconazole and/or itraconazole refractory oropharyngeal and/or OEC candidiasis. It has been approved by EMA in such context. In addition, the use of posaconazole is well tolerated up to 90 days of therapy, but relapses do also occur during the follow-up [66,67] (AII).

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Voriconazole appears to be active against fluconazole-resistant *Candida* isolates isolated from mucosal infections [68] although cross-resistance has also been demonstrated [69]. Voriconazole has been shown effective in a limited number of refractory OEC cases [68] (CII). If prolonged azole therapy is anticipated, periodic monitoring of liver enzymes should be considered (BIII).

Caspofungin can be used for HIV-infected patients with clinically fluconazole-refractory OEC or microbiologically resistant disease. A favourable response is obtained in 83% and 79% of cases, respectively [70]. Caspofungin can also be used for patients with refractory OPC/OEC who have experienced failure or intolerance to polyenes [71] (AII). Anidulafungin can also be used in this setting. An open-label clinical trial also studied anidulafungin in fluconazole-resistant OPC/OEC in 19 patients with a 95% successful clinical response, including 11/12 patients with OEC who had endoscopic cure (92%). Tolerance was acceptable [72] (AII). In addition, azole-refractory mucosal candidiasis can also be treated with micafungin 150 mg/day although it has not been specifically studied in that setting (AII).

Amphotericin B deoxycholate, amphotericin B lipid complex and liposomal amphotericin B may also be effective in such setting, but their toxicity profiles should receive considerable attention (CII). Preliminary studies have suggested a potential benefit of adjunctive GM-CSF therapy [73] (CII). Finally, any perspective of a new HAART regimen appears crucial in this context [74] (AIII).

Vulvovaginal candidiasis

Vulvovaginal candidiasis usually responds readily to topical agents (AII). Short-course oral azole therapy although effective should be avoided (fluconazole (DII), itraconazole oral solution (DII)). In case of multiple episodes, oral fluconazole (150 mg/week) should be used to prevent recurrences as evidenced outside the HIV setting (AI).

Prevention of recurrences

Maintenance therapy or secondary prophylaxis to prevent recurrences is usually not recommended (DIII). However, when relapses are frequent and/or severe, long-term oral triazole use may be considered providing cost and toxicity are acceptable. Fluconazole maintenance therapy has been well documented as effective in several randomized studies performed during the pre-HAART era. It should be reserved for patients with relapsing OPC/OEC caused by a fluconazole-susceptible isolate after HAART optimization (or failing HAART therapy). The range of dosages is large: 50–200 mg/day or 150–400 mg/week] (BI) [9,18,19,75–78] (Table 2).

Maintenance therapy with fluconazole 100–200 mg 3×/week should be considered for the case of recurrent infections to prevent further relapse (AI), but daily administration of fluconazole should be favoured (BI). A more recent randomized clinical trial has documented that fluconazole (200 mg three times a week) vs. episodic treatment of recurrences therapy was significantly associated with fewer cases of OPC or OEC and fewer invasive fungal infections, but not with improved survival in HIV patients with CD4+ count <150 cells/μL. In the latter study, no difference in the rate of fluconazole-refractory candidiasis was noticed provided that patients received HAART [79]. Oral posaconazole 400 mg twice daily can be proposed in case of relapsing OEC due to fluconazole-resistant *Candida* isolates (BII). Triazole therapy is precluded in pregnancy (AIII). Clinical experience, but no specific study, suggests that maintenance therapy is not required in the context of immune reconstitution to CD4-positive cells >200/μL (AIII).

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G.P. has received research grants from Gilead, Astra Zeneca, Novartis, Astellas Pharma, GSK, Pfizer and MSD, has acted as paid consultant to Janssen Cilag, Gilead, Astellas and MSD and is a member of the Gilead, Astellas and MSD speaker' s bureaus. He has also received travel support from Gilead, Astellas, Pfizer and ESCMID.

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M.B. has received research grants from Pfizer, MSD and Astellas and is/was an advisor or received lecture honorarium from Astellas, Angelini Farmaceutici, Astra Zeneca, Aventis, Bayer, Cephalon, Cubist, Gilead, MSD, Novartis, Shionogi, Pfizer, Teva and Vifor. He also advises on the board for Pfizer, Angelini Farmaceutici, Cubist, MSD, Astellas, Novartis, Astra Zeneca.

J.B. has nothing to declare.

T.C. is member of the Speaker bureau and is advisor or consultant for Astellas, Baxter; bioMérieux, EISAI, Evolva, Novartis, Immunexpress, Eli Lilly Suisse, Institut Pasteur, Merck Sharp & Dohme-Chibret AG, Pfizer. Grant support from Baxter, bioMérieux, Merck Sharp & Dohme-Chibret AG, Roche Diagnostic. He has received travel support from Astellas, Prizer, MSD and royalties from Elsevier.

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R.H. has been a consultant or at the advisory board for Astellas pharma, Basilea, Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer and Schering Plough. He has also received investigator fees for a clinical trial for Pfizer and travel support from Pfizer and Gilead. He has received grant support and/or has been paid for talks on behalf of Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer, and Schering Plough.

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