

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

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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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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 providing 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

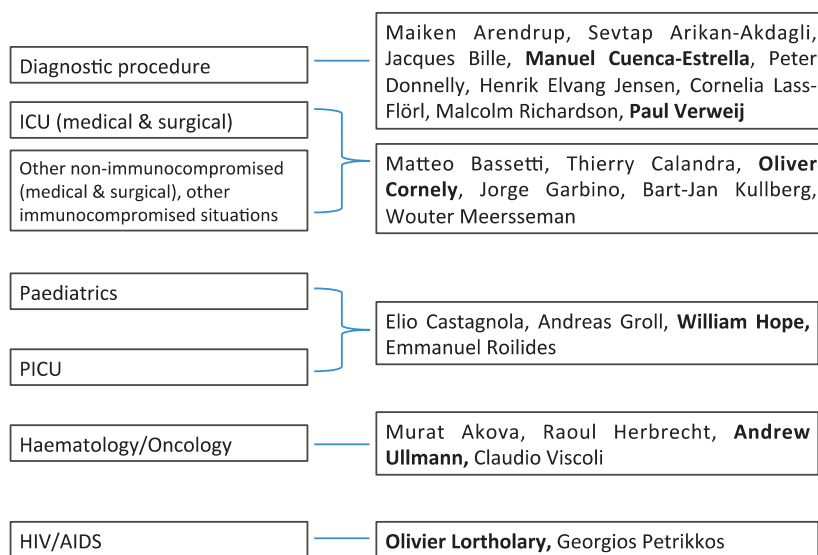


FIG. 1. Working modules and experts participating in the development of the guidelines (susceptibility testing is included for the diagnostic procedures).

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

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.
^aPathologist.
^bHaematologist.
^cDual trained in ID and haematology.
^dDual trained in ID and CM.

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.

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

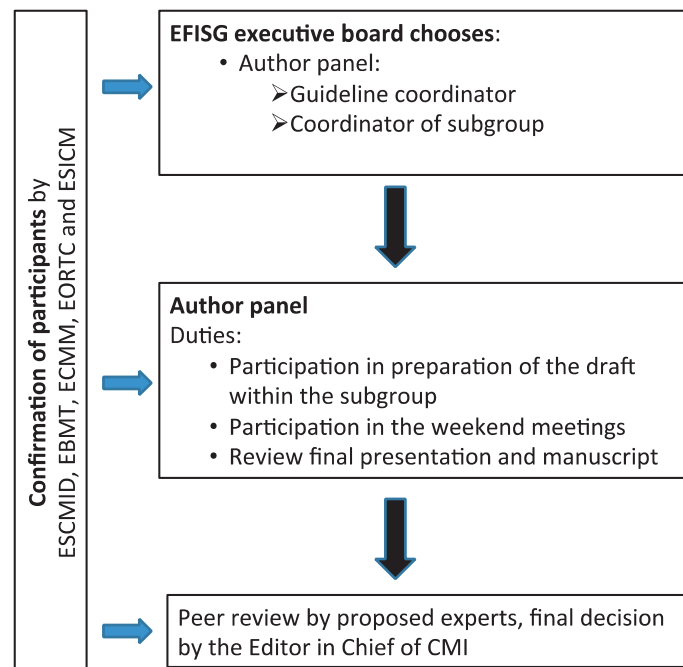


FIG. 2. Organization plan of the guidelines.

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 administering 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 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:
 †: Meta-analysis or systematic review of randomized controlled trials.
 ‡: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.
 ††: Comparator group is a historical control.
 ‡‡: Uncontrolled trial.
 ‡‡‡: Published abstract (presented at an international symposium or meeting).

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

^aAccuracy 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.

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 speaker honoraria from Merck and Pfizer. She has been at the Advisory Board for Pfizer-Turkey.

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.

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, bioMérieux, 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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