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Article type   : Original Article

Developing definitions for invasive fungal diseases in critically ill adult patients in intensive care units. Protocol of the FUNgal infections Definitions in ICU patients (FUNDICU) project.

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Short title: IFD definitions in ICU patients

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Summary

Background: The reliability of diagnostic criteria for invasive fungal diseases (IFD) developed for severely immunocompromised patients is questionable in critically-ill adult patients in intensive care units (ICU).

Objectives: To develop a standard set of definitions for IFD in critically-ill adult patients in ICU.

Methods: Based on a systematic literature review, a list of potential definitions to be applied to ICU patients will be developed by the ESCMID Study Group for Infections in Critically Ill Patients (ESGCIP) and the ESCMID Fungal Infection Study Group (EFISG) chairpersons. The proposed definitions will be evaluated by a panel of 30 experts using the RAND/UCLA appropriateness methods. The panel will rank each of the proposed definitions on a 1-9 scale trough a dedicated questionnaire, in two rounds: one remote and one face-to-face. Based on their median rank and the level of agreement across panel members, selected definitions will be organized in a main consensus document and in an executive summary. The executive summary will be made available online for public comments.

Conclusions: The present consensus project will seek to provide standard definitions for IFD in these patients, with the ultimate aims of improving their clinical outcome and facilitating the comparison and generalizability of research findings.

Key words: *Aspergillus*; *Candida*; diagnosis; biomarker; candidiasis; cryptococcosis; pneumocystosis.

Introduction

Invasive fungal diseases (IFD) are a leading cause of morbidity and mortality in a wide range of patients with defects of the immune system or severe underlying organ dysfunction [1-5]. Because of the poor sensitivity and/or specificity of some diagnostic tests, the diagnosis of IFD usually relies on different degrees of certainty, ranging from possible to proven disease, according to the 2008 definitions of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) [6, 7]. These definitions have been originally designed for research protocols and their application in clinical practice has been debated, in particular for cases classified as possible IFD for which the choice of initiating or refraining from administering antifungal therapy may have important consequences and should be assessed on a "case-by-case" approach. Thus, the development and use of standard definitions for IFD remain crucial, aiming to reach the most favorable, and reproducible net balance between benefits and harms in the intended target population.

The 2008 EORTC-MSG definitions of IFD have been initially designed for immunocompromised patients with cancer and hematopoietic stem cell transplant recipients [6, 7]. However, their validity for diagnosing IFD in critically ill adult ICU patients not belonging to that target population has been

questioned, in view of differences in host factors, disease presentation and performance of diagnostic tests in this setting, especially for invasive aspergillosis and intra-abdominal candidiasis [11-13]. Possible alternative diagnostic algorithms for ICU patients have been proposed [14-19].

We report here the steps we will implement to develop a standard set of definitions for IFD in critically ill patients in ICU, starting from a systematic assessment of the strengths and limitations of the definitions and algorithms already available in the literature. By publicly declaring our aims, we wish to stimulate debate and involve other potentially interested stakeholders as future external reviewers of project results. Also, any post-hoc deviations from the protocol, potentially biasing results, will be easily tracked and transparently discussed.

Objective and scope

The objective of the project is to develop a consensus set of definitions for IFD in critically-ill adult patients in ICU, with two main goals: (*i*) to maximize the net balance between benefits and harms when diagnosing and treating fungal infections in critically ill adult patients in the daily clinical practice; (*ii*) to provide consistent and reproducible results in research studies on the diagnosis and outcome of these infections.

Definitions will be developed separately for the following IFD: (*i*) invasive candidiasis (IC); (*ii*) invasive aspergillosis (IA); (*iii*) *Pneumocystis jirovecii* pneumonia (PJP); (*iv*) cryptococcosis; and (*v*) other rare IFD for which a sufficient body of literature is available for developing definitions.

Methods

Participants, roles and task delegation

A multidisciplinary panel of 30 experts and 5 juniors (DRG, ER, VZ, CG, and FL) has been selected by the ESCMID Study Group for Infections in Critically Ill Patients (ESGCIP) and the ESCMID Fungal Infection Study Group (EFISG) chairpersons (MB and CLF), based on their experience and expertise in the topic or in methodology (Table 1). The panel has been approved by ESGCIP and EFISG for ESCMID, and by the executive committee of ESICM, ECCM, and MSGERC. An email invitation was sent to all the selected panel members, and all agreed to participate. An external review board including patients' representatives, European Federation of Pharmaceutical Industries and Associations (EFPIA) representatives and other stakeholders will be selected and asked to review the final document and provide input. The final document will undergo a public consultation phase according to ESCMID procedures for endorsement.

Project work packages

The development of definitions will follow four consecutive stages: (*i*) identification of relevant literature; (*ii*) drafting of definitions; (*iii*) consensus development; (*iv*) public sharing of the consensus executive summary.

Coordination will be provided by MB and TC. The entire project will be managed remotely, with only one face-to-face meeting expected during the 29th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID, 13-16 April 2019, Amsterdam, Netherlands).

WP1: Identification of relevant literature

A systematic review will be conducted (CR) to identify all the definitions for IFD available in the literature, without restriction to ICU patients. We expect most definitions will have been developed for other-than-ICU settings. The expert panel's role will be to judge the applicability of definitions developed in other settings to ICU patients, and to determine if modifications are needed.

Eligibility criteria for full text inclusion:

- Study design: cross sectional studies, longitudinal (cohort) prospective or retrospective studies, randomized controlled trials, single-arm studies, quasi-experimental studies (case series and case-control studies will be excluded)

- Patient populations: all

- Patient's age: adult patients (explicitly defined as ≥18 years)

- Settings: all

- IFD of interest: IC, IA, PJP, cryptococcosis, other

- Explicit definition of the IFD of interest

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Sources and limits/restrictions

We will search the MEDLINE and EMBASE (OvidSP), CINAHL (EBSCOHost), and the Cochrane Database (Wiley). We will use medical subject headings (MeSH) and terms for IFD (e.g., aspergillosis, candidiasis) and definitions. The search period will be from 2003 to 2018 (15 years). No language restrictions will be applied.

Data management

All abstract and full text will be imported and managed into an EndNotesWeb database, shared among the 5 Juniors and librarian.

Selection process

According to the IFD of interest, five search strings will be built and four reviewers (DRG, FL, VZ and CG) will perform abstract screenings and full-text review. The reviewers will work in pairs and each pair will be in charge of 2/3 topics: IC and PJP for DRG and VZ while IA, cryptococcosis, and other IFD for FL and CG. The reference lists of retrieved full-texts will also be screened, to identify further papers suitable for inclusion. The two members of each pair will work independently; decisions will be compared and any possible disagreement will be resolved by a fifth independent reviewer (ER).

Data extraction

Data will be extracted on a standard extraction form; the form will be drafted by VZ, and piloted by DRG, ER, and FL on a subset of 2 full-text each. This stage will be supervised by LS. For all data items, both a descriptive field for verbatim data extraction and a categorical field with a limited number of mutually exclusive classification options will be used.

Data extraction will be performed analogously to the selection process.

Data items

Each definition will be summarized descriptively or (whenever applicable) quantitatively according to:

- target IFD/s

- target population/s

- number of diagnostic categories (e.g. positive/negative vs positive/indeterminate/negative vs proven/probable/possible/excluded)

- number of patients enrolled

- reference standard applied

- diagnostic performance (sensitivity, specificity, negative predictive value, positive predictive value, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio whenever an appropriate diagnostic gold standard is available; repeatability and reproducibility in absence of an appropriate diagnostic gold standard)

- need for microbiological/biochemical testing, including costs

- strengths and limitations, overall and with regard to the applicability to critically ill patients in ICU

- clinical outcomes used for validation (including net balance between benefits and harms), if any

- risk of bias of studies (see later).

Each of the 30 experts of the panels will be asked to provide comments and to critically review the results and the summary of the systematic review.

Risk of bias of included studies

The risk of bias of included studies will be assessed by a simple scoring system specifically designed

for this project: 1 point for each of the following:

1) retrospective study

2) missing IFD classification of >10% of included patients (for loss of follow-up or other reasons)

3) developed in populations other than ICU

4) exclusion of patients difficult to diagnose from the study

5) combination of adults and children

6) ad hoc selection of the cut-off value (where applicable)

7) unreliability of the reference standard (according to expert judgement)

8) Classification as IFD after knowledge of the result of the reference standard

Higher total scores will therefore correspond to higher risk of bias.

Data synthesis

No attempt at formal data synthesis is applicable to our aims (see WP2).

WP2: Drafting of IFD definitions

On the basis of the results of the literature review, chairperson of ESGCIP (MB) and EFISG (CLF), will

draw a list of potential definitions or diagnostic strategies for each IFD (aspergillosis, candidiasis, PJP,

cryptococcosis, and other IFD) in critically-ill adult patients in ICU. According to the degree of

certainty of mycological diagnosis and the level of scientific rigor if adopted in research studies, the

project coordinators (MB and TC) will also categorize IFD, within each definition, as follows : (*i*) possible IFD; (*ii*) probable IFD; (*iii*) proven IFD. For each IFD, definitions will not need to be mutually exclusive, since they will be scored individually. The list will be organized in a questionnaire format to be answered by all panel members, as described below.

WP3: Consensus development

With the results of the systematic review provided as background information to the selected 30 experts, the proposed definitions will be evaluated using the RAND/UCLA appropriateness methods (RAND/UCLA) [20]. In a first phase, mail invitations to participate in the questionnaire will be sent to the 30 experts. Responses will be collected using the REDCap[TM] software [21]. The experts will be asked to rank each of the proposed definitions on a 1-9 scale, with 1 indicating that the expected harms of adopting the **proposed definition in ICU patients** considerably outweigh the expected benefits (i.e. not appropriate) , and 9 conversely indicating that the expected benefits outweigh the expected harms (i.e. always appropriate). In this regard, experts will be instructed that the expected benefits in the context of disease definitions might involve increased access to treatment with beneficial effects on both health and non-health outcomes, while expected harms might involve physical harms of diagnosis and treatment, psychological effects, and social and economic consequences [10]. The median score will be used to classify each definition as inappropriate (1-3), "definition that might be considered" (4-6), "appropriate definition" (7-9). Experts will also be given the opportunity to provide additional potential definitions to be evaluated by the panel, that will be assessed in another round of rating trough the REDCap[TM] software. Additional rounds will be conducted until no new proposals of definition are added by the experts during the rating process.

In a second phase, the 30 experts will be involved in a face-to-face meeting during the 29th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID, 13-16 April 2019, Amsterdam, Netherlands), in which the results of the online questionnaire will be made available to each individual member of the panel. Only definitions "that might be considered" and "appropriate" will be discussed. Chaired by a facilitator (LS), the 30 experts will discuss each of the rated definitions, as well as their categorization, and finally vote anonymously as to whether adopt or reject each definition. Consensus will be defined as ≥ 70% agreement towards acceptance, with <15% disagreeing. The process will be repeated until consensus is reached. As a final step, if contradictory definitions for the same etiological pathogen will be present in the same category (possible, probable, or proven), experts will discuss and vote anonymously on which one should be retained, with only the one receiving more votes being ultimately included in the consensus document.

WP4: Public sharing of the consensus executive summary

The project will be presented through a slide set presentation during the 29th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID, 13-16 April 2019, Amsterdam, Netherlands), and where the public consultation phase will be duly advertised. The public consultation phase will be performed remotely by means of email exchanges and email Delphi rounds to respond to comments. Formal approval by all experts will be required prior to submission for publication.

The selected definitions and the background information for each of them (i.e., results of the systematic reviews and experts' comments) will be organized in a main consensus document and in an executive summary.

Publication

The ICMJE criteria for authorship will apply. The first author will draft the manuscript and coordinate input from all other authors; the last author will be guarantor. Three members from each Society will be in the authors byline with their full name.

Authorship byline will include the study group name, and a table with all the FUNDICU study group names will be included in the manuscript (each member will qualify as author).

Timeline

All activities are expected to cover a 14 months period (Figure 1).

Discussion

Existing guidance on how to properly diagnose IFD in critically ill adult patients in ICU is still limited. Most IFD definitions are aimed at severely immunocompromised patients. However, most often those definitions do not apply to ICU patients, who usually show considerable differences with the populations mentioned above in terms of risk factors and performances of various diagnostic procedures.

The impact of such differences could be somewhat elusive at first glance, but for this very reason they may considerably bias clinical reasoning, as well as the way we interpret research results. For example, sensitivity and specificity both of galactomannan and of the 2008 EORTC/MSG definition of probable IA may be very different between hematology patients and non-immunocompromised patients with severe COPD in the ICU [15-17]. As a consequence, interpreting and weighing

possibility and *probability* of IFD in the same way we do it in hematology patients might not always lead to the most cost-effective choice in the ICU, for several reasons. First, what is probable in hematology may just be possible in the ICU, or *vice versa*, since lesions and symptoms of IFD in ICU are often different from those developing in hematology patients, and they also present with a different spectrum of potential alternative diagnoses. Second, there may be more heterogenous levels of urgency in the ICU than in hematology patients, and a slight delay in prompting empirical treatment in favor of further diagnostics might be preferable in some selected cases. Third, specific ICU-related risk factors and tests performances should be considered and weighed carefully when categorizing the risk of some IFD such as candidemia, in order not to put some truly candidemic patients at risk of delayed antifungal therapy and reduced survival [22,23].

Classifying ICU patients according to their specific likelihood of having an IFD is therefore extremely important to properly guide and maximize the benefits of diagnostic and treatment decisions, in order to reduce both overtreatment and undertreatment. This is also intimately connected with our ability to conduct good clinical research on IFD in ICU. For example, overtreatment due to lack of appropriate diagnostics also reduces the reliability of epidemiological studies on the incidence and prevalence of probable/proven IFD in the ICU, because of possible missed episodes (randomly or systematically). Misclassification might also influence other types of observational and investigational research, since IFD can also be the outcome of clinical trials of preventive strategies, or of diagnostic studies of new lab or radiology tests. Furthermore, they can also represent the patient population (the "P" of the PICO acronym) in treatment studies.

The development of standard definitions of IFD in ICU patients is in line with the Measures in Effectiveness Trials (COMET) initiative, which supports development and application of "core outcome sets" (COS) [25]. A COS is an "agreed standardised set of outcomes representing the minimum that should be measured and reported in all clinical trials of a specific condition". In this regard, standardization would make it easier for the results of clinical studies to be compared,

contrasted and combined as appropriate in systematic reviews and meta-analyses, thus reducing "waste" in information and in resources [25,26].

The rigorous and systematic interpretation of the current literature is also the basis of the present consensus development project; on the other hand, among the potential limitations of our initiative, we acknowledge the possible limited availability of good quality literature for some definitions, and the possible lack of ICU-dedicated studies for certain IFD and laboratory or radiological tests.

We welcome comments and expressions of interest for participation to the external review group (please address any correspondence to the corresponding author).

We ultimately hope these definitions will help to improve the outcome of IFD in ICU patients, as well as to facilitate the comparison and generalizability of research findings.

Ethics and consent

The protocol does not involve patients and does not require approval by Ethical Review Board. It has been extensively reviewed from the scientific point of view.

The protocol for the systematic review component will be registered at the PROSPERO database.

Funding

The present project will not require additional funding from routine research activities. Costs for open access publications will be covered by research funds of the main authors.

Conflicts of interest (CoI)

CoI declarations will be collected at the beginning and at the end of the project (with mandatory update in case of intervening new CoI) and reviewed by an independent panel. The ICMJE form will be adopted.

Availability of data and material

Not applicable to the current protocol.

Authors' contribution

Authors' contributions are detailed in Table 1.

Table 1: FUNGICU project participants

Name	Institution	Role	Tasks
Matteo Bassetti	Infectious Diseases Division, Santa Maria Misericordia Hospital, Udine, Italy	Principal investigator, ESGCIP chair, expert panel member	Coordination, first drafting of IFD definitions after systematic review, development of IFD definitions and consensus document (RAND/UCLA method)
Thierry Calandra	Infectious Diseases Service, Department of Medicine, Lausanne University, Lausanne, Switzerland	Co-Principal investigator, expert panel member	Coordination, development of IFD definitions and consensus document (RAND/UCLA method)
Cornelia Lass-Flörl	Division of Hygiene and Medical Microbiology, Medical University Innsbruck, Innsbruck, Austria.	EFISG chair, expert panel member	first drafting of IFD definitions after systematic review, development of IFD definitions and consensus document (RAND/UCLA method)
Luigia Scudeller	IRCCS Policlinic San Matteo, Pavia, Italy	Methodology supervision	Protocol development, supervision of systematic review, facilitation of face-to-face meeting/s
Daniele R. Giacobbe	Clinica Malattie Infettive, Ospedale Policlinico San Martino – IRCCS per l'Oncologia, Genoa, Italy	Methodology, junior panel member	Protocol development, systematic review, drafting of consensus document
Frederic Lamoth	Infectious Diseases Service, Department of Medicine, Lausanne University, Lausanne, Switzerland, and Institute of Microbiology, Lausanne University Hospital, Lausanne, Switzerland	Methodology, junior panel member	Protocol development, systematic review, drafting of consensus document
Elda Righi	Infectious Diseases Division , Santa Maria Misericordia Hospital , Udine , Italy	Methodology, junior panel member	Protocol development. Systematic review, drafting of consensus document
Valentina Zuccaro	IRCCS Policlinic San Matteo, Pavia, Italy	Methodology, junior panel member	Protocol development. Systematic review
Cecilia Grecchi	IRCCS Policlinic San Matteo, Pavia, Italy	Methodology, junior panel member	Protocol development. Systematic review

Chiara Rebuffi	IRCCS Policlinic San Matteo, Pavia, Italy	Expert medical librarian	Protocol development. Systematic review
Murat Akova	Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Hacettepe University Ankara, Turkey	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
Ana Alastruey-Izquierdo	Spanish Center for Microbiology, Instituto de Salud Carlos III, Madrid, Spain	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
Sevtap Arıkan Akdagli	Department of Medical Microbiology, Faculty of Medicine, Hacettepe University, Ankara, Turkey	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
Elie Azoulay	AP-HP, Saint-Louis Hospital, Medical Intensive Care Unit, Paris (LZ, EA), ECSTRA Team, Biostatistics and Clinical Epidemiology, UMR 1153 INSERM, Paris Diderot, Sorbonne University, Paris, France	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
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Jan J. De Waele	Department of Critical Care Medicine, Ghent University Hospital, Ghent, Belgium	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
George Dimopoulos	Department of Critical Care, University Hospital Attikon, Medical School, University of Athens, Athens, Greece	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
Jose Garnacho-Montero	Unidad Clínica de Cuidados Intensivos, Hospital Universitario Virgen Macarena and Institute of Biomedicine of Seville, IBiS/CSIC/University of Seville, Seville, Spain	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
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Johan Maertens	Hematology,	Expert panel member	Development of IFD

	Department of Immunology and biology, KU Leuven, Leuven, Belgium		definitions and consensus document (RAND/UCLA method)
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Jordi Rello	CIBERES, Universitat	Expert panel member	Development of IFD

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Maurizio Sanguinetti	Institute of Microbiology, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
Fabio Silvio Taccone	Department of Intensive Care, CUB – Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
Jean-François Timsit	Université Paris Diderot/Hopital Bichat-Réanimation Medicale et Des Maladies Infectieuses, Paris, France, and UMR 1137-IAME Team 5-DeSCID: Decision Sciences in Infectious Diseases, Control and Care, Inserm/Univ Paris Diderot, Sorbonne Paris Cité, Paris, France	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
Antoni Torres	Department of Pulmonary Medicine, Hospital Clinic of Barcelona, University of Barcelona, CIBERES, IDIBAPS, Barcelona, Spain	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)
Jose A. Vazquez	Department of Medicine, Division of Infectious Diseases, Medical College of Georgia/Georgia Regents University, Augusta, USA	Expert panel member	Development of IFD definitions and consensus document (RAND/UCLA method)

Figure legends

Figure 1. Study timeline.

References

1. Vincent J-L, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302:2323–2329.

2. Bassetti M, Righi E, Ansaldi F, Merelli M, Trucchi C, De Pascale G, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. Intensive Care Med. 2014; 40:839–845.

3. Taccone FS, Van den Abeele AM, Bulpa P, Misset B, Meersseman W, Cardoso T, et al. Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. Crit Care 2015; 12:7.

4. Garnacho-Montero J, Olaechea P, Alvarez-Lerma F, Alvarez-Rocha L, Blanquer J, Galván B, et al. Epidemiology, diagnosis and treatment of fungal respiratory infections in the critically ill patient. Rev Esp Quimioter. 2013; 26:173–188.

5. Bassetti M, Bouza E. Invasive mould infections in the ICU setting: complexities and solutions. J Antimicrob Chemother. 2017;72 Suppl 1:i39-i47

6. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis. 2002; 34:7-14.

7. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46:1813–21.

8. Clancy CJ, Nguyen MH. Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis. 2013; 56:1284–1292.

9. Lamoth F, Calandra T. Early diagnosis of invasive mould infections and disease. J Antimicrob Chemother. 2017; 72(suppl_1):i19-i28.

10. Doust J, Vandvik PO, Qaseem A, Mustafa RA, Horvath AR, Frances A, et al. Guidance for Modifying the Definition of Diseases: A Checklist. JAMA Intern Med. 2017; 177:1020-1025.

11. Blot S, Taccone F, Van den Abeele A, Bulpa P, Meersseman W, Brusselaers N, et al.. A clinical algorithm to diagnose invasive pulmonary aspergillosis in ICU patients. Am J Respir Crit Care Med. 2012; 186:56–64.

12. Meersseman W, Vandecasteele SJ, Wilmer A, Verbeken E, Peetermans WE, VanWijngaerden E. Invasive aspergillosis in critically ill patients without malignancy. Am J Respir Crit Care Med. 2004; 170:621–625.

13. Vandewoude KH, Blot SI, Depuydt P, Benoit D, TemmermanW, Colardyn F, Vogelaers D. Clinical relevance of Aspergillus isolation from respiratory tract samples in critically ill patients. Crit Care 2006;10:R31.

14. León C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Alvarez-Lerma F, et al. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med. 2006; 34:730–737.

15. Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. Eur Respir J. 2007: 30; 782-800.

16. Bulpa P, Bihin B, Dimopoulos G, Taccone FS, Van den Abeele AM, Misset B, et al. Which algorithm diagnoses invasive pulmonary aspergillosis best in ICU patients with COPD? Eur Respir J. 2017;50.

17. Huang L, He H, Jin J, Zhan Q. Is Bulpa criteria suitable for the diagnosis of probable invasive pulmonary Aspergillosis in critically ill patients with chronic obstructive pulmonary disease? A comparative study with EORTC/ MSG and ICU criteria. BMC Infect Dis. 2017; 17:209.

18. Giacobbe DR, Mikulska M, Tumbarello M, Furfaro E, Spadaro M, Losito AR, et al. Combined use of serum (1,3)-β-D-glucan and procalcitonin for the early differential diagnosis between candidaemia and bacteraemia in intensive care units. Crit Care 2017; 21:176.

19. Schroeder M, Simon M, Katchanov J, Wijaya C, Rohde H, Christner M, et al. Does galactomannan testing increase diagnostic accuracy for IPA in the ICU? A prospective observational study. Crit Care 2016; 20:139.

20. Brook RH, Chassin MR, Fink A, Solomon DH, Kosecoff J, Park RE. A method for the detailed assessment of the appropriateness of medical technologies. Int J Technol Assess Health Care 1986; 2:53–63.

21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Infor. 2009; 42:377–81.

22. Denning DW, Perlin DS, Muldoon EG, Colombo AL, Chakrabarti A, Richardson MD, et al. Delivering on Antimicrobial Resistance Agenda Not Possible without Improving Fungal Diagnostic Capabilities. Emerg Infect Dis. 2017; 23:177-183.

23. Pfaller MA, Castanheira M. Nosocomial candidiasis: antifungal stewardship and the importance of rapid diagnosis. Med Mycol. 2016; 54:1–22.

24. COMET initiative: Core Outcome Measures in Effectiveness Trials Initiative (COMET). http://www.comet-initiative.org/. Accessed 22 Aug 2018.

25. Prinsen CA, Vohra S, Rose MR, King-Jones S, Ishaque S, Bhaloo Z, et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a "core outcome set". Trials 2014; 15:247.

26. Ioannidis JPA, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, et al. Increasing value and reducing waste in research design, conduct, and analysis. The Lancet 2014; 383:166–175.

Task	Jul-18	Aug	Sept	Oct	Nov	Dec	Jan-19	Feb	Mar	Apr	May	Jun	July	Aug
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Preparation of protocol	x													
Building search string	x	x												
Abstract screenings		x	x	x										
full text retrieval			x	x										
full text screeening			x	x	x									
Data extraction				x	x	x								
Data synthesis & Analysis					x	x	x	x						
Drafting of definitions							x	x						
Consensus development									x	x	x			
Write final paper												x	x	
Submit paper														x