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ECMM *Candi*Reg – A Ready to use Platform for Outbreaks and Epidemiological Studies

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Philipp Koehler, Martin Hoenigl and Oliver A. Cornely conceived the project idea, drafted the manuscript, revised, discussed and approved the final manuscript. Maiken Cavling Arendrup, Sevtap Arikan-Akdagli, Matteo Bassetti, Stéphane Bretagne, Lena Klingspor, Katrien Lagrou, Jacques F. Meis, Riina Rautemaa-Richardson, Silke Schelenz, Axel Hamprecht, Felix C. Koehler, Oliver Kurzai, Jon Salmanton-Garcia, Jörg-Janne Vehreschild, Alexandre Alanio, Ana Alastruey-Izquierdo, Valentina Arsic Arsenijevic, Jean-Pierre Gangneux, Neil A.R. Gow, Suzana Hadina, Petr Hamal, Elizabeth Johnson, Nikolay Klimko, Cornelia Lass-Flörl, Mihai Mares, Volkan Özenci, Tamas Papp, Emmanuel Roilides, Raquel Sabino, Esther Segal, Alida Fe Talento, Anna Maria Tortorano and Paul E. Verweij revised, discussed and approved the final manuscript.

Conflicts of Interests

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Abstract

Background

Recent outbreaks of *Candida auris* further exemplify that invasive *Candida* infections are a substantial threat to patients and health care systems. Even short treatment delays are associated with higher mortality rates. Epidemiological shifts towards more resistant *Candida* spp. require careful surveillance.

Objectives

Triggered by the emergence of *C. auris* and by increasing antifungal resistance rates the European Confederation of Medical Mycology developed an international Candida Registry (FungiScope™ *Candi*Reg) to allow contemporary multinational surveillance.

Methods

*Candi*Reg serves as platform for international cooperation to enhance research regarding invasive *Candida* infections. *Candi*Reg uses the General Data Protection Regulation compliant data platform ClinicalSurveys.net that holds the electronic case report forms (eCRF). Data entry is supported via an interactive macro created by the software that can be accessed via any internet browser.

Results

*Candi*Reg provides an eCRF for invasive *Candida* infections that can be used for a variety of studies from cohort studies on attributable mortality to evaluations of guideline adherence, offering to the investigators of the 28 ECMM member countries the opportunity to document their cases of invasive *Candida* infection. *Candi*Reg allows the monitoring of epidemiology of invasive *Candida* infections, including monitoring of multinational outbreaks. Here, we describe the structure and management of the *Candi*Reg platform.

Conclusion

*Candi*Reg supports the collection of clinical information and isolates to improve the knowledge on epidemiology and eventually to improve management of invasive *Candida* infections. *Candi*Reg promotes international collaboration, improving the availability and quality of evidence on invasive *Candida* infection and contributes to improved patient management.

Introduction

Invasive *Candida* infections are among the most common bloodstream infections and are associated with high morbidity and mortality.[1-3] *Candida* species are commensals of the human gastrointestinal microbiota and skin, but may translocate to the bloodstream and cause life-threatening infections. Invasive *Candida* infection (ICI) is an increasing threat to patients in the ICU, patients undergoing complicated or repeated gastrointestinal surgery and for immunocompromised patients, e.g., cancer patients, or recipients of solid organ or stem cell transplants.[4] In some cases, dissemination complicates acute blood stream infection with deep tissue and organ involvement. Due to novel medical and immunological interventions and treatments, an increasing number of critically ill patients are at risk ICI. Common etiological agents are *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis* and *Pichia kudriavzevii* (formerly *Candida krusei*) – depending on geographical region and patients' risk groups. The emergence of *C. auris*, a novel, usually fluconazole-resistant and often multidrug-resistant *Candida* species has caused outbreaks worldwide and led to clinical alerts to U.S. and European healthcare facilities.[5-8] In an Indian hospital *C. auris* has become the second most common cause of candidemia after *C. tropicalis.*[9] The ECMM *Candida* Registry (*Candi*Reg) was founded in January 2018, triggered by the recent *C. auris* candidemia outbreaks in Spain and the United Kingdom.[10-12]

The main objective of *Candi*Reg is to overcome the lack of knowledge on epidemiology, clinical course, and molecular characteristics of invasive *Candida* infections and to function as a platform for international multicenter studies and surveillance of multinational *C. auris* outbreaks. The specific objectives are to describe the incidence, to monitor trends globally and locally over time, to define patient risk groups, to assess antifungal resistance among *Candida* spp. causing invasive diseases worldwide, to assess attributable mortality and to assess to the cost augmentation associated with invasive *Candida* infection. A further goal of this platform is to set up a multinational collection of resistant *Candida* isolates with characterization at a molecular level, including the evaluation of resistance genes.

We herein describe how FungiScope™ *Candi*Reg is set up, maintained, and how it can be used to investigate the occurrence of ICI and potential outbreaks in future.

Methods

*Candi*Reg is an international non-interventional multicenter registry project. Treating physicians and medical microbiologists alike are invited to participate in the collection of clinical data and fungal isolates from cases of candidemia and tissue invasive candidiasis. The registry was founded in January 2018 and is ongoing without a defined endpoint. *Candi*Reg uses an electronic case report form (eCRF) using the online electronic data capture platform www.clinicalsurveys.net (in cooperation with Questback GmbH, Cologne, Germany). The eCRF structure is modular and the system is programmed to adapt the eCRF by displaying or hiding items according to the documented case (e.g. candidemia vs. control patient). Case registration is on a voluntary basis. Target groups are patients with invasive candidiasis or candidemia. Export will be performed in SPSS-labelled data files in SPSS binary format. Statistical analyses will be performed with IBM SPSS Statistics software v.25.0 (IBM Corp., Armonk, NY, USA/United States).

Ethical and General Data Protection Regulation considerations

*Candi*Reg is approved by the local Institutional Review Board and Ethics Committee of the University Hospital Cologne (UHC) (Identifier of the University of Cologne Ethics Committee: 17-485). If needed, further local Ethics Committee approvals will be included. The study is registered at clinicaltrials.gov, identifier NCT03450005. *Candi*Reg uses the General Data Protection Regulation (GDPR) compliant platform ClinicalSurveys.net. Data entry is carried out via any internet browser using encrypted communication. All documented data are automatically collected in a database. All Good Epidemiological Practice (GEP) requirements are met by the software.

Results

Case documentation and data collection

Patients with candidemia or invasive candidiasis confirmed by culture, histopathology or microscopy can be included. A second cohort is defined by patients with signs of disseminated *Candida* infection without culture, histological or microscopical evidence (e.g. CT-imaging of target-lesions in liver and spleen and positive Candida antigen or Beta-D-Glucan tests in a neutropenic patient), so that chronic disseminated, culture negative candidiasis can be documented in an adjusted eCRF separable from patients with candidemia. Patients without evidence of invasive disease or those with colonization

only are not eligible.

The following demographic data are collected: age group at the date of diagnosis, gender, year of infection, weight, ethnicity, details on primary underlying disease or conditions, immunosuppression, further risk factors, echocardiography and ophthalmology results, and mycological procedures allowing ICI diagnosis and sites of infection (Table 1). Details on management including antifungal treatment; recording drug, dose, duration, route of administration, therapeutic drug monitoring, reason for stopping, drug-related adverse events and surgical procedures, catheter management, clearance of bloodstream infection or infected sites are documented. Treatment indication is differentiated into prophylaxis, empiric, pre-emptive and targeted treatment for ambulatory and inpatient parenteral antifungal therapy.
Response to antifungal therapy is evaluated after two and four weeks, three and six months and on the final day of observation. In addition, treatment response and outcome of the underlying disease as well as potential prolongation of hospital stay are also documented. Information on outcome includes overall mortality and attributable mortality. If available, autopsy results are recorded. Quality Management is covered once yearly from participating centers with regard to guideline implementation and adherence (ECIL, ESCMID, / ECMM, IDSA; EQUAL *Candida* Score, Infectious Diseases / Microbiology consulting services; Fellow of the ECMM availability, treatment in an ECMM Excellence Centre).[13-18] Furthermore economic key figures and hospital characteristics with normal ward vs. ICU beds, candidemia per year, admissions per year, medical vs. surgical ward / ICU, consumption of antifungals in defined daily doses (DDD) are gathered. To implement health economic analyses on the incremental costs and attributable mortality analysis the study will in part use a matched case control design. Controls will be included from the same hospitals that include cases (i.e. one control per case, both from the same hospital). Controls will be matched by demographics, underlying diseases and risk factors as well as duration of hospitalization.[19,20]

Isolates collection

In addition to clinical data, partners can contribute with *Candida* isolates considered as emergent (e.g. *Candida auris*) for formal species identification and susceptibility testing. Isolates will be stored and made available to all collaborating partners for developing research projects. The following laboratory-based research will be conducted: isolate identification, macro-morphology, *in vitro* susceptibility testing according to EUCAST, evaluation and analysis of resistance mechanisms. Isolates are processed de-centrally at National Reference Centers or ECMM Excellence Centers, which serve as the central mycology reference laboratories.[21,22] Species identification and

susceptibilities of all isolates are determined or confirmed using reference methods including mass spectrometry (MALDI- TOF MS/VITEK MS) and molecular methods (sequencing ITS, IGS or equivalent informative target). Mass- spectra and molecular data are analyzed using the MALDI- TOF libraries as well as sequencing databases such as MycoBank (http://www.mycobank.org/) and CBS-KNAW GenBank (http://www.westerdijkinstitute.nl/collections/). In addition, all isolates are stored in triplicate at −80°C for research exchange among *Candi*Reg collaborators. Any such exchange is preceded by the contributor's approval. The only exception from this self-rule is, if a contributor cannot be reached despite all efforts. Results of these analyses are also included in *Candi*Reg, while the isolate remains stored in that reference laboratory.

Case recruitment and data analyses and use

The main variables to be analyzed are: clinical course and features of ICI, diagnostic procedures performed to confirm the diagnosis, description of antifungal treatment regimens, guideline implementation and adherence and their efficacy and impact on patient survival. The aim is to analyze the efficacy of current recommendations for diagnosis and treatment, to inform future consensus guidelines and to develop clinical screening and diagnostic procedures.

Discussion and outlook

*Candi*Reg serves as platform for international cooperation and studies on attributable mortality, Candida-reactive T cells, evaluations of guideline adherence[23-25], and recently the third multicenter ECMM study[26,27] on incremental costs associated with nosocomial invasive candidiasis in Europe, CANDIDA III was initiated taking advantage of this platform. The CANDIDA III study focuses on evaluating the attributable mortality and costs as well as diagnostic and therapeutic approaches (including prolonged hospital stay for completion of parenteral antifungal treatment) of nosocomial invasive candidiasis in Europe. As a secondary objective, it will evaluate the antifungal resistance among *Candida* spp. causing invasive disease across Europe. The study will use a matched case control design, which will allow the implementation of health economic analysis on the incremental costs associated with invasive *Candida* infections. The ECMM will use the platform for future multinational surveillance studies on invasive candidemia in Europe. Moreover, investigators maintain familiarity with the platform, which may enable more rapid case entry in case of an outbreak. To date, 265 patients have been enrolled in the register as part of five open or completed studies.[23-25,28] The results derived from this platform will be promoted as poster or oral presentations

at national and international infectious diseases, mycological and health-economic conferences. Internationally visible publications obtained from the *Candi*Reg registry have already been published in or will be submitted to peer-reviewed journals.

*Candi*Reg will enhance knowledge about ICI and facilitate the analysis of epidemiological shifts and resistance trends. Currently, clinicians, microbiologists and researchers from 28 countries are involved (Figure 1). With this registry, we collect real life data with long-term observations. The registry will provide controlled or uncontrolled level II evidence and is ready in case of an outbreak situation similar to other FungiScope™ Registries.[29]

There are a number of limitations of registry based studies. The retrospective acquisition of anonymized data of the individual patient reduces data quality, but is indispensable to protect privacy and comply with data protection guidelines. Also, the follow-up time of the cases may often be somewhat short. However, these registries offer the opportunity to contribute to progress in the understanding of epidemiology, pathophysiology, natural history and efficacy of treatments on a pan-European or even worldwide scale. As proven ICI is a relatively rare condition, pooling these cases and analyzing them in large cohorts can significantly improve our knowledge of ICI in real life settings and contribute to the design of clinical trials. Furthermore, they provide data unobtainable by controlled trials.

In conclusion, the *Candi*Reg platform promotes international collaboration, increases the quality of available evidence on invasive *Candida* infection and can contribute to improvement of patient management.[23]

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Table 1. ECMM Candida Registry – Information categories captured

Category	Subcategory
Demographics	Age group at diagnosis, gender, year of infection, weight, ethnicity
Host and risk factors	Malignancy, SOT, HIV/AIDS, surgery trauma, burn, chronic diseases, autoimmune disease, alcoholism, iv drug use, ICU stay, neutropenia, obesity, premature birth, central venous catheters, foreign bodies, low albumin levels, extracorporeal membrane oxygenation (ECMO)
Clinical presentation	Signs and symptoms, site(s) of infection
Diagnostics	Mycological procedures for diagnosis of ICI. Echocardiography and ophthalmoscopy
Treatment of IFD	Prophylaxis, empiric and targeted therapy (antifungal drug, dose, duration, route of administration, reason for stopping, drug related adverse events, ambulatory parenteral antifungal treatment) surgical procedures, catheter management, clearance of *Candida* spp. from bloodstream or infected sites.
Treatment response and outcome	Response to antifungal treatment, outcome of ICI and underlying disease, prolongation of hospital stay
Economics	Hospital characteristics (normal ward / ICU beds; admissions per year), consumption of antifungals in defined daily doses (DDD)
Quality	Guideline Implementation and Adherence (ECIL, ESCMID/ECMM, IDSA), EQUAL Candida Score, Infectious Diseases / Microbiology consulting services; Fellow of the ECMM available, ECMM Excellence Center

AIDS= acquired immune deficiency syndrome; ECIL= European Conference on Infections in Leukaemia; ECMM= European Confederation of Medical Mycology; ESCMID= European Society of Clinical Microbiology and Infectious Diseases; HIV= human immunodeficiency virus; ICI= invasive *Candida* infection; ICU=intensive care unit; IDSA= Infectious Diseases Society of America; SOT=solid organ transplantation.

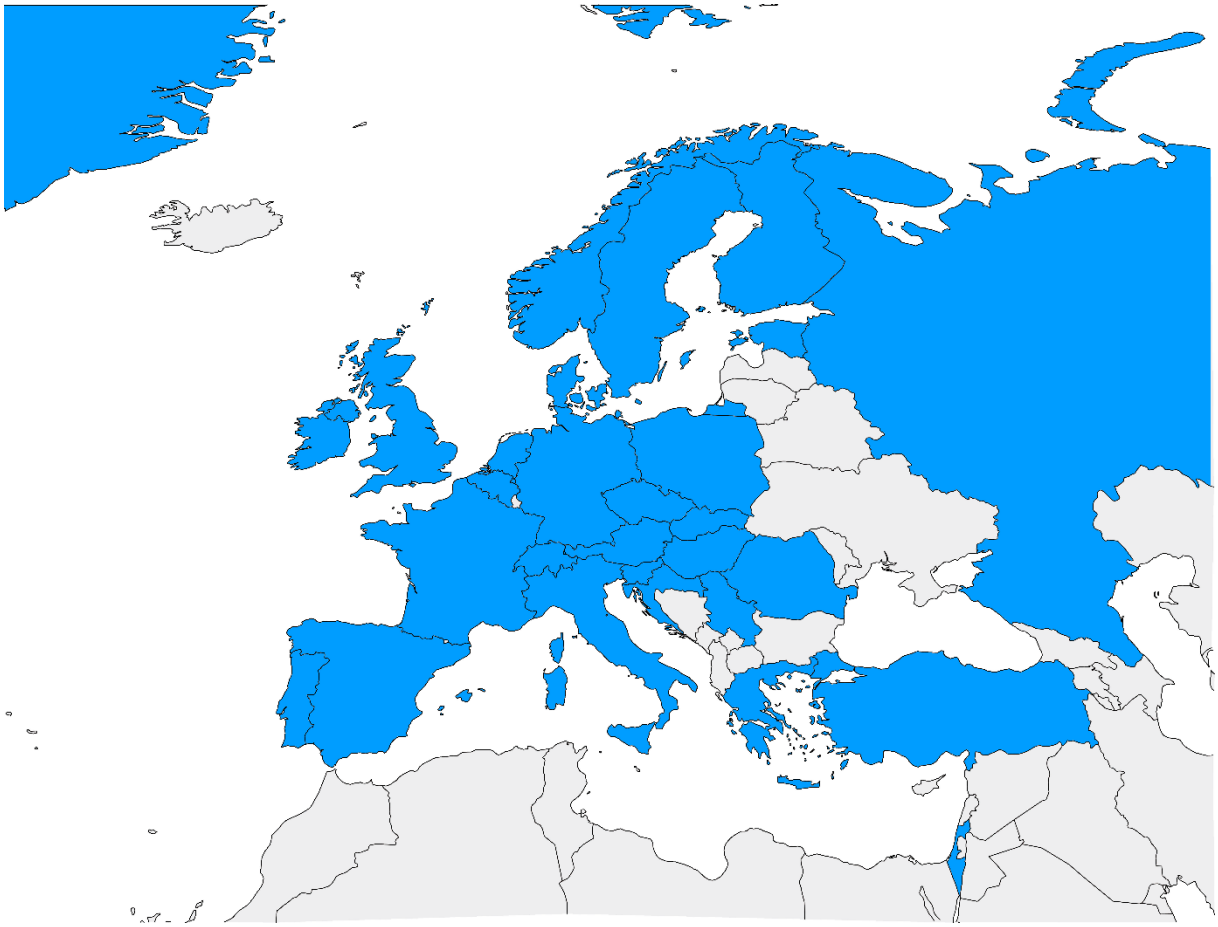

Figure 1. ECMM Member countries contributing to *Candi*Reg, as of May 2019. The current 28 member countries are colored in blue.