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Study Protocol

FungiScope®

Global Emerging Fungal Infection Registry

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Table of Contents

1. Introduction

Invasive fungal diseases (IFD) remain a challenging problem with increasing incidence rates worldwide. At the same time, significant regional and local variations can be observed. Although the etiology of this epidemiological development is not fully understood, the widening of indications for intensive chemotherapy and the growing number of transplantations seem to be important contributing factors.

Patients with hematological malignancies and profound, prolonged neutropenia (defined as <500 cells/µl >10 consecutive days), solid organ transplant recipients and otherwise immunocompromised patients are at a high risk of contracting IFD [1]. Apart from *Candida glabrata*, *Aspergillus fumigatus* and *Cryptococcus neoformans*, which are the most frequent causative pathogens for IFD, the so-called "emerging fungi" are gaining importance, for example *C. auris*, *A. terreus*, Mucorales, *Fusarium* and other less common infections caused by *Scedosporium* spp., *Penicillium* spp., *Acremonium* spp., *Paecilomyces* spp., *Trichoderma* spp., and other rare fungi [2-7].

Therapeutic standards have been established for aspergillosis [8] and cryptococcosis [9], and detailed guidelines for diagnosis and management of *Candida*-related diseases have been developed in 2012 [10-14]. In 2014 an international team of experts, including members of EFISG-ESCMID and/or ECMM, developed clinical guidelines for the diagnosis and management of rare and emerging fungi [15] covering rare hyalohyphomycosis [16], invasive yeast infections [17], mucormycosis [18], and systemic phaeohyphomycosis [19]. Current recommendations largely rely on a collection of case series, single-center studies and expert opinions [20]. In order to establish evidence-based treatment recommendations analyses of a comprehensive cohort is required.

2. Objectives

The objective of this study is to overcome the lack of knowledge on epidemiology, clinical course, and molecular characteristics of invasive infections due to emerging fungal pathogens, in order to develop evidence-based diagnostic and therapeutic recommendations. The specific objectives are:

1. Epidemiology
    - To describe the global incidence of emerging fungal infections
    - To monitor trends over time
    - To define risk groups

2. Clinical course
    - To describe the clinical pattern of disease
    - To document diagnostic procedures performed for confirmation of diagnosis
    - To describe first-line and salvage treatment regimens applied, their efficacy and impact on patient survival

3. Recommendations for diagnosis and treatment
    - To inform consensus guidelines
    - To develop clinical screening procedures
    - To identify treatment approaches for first-line and salvage therapy

3. Study Period

Start date of amendment: March 1, 2022

End date: not determined

4. Patient Population

1. Inclusion criteria
    - Cultural, histopathological, antigen or DNA evidence of invasive fungal infection with emerging fungal pathogen

2. Exclusion criteria
    - Infections due to endemic fungi, e.g. *Coccidioides* or *Histoplasma*
    - Colonisation or other non-invasive infection, including superficial skin infections irrespective of causative pathogen

We enroll patients retrospectively who were diagnosed within the past 10 years prior to the day of the signed Agreement with the respective study site.

5. Case Report Form

The Case Report Form (CRF) will be created using the survey software EFS Survey™ (QuestBack). This software is used by many international research groups for epidemiological and sociological research projects. Data entry is carried out via an interactive macro created by the software that can be accessed via any internet browser. All documented data are automatically collected in a database. Detailed information on data protection regulations are provided under 9.1.

The CRF will be accessible through at least the following website:

www.fungiscope.net

The study protocol, the full CRF as portable document file, and the ethics committee´s approval of the study will be available on this site. Participants wishing to contribute cases will receive account-details for login. Account details have to be requested via E-mail. Full name, institution and E-mail address have to be supplied.

The following core data set will be collected:

1 Epidemiological data: country, institution, level of care of the institution, catchment area
2 Demographic data: age-group, sex, ethnicity
3 Data of fungal infection: year of infection, species identification, co-infections with other fungi, clinical characteristics upon diagnosis
4 Data of concomitant diseases: diagnosis, duration of diagnosis, current status and treatment
5 Potential risk factors for developing fungal infection: immunosuppressive therapy, chemotherapy, biopharmaceuticals, use of corticosteroids, radiotherapy, solid organ or human stem cell transplantation, chronic pulmonary disease, diabetes mellitus, renal failure and dialysis, trauma and major surgery, HIV/AIDS, neutropenia, mucositis, and other risk factors
6 Antifungal prophylaxis if given: drug, route, dose, duration prior to diagnosis of invasive fungal infection
7 Diagnostic measures and findings (CT, MRI, endoscopy, ultrasound, micro- and molecular biological analyses, pharmacological analyses)

8 Antifungal treatment: drug, route of administration, dose, drug levels, duration, side effects, and treatment outcome
9 Treatment response at day 14, 28, 42, 84 and status at most recent follow up
10 Cause of death, autopsy results if applicable

6. Data Analysis

Data will be analyzed using descriptive statistical methods using IBM SPSS™, Stata, and R software.

7. Specimen Collection and Laboratory-Based Research

In addition to clinical data, partners can contribute fungal isolates for formal species identification and susceptibility testing done by the central laboratory. Isolates will be stored and made available for collaboration partners for research projects. The following laboratory-based research will be conducted:

1 Strain identification by micro- and macromorphology, culture and molecular tools
2 In vitro susceptibility testing according to EUCAST and CLSI [21]

8. Budgetary Information

For evaluable patient documentations filled in by the participating center a compensation of € 100 each will be paid. If the documentation workload is too high, centers are encouraged to ask the study office for personnel to be sent to the site. For isolates made available to the central laboratory an additional S&P compensation of € 50 will be paid.

9. Ethical Considerations and Data Privacy Protection

In the current study, two aspects of the study have to be considered separately:

1. Documentation of clinical data
2. Work with fungal isolates

Regarding aspect 1. Only data created during standard medical care will be documented in the CRF. There is no interventional aspect to this study. Therefore, there are neither associated risks nor benefits for the patient when participating in the study. The digital documentation of the clinical data will take place in an anonymized fashion. No identifiable data, e.g. name or date of birth will be entered into the database. There will also be no pseudonyms, which would make a retrospective re-identification of the patient possible. Clinical data collected refers to common conditions and treatment modalities in medical care, such that no re-identification of the individual case on the basis of these data will be possible. Under these circumstances, we consider an informed consent of the patient not necessary. FungiScope® uses the General Data Protection Regulation (GDPR) compliant platform ClinicalSurveys.net. ClinicalSurveys.net is hosted by QuestBack, Oslo, Norway on servers in Cologne, Germany as part of a software-as-a-service agreement. Study participants log into the system with username and password including letters, numbers, and symbols. Participants can only view and modify their own contributions. All data transmissions are encrypted via TLS 1.2 with an AES 256 GCM bit key and ECDHE RSA key exchange; certificate provided by COMODO RSA Domain Validation Server. Data is only documented anonymously, no directly identifying data other than the investigator names and sites are stored on QuestBack servers. Administration of the eCRF is limited to selected and named administrators at UHC, who receive comprehensive training in the system before access is granted. Secure passwords are also enforced for administrators and they have to regularly change their passwords. Any data manipulation by users and administrators is logged in an audit trail allowing complete data reconstruction. Server administration is performed by QuestBack, and includes regular updates of the linux-based servers, rigid firewall configuration, current virus and threat detection, and daily backups (on-site and off-site with secure storage). Contracts between the UHC and QuestBack regulate ownership and responsibility for data and eCRFs. Regular on-site audits of security and data protection measures are

performed at QuestBack Cologne by UHC. All study procedures are liable to Good Epidemiological Practice (GEP) requirements German and European legislation [22]. All clinical data fall under medical confidentiality. All data and results will be stored for at least 10 years after publication of results.

Regarding aspect 2. To ensure anonymity of all patients in the context of microbiological reference analyses, these analyses must have been completed and the results must have been included into the respective patient file, before the entire case is documented into the database as described in 1). This procedure aims to ensure anonymous documentation of patient data. The microbiological analyses of isolates of emerging fungi does not require informed consent of the patient, as there is no patient material involved.

10. Authorship Policy

Authorship will be restricted to those centers contributing clinical/microbiological data or translational work. For each contributing center, there will be authorship positions available.

11. Contact Information

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12. References

1. Ruping, M.J., J.J. Vehreschild, and O.A. Cornely, *Patients at high risk of invasive fungal infections: when and how to treat.* Drugs, 2008. **68**(14): p. 1941-62.
2. Suzuki, Y., et al., *Epidemiology of visceral mycoses in autopsy cases in Japan: the data from 1989 to 2009 in the Annual of Pathological Autopsy Cases in Japan.* Med Mycol, 2013.
3. Pagano, L., et al., *The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study.* Haematologica, 2006. **91**(8): p. 1068-75.
4. Perkhofer, S., et al., *The Nationwide Austrian Aspergillus Registry: a prospective data collection on epidemiology, therapy and outcome of invasive mould infections in immunocompromised and/or immunosuppressed patients.* Int J Antimicrob Agents, 2010. **36**(6): p. 531-6.
5. Duran Graeff, L., et al., *Invasive infections due to Saprochaete and Geotrichum species: Report of 23 cases from the FungiScope Registry.* Mycoses, 2017. **60**(4): p. 273-279.
6. Hassler, A., et al., *Disseminated Fusariosis in Immunocompromised Children-Analysis of Recent Cases Identified in the Global Fungiscope Registry.* Pediatr Infect Dis J, 2017. **36**(2): p. 230-231.
7. Seidel, D., et al., *Prognostic factors in 264 adults with invasive Scedosporium spp. and Lomentospora prolificans infection reported in the literature and FungiScope(R).* Crit Rev Microbiol, 2019: p. 1-21.
8. Walsh, T.J., et al., *Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America.* Clin Infect Dis, 2008. **46**(3): p. 327-60.
9. Thursky, K.A., et al., *Recommendations for the treatment of established fungal infections.* Intern Med J, 2008. **38**(6b): p. 496-520.
10. Cornely, O.A., et al., *ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients.* Clin Microbiol Infect, 2012. **18 Suppl 7**: p. 19-37.
11. Cuenca-Estrella, M., et al., *ESCMID* guideline for the diagnosis and management of Candida diseases 2012: diagnostic procedures.* Clin Microbiol Infect, 2012. **18 Suppl 7**: p. 9-18.
12. Hope, W.W., et al., *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.* Clin Microbiol Infect, 2012. **18 Suppl 7**: p. 38-52.
13. Lortholary, O., et al., *ESCMID* guideline for the diagnosis and management of Candida diseases 2012: patients with HIV infection or AIDS.* Clin Microbiol Infect, 2012. **18 Suppl 7**: p. 68-77.
14. Ullmann, A.J., et al., *ESCMID* guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT).* Clin Microbiol Infect, 2012. **18 Suppl 7**: p. 53-67.
15. Cornely, O.A., et al., *European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Fungal Infection Study Group (EFISG) and European Confederation of Medical Mycology (ECMM) 2013 joint guidelines on diagnosis and management of rare and emerging fungal diseases.* Clin Microbiol Infect, 2014. **20 Suppl 3**: p. 1-4.
16. Tortorano, A.M., et al., *ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others.* Clin Microbiol Infect, 2014. **20 Suppl 3**: p. 27-46.
17. Arendrup, M.C., et al., *ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections.* Clin Microbiol Infect, 2014. **20 Suppl 3**: p. 76-98.
18. Cornely, O.A., et al., *ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013.* Clin Microbiol Infect, 2014. **20 Suppl 3**: p. 5-26.
19. Chowdhary, A., et al., *ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi.* Clin Microbiol Infect, 2014. **20 Suppl 3**: p. 47-75.
20. Nucci, M., et al., *Improvement in the outcome of invasive fusariosis in the last decade.* Clin Microbiol Infect, 2014. **20**(6): p. 580-5.
21. Cuenca-Estrella, M. and J.L. Rodriguez-Tudela, *The current role of the reference procedures by CLSI and EUCAST in the detection of resistance to antifungal agents in vitro.* Expert Rev Anti Infect Ther, 2010. **8**(3): p. 267-76.
22. IEA. *Good Epidemiological Practice*. February 2008 9.11.2012]; Available from: http://ieaweb.org/wp-content/uploads/2012/06/cioms.pdf.