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Study Protocol

Fungiscope

Global Emerging Fungal Infection Registry

Oliver A. Cornely, MD, FIDSA, FACP, FAAM
Maria J.G.T. Vehreschild, MD

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Table of Contents

1. Study Coordinators ..... - 3 -
2. Introduction ..... - 6 -
3. Objectives ..... - 6 -
4. Study Period ..... - 7 -
5. Patient Population ..... - 7 -
6. Case Report Form ..... - 8 -
7. Data Analysis ..... - 9 -
8. Specimen Collection and Laboratory-Based Research ..... - 9 -
9. Budgetary Information ..... - 9 -
10. Ethical Considerations and Data Privacy Protection ..... - 10 -
11. Authorship Policy ..... - 11 -
12. Contact Information ..... - 11 -
13. References ..... - 12 -

1. Study Coordinators

Clinical ID	Microbiology	Molecular Biology	Pharmacology	Pathology
Austria				
Elisabeth Presterl, MD Allgemeines Krankenhaus - Universitätskliniken Wien Währinger Gürtel 18-20 1090 Wien T +43-1-40400-4440 F +43-1-4400-4418 elisabeth.presterl@meduni wien.ac.at	Cornelia Lass-Flörl, MD Institute of Hygiene, Microbiology and Social Medicine Universität Innsbruck Fritz-Pregl-Str. 3 6020 Innsbruck T +43-512-9003-70725 F +43-512-9003-73700 cornelia.lass-floerl@uibk.ac.at	Walter Buzina, MD Institut für Hygiene Medizinische Universität Universitätsplatz 4 8010 Graz T +43-316-380-7719 F +43-316-380-9648 walter.buzina@meduni-graz.at		Ulrich Strasser, MD Institut für Pathologie Medizinische Universität Innsbruck Müllerstr. 44 A-6020 Innsbruck T +43-512-9003-71304 F +43-512-582-088 ulrich.strasser@i-med.ac.at
Brazil				
Marcio Nucci, MD Hospital Universitário Universidade Federal do Rio de Janeiro Av. Brigadeiro Trompovsky S/N 21941-590 Rio de Janeiro T +55-21-2562-2463 F +55-21-2562-2460 mnucci@hucff.ufrj.br				
Czech Republic				
Zdeněk Ráčil, MD Dept. of Internal Medicine Hemato-Oncology University Hospital Brno Jihlavska 20 62500 Brno T +420-53223-2830/3642 F +420-53223-3603 zracil@fnbrno.cz	Iva Kocmanova, MD Dept. of Microbiology University Hospital Brno, Jihlavska 20 62500 Brno T +420 53223 2974 ikocmanova@fnbrno.cz	Martina Lengerova, MD Dept. of Internal Medicine Hemato-Oncology University Hospital Brno Jihlavska 20 62500 Brno T +420 53223 3642 mlengerova@nbrno.cz	Mojmir Moulis, MD Dept. of Pathology University Hospital Brno Jihlavska 20 62500 Brno T +420 53223 1111 mmoulis@fnbrno.cz	Ludmila Malaskova, MD Dept. of Biochemistery University Hospital Brno Jihlavska 20 62500 Brno T. +420 53223 3073 lmalas@fnbrno.cz

Clinical ID	Microbiology	Molecular Biology	Pharmacology	Pathology
Germany				
Oliver A. Cornely, MD, FIDSA, FACP Klinikum der Universität Klinik I für Innere Medizin 50924 Köln T +49-221-478-6494 F +49-221-478-3611 oliver.cornely@ctuc.de	Hilmar Wisplinghoff, MD Klinikum der Universität Institut f. Mikrobiologie, Immunologie u. Hygiene Goldenfelsstr. 19-2 50935 Köln T +49-221-478 32017 F +49-221-478-32134 hilmar.wisplinghoff@uk-koeln.de	Ralf Bialek, MD MVZ Labor Dr. Krause Steenbeker Weg 25 24106 Kiel T +49-431-388-252 bialek@labor-krause.de	Fedja Farowski, Biochemist Klinikum der Universität Institut für Pharmakologie 50924 Köln T +49-221-478-87275 fedja.farowski@ctuc.de	Birgid Markiefka, MD Klinikum der Universität Institut für Pathologie 50924 Köln T +49-228-478-6370 F +49-228-478-6360 birgid.markiefka@uk-koeln.de
		Volker Rickerts, MD Robert Koch Institute Postbox 650280 13302 Berlin T +49-30-18754-2862 F +49-30-18754-2614 rickertsv@rki.de		
India				
	Anupma Jyoti Kindo, MD Dept. of Microbiology Sri Ramachandra Medical College/Research Institute No.1, Ramachandra Nagar Porur, Chennai, 600 116 T +91-944-523-9196 F +91 44 2476 5608 anupmalakra@yahoo.com			
	Anuradha Chowdary Department of Medical Mycology Vallabhbhai Patel Chest Institute University of Delhi Delhi 110 007 T +91-11-2766-7560 F -91-98-1030-0258 dranuradha@hotmail.com			

Clinical ID	Microbiology	Molecular Biology	Pharmacology	Pathology
Israel				
Morad Wattad, MD Rabin Medical Center Infectious Diseases Unit 39 Jabotinski St. 49100 Petah Tikva T +972-3-937-7377 F +972-3-937-6365 Moradv@clalit.org.il				
Italy				
Livio Pagano, MD Dipartimento di Ematologia Universita Cattolica del Sacro Cuore (Roma) Largo Francesco Vito 1 00168 Roma T +39-6-355-03953 F +39-630-51343 lpagano@rm.unicatt.it	Maurizio Sanguinetti, MD Istituto di Microbiologia (Roma) Università Cattolica del Sacro Cuore Largo Francesco Vito 1 00168 Roma T +39-6-3015-4964 F +39-6-3051-152 msanguinetti@rm.unicatt.it	Annamaria Tortorano, MD Dip. Sanità Pubblica-Microbiologia-Virologia Milano Università di Milano Via Pascal, 36/38 20133 Milano T +39-2-503-15145 F +39-2-503-15146 annamaria.tortorano@unimi.it	Andrea Novelli, MD Dipartimento di Farmacologia Università degli Studi di Firenze Viale Pieraccini, 6 50139 Firenze T +39-055-4271-286 F +39-055-4271-280 andrea.novelli@unifi.it	Gianluigi Vago, MD Department of Clinical Sciences Luigi Sacco Hospital University of Milan Via Pascal, 36/38 20133 Milano T +39-285994869 F +39-285994800 gianluca.vago@unimi.it
Turkey				
	Sevtap Arikan-Akdagli, MD Mycology Laboratory (Ankara) Hacettepe University 06100 Ankara F +90-312-3115250 sevtap.arikan@gmail.com			

2. 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]. While candidiasis, aspergillosis and cryptococcosis are still the most common entities [2-4], the so-called “emerging fungi” are gaining importance, for example mucormycosis, fusariosis and other less common infections caused by *Scedosporium* spp., *Penicillium* spp., *Acremonium* spp., *Paecilomyces* spp., *Trichoderma* spp., and other rare fungi.

Therapeutic standards have been established for aspergillosis [5] and cryptococcosis [6], and detailed guidelines for diagnosis and management of *Candida*-related diseases have been developed in 2012 [7-11]. 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 [12] covering rare hyalohyphomycosis [13], invasive yeast infections [14], mucormycosis [15], and systemic phaeohyphomycosis [16]. Current recommendations largely rely on a collection of case series, single-center studies and expert opinions [17]. In order to establish evidence-based treatment recommendations analyses of a comprehensive cohort is required.

3. 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:

3.1. Epidemiology

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

3.2. 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

3.2. Recommendations for diagnosis and treatment

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

4. Study Period

Start date of amendment: March 1, 2015

End date: not determined

5. Patient Population

5.1. Inclusion criteria

- Cultural, histopathological, antigen or DNA evidence of invasive fungal infection with emerging fungal pathogen

5.2. Exclusion criteria

- Infection due to *Aspergillus* spp., *Candida* spp., *Cryptococcus neoformans, Pneumocystis jiroveci*
- Infections due to endemic fungi, e.g. *Coccidioides* or *Histoplasma*
- Colonisation or other non-invasive infection, including superficial skin infections irrespective of causative pathogen

6. 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. Regular data-backup, hierarchized management of rights and authentication protocols ensure the protection of data from unauthorized access and loss. All Good Epidemiological Practice (GEP) requirements are met by the software [18].

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, gender, 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, 30 and status at most recent follow up
10 Cause of death, autopsy results if applicable

7. Data Analysis

Data will be analyzed using descriptive statistical methods using IBM SPSS™ software.

8. 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 E-test

9. 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.

10. 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 isolates of emerging fungi

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. Regular data backup, hierarchized management of rights and authentication protocols ensure the protection of data from unauthorized access and loss. Contributors can only view the cases submitted by themselves. All study procedures are liable to Good Epidemiological Practice (GEP) requirements German and European legislation [18]. 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.

11. 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. This will extend to a maximum of two: one clinician, and one microbiologist/medical mycologist, if applicable.

12. Contact Information

Chair

Prof. Oliver A. Cornely MD, FIDSA, FACP, FAAM
Uniklinik Köln
50937 Köln
Germany
Tel: +49-221-478-6494
Fax: +49-221-478-3611
oliver.cornely@uk-koeln.de

Project Manager

Danila Seidel, MS, PhD
Uniklinik Köln
50937 Köln
Germany
T +49-221-478-97343
F +49-221-478-3611
danila.seidel@uk-koeln.de

Coordinating physicians

Maria J.G.T. Vehreschild, MD
Uniklinik Köln
50937 Köln
Germany
T +49-221-478-88267
F +49-221-478-3611
maria.vehreschild@uk-koeln.de

13. 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. 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.
6. Thursky, K.A., et al., *Recommendations for the treatment of established fungal infections.* Intern Med J, 2008. **38**(6b): p. 496-520.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. Nucci, M., et al., *Improvement in the outcome of invasive fusariosis in the last decade.* Clin Microbiol Infect, 2014. **20**(6): p. 580-5.
18. IEA. *Good Epidemiological Practice*. February 2008 9.11.2012]; Available from: http://ieaweb.org/wp-content/uploads/2012/06/cioms.pdf.